Statistical Review and Evaluation

NDA/IND #:	NDA 22-037/SN0302 (SDN58); IND 63,551/SN0283 (SDN297)
CDER Stamp Date:	June 18, 2010; February 24, 2010
Applicant:	Shire Development, Inc.
Drug Name:	Intuniv™ (guanfacine) Extended-release tablets/SPD503
Indication:	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Medical Officer:	Cheri Lindberg, M.D.
Statistical Reviewer:	Yang Yang, Ph.D.
Protocol Number and Title:	SPD503-312: "*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)*"

1 BACKGROUND

Reference is made to NDA 22-037 for the use of Intuniv (SPD503) in the treatment of ADHD in children and adolescents aged 6-17, which was approved on 2 September 2009. Reference is also made to the pediatric efficacy and safety study SPD503-313 (IND 63,551/SN0275; Title: A Phase III, Double-Blind, Randomized, Placebo-Controlled, Multi-Center, Dose Optimization Study Evaluating the Efficacy and Safety of SPD503 in Combination with Psychostimulants in Children and Adolescents Aged 6-17 Years with a Diagnosis of ADHD), which differs from the study described in the Pediatric Written Request (PWR) issued for Intuniv on October 30, 2009. On 13 April 2010, a teleconference was held between Shire and the Agency to discuss potential changes to that PWR so that Study SPD503-313 along with two Phase I studies in adults (114 and 115) will not be invalidated for use in fulfilling a PWR. It was agreed during that teleconference that the original PWR would be rescinded and a new PWR would be issued by the Agency with a focus on obtaining data in the adolescent population. It was also agreed that another study SPD503-312 would serve as the central component of the new PWR (only requested study) and that the sponsor would await pending comments on its study protocol from the Agency.

The Agency's clinical comments on Study SPD503-312 were received on May 7, 2010 and this Type C teleconference has been requested to ensure that those comments are addressed before the start of Study SPD503-312. The meeting briefing package in this submission (NDA 22-037/ includes the modified protocol languages and also the protocol synopsis for Study SPD503-312.

Submission IND 63,551/SN0283 (dated 24 February 2010) included the original protocol of SPD503-312: \\Cdsesub1\evsprod\IND063551\0045\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5351-stud-rep-contr\spd503-312\spd503-312-protocol.pdf

The meeting materials and pertinent background info are in:
http://eroom.fda.gov/eRoom/CDER/CDER-NPC/0_9f8c2.

2 SUMMARY OF TRIAL DESIGN (STUDY SPD503-312)

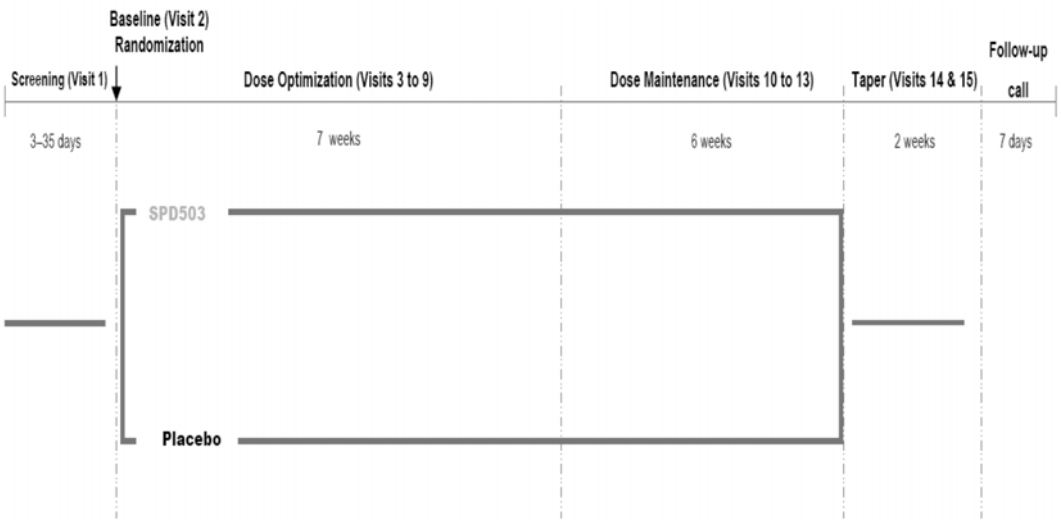
[1] **Objectives:**

– **Primary:** To assess the efficacy of once-daily dosing with optimized SPD503 compared with placebo in the treatment of adolescents aged 13-17 years with a diagnosis of ADHD

– **Secondary:**
  - To evaluate the effect on the clinician's global impressions of ADHD severity and clinician's global impressions of ADHD improvement with optimized SPD503 compared with placebo
  - To evaluate the changes in functional impairment associated with ADHD with optimized SPD503 compared with placebo
  - To evaluate the safety and tolerability of once-daily dosing of optimized SPD503 compared with placebo.

[2] **Structure:** this is a 13-week, multi-center, double-blind, randomized, placebo-controlled, monotherapy, flexible-dose Phase III study. The study will be conducted in ~ 40 US sites. The study design is shown in Figure 1.

Figure 1: Study Design Flow Chart



[3] **Treatment Arms:** eligible patients will be randomized in a 1:1 ratio to receive

– **Investigational arm:** SPD503 or
– **Control arm:** placebo.

Treatment allocation will be balanced within each weight group (34.0-41.4kg, 41.5-49.4kg, 49.5-58.4kg, and 58.5-91.0kg). Dosing of all subjects will initiate with 1mg/day, and may be increased by 1mg increments after a minimum of 1 week on the current dose to the maximum doses based on weight.

[4] **Primary Efficacy Measure:** change from baseline to Week 13 (Visit 13/Early Termination Visit) in ADHD-RS-IV total score.

– **Primary Analysis:** LOCF ANCOVA on Full Analysis Set (FAS). FAS is defined as all subjects who are randomized and take at least 1 dose of investigational product.

- **Model:** factors: treatment, weight group (stratification factor used in randomization), covariate: baseline score.

– **Sensitivity Analyses:**
  - Rank ANCOVA will be used if the normality assumption for parametric ANCOVA is not met
  - MMRM with an unstructured covariance matrix on observed cases:
    - **Model:** fixed effects: treatment, weight group (4 levels), time (11 levels), time-by-treatment; covariate: baseline score.

– **Supportive Analyses:** The primary efficacy analysis will be repeated for the ADHD-RS-IV total score change from baseline at each visit (3-13), using LOCF methodology and observed, respectively.

[5] **Secondary Efficacy Measures:** include change from baseline hyperactivity/impulsivity subscale score and inattentiveness subscale score of the ADHD-RS-IV, CGI-S, CGI-I, and Weiss Functional Impairment Rating Scale – Parent Report (WFIRS-P). None of those endpoints were pre-specified as **KEY** secondary endpoints.

[6] **Efficacy Assessment Schedule**:

Period	Screening[a]	Baseline	Dose Optimization	Dose Maintenance		Dose Tapering	Follow-up Call
Study Visit[b]	Visit 1	Visit 2	Visits 3-9	Visits 10,11 & 12	Visit 13 Final Maintenance /Early Term	Visits 14-15	Follow-up Call
Time of Visit(s)	Day -35 to -3	Day 0	Wks 1-7	Wks 8, 9 & 11	Wk 13	Wks 14 -15	Wk 16
ADHD-RS-IV		X	X	X	X		
CGI – S		X	X	X	X		
CGI – I			X	X	X		
PDSS		X	X	X	X		
WFIRS-P		X	X (Visit 9)	X (Visit 11)	X		

[b] A visit every 7 (± 2) days is permitted for Visits 3–11 and 14-15. A visit every 14 (± 2) days is permitted for Visits 12-13. A visit 7 (+2) days after last dose is permitted for the follow-up call.

[7] **Planned Sample Size Calculation:** it is assumed that 5% of randomized subjects will drop out without providing a valid post-baseline value for the ADHD-RS-IV total score. At least 25% of the subjects randomized will be female.
- **Planned number of randomized patients**: 280 subjects (140/arm)
- **Anticipated number of evaluable patients**: 266 subjects (133/arm)
- **Type-1 error rate (two-sided *t*-test):** 0.05
- **Power:** 90%
- **Difference to be detected:** 4 points between SPD503 and placebo (standard deviation of 10 points)

[8] **Interim Analysis:** NA

3 STATISTICAL COMMENTS TO BE CONVEYED TO THE SPONSOR

[1] We would like to know the anticipated dropout rate at Week 13 (Visit 13) for full analysis set in Study SPD503-312. Please be reminded that analysis results may not be interpretable if the dropout rate is large, particularly for studies where missingness might be informative. Since the validity of the LOCF and the MMRM analyses heavily relies on the missing data mechanism, please make an effort to reduce the number of dropouts and explore dropout patterns after data unblinding. To assess the validity of the primary LOCF ANCOVA analysis and the MMRM analysis, sensitivity analyses to deal with possible scenarios where the missing mechanism is not "missing at random" need to be pre-specified in detail.

[2] Will you designate "change from baseline in ADHD-RS-IV total score at each post-baseline visit before endpoint" as a key secondary endpoint? If yes, please pre-specify the multiplicity adjustment for comparisons of the primary and the key secondary endpoints to control the study-wise Type I error rate at the two-tailed 0.05 level.

[3] For other statistical comments, please refer to the new pediatric written request.

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Yang Yang, Ph.D.
Statistical Reviewer, DB1

Concur:
Peiling Yang, Ph.D.
Team Leader, DB1

Mahjoob Kooros, Ph.D.
Deputy Division Director, DB1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-63551	ORIG-1	SHIRE DEVELOPMENT INC	SPD 503 TABLETS/ 1MG(GUANFACINE HCL)
NDA-22037	GI-1	SHIRE DEVELOPMENT INC	INTUNIV: Guanfacine SR; tablet form

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

/s/

YANG YANG
07/07/2010

PEILING YANG
07/13/2010

KOOROS MAHJOOB
07/13/2010
This review was discussed with me. My viewes/comments are incorporated in this version and I concur with it.