# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-037**

# OTHER REVIEW(S)

**Department of Health and Human Services**

**Public Health Service**

**Food and Drug Administration**

**Center for Drug Evaluation and Research**

**Office of Surveillance and Epidemiology**

| | |
|---|---|
| Date: | July 17, 2009 |
| To: | Thomas Laughren, MD, Director<br>Division of Psychiatry Products |
| Thru: | Carlos Mena-Grillasca, R.Ph., Acting Team Leader<br>Denise Toyer, PharmD, Deputy Director<br>Carol Holquist, R.Ph., Director<br>Division of Medication Error Prevention and Analysis |
| From: | Walter Fava, R.Ph., Safety Evaluator<br>Division of Medication Error Prevention and Analysis |
| Subject: | Label and Labeling Review |
| Drug Name(s): | Intuniv (Guanfacine Hydrochloride) Extended-release Tablets<br>1 mg, 2 mg, 3 mg, and 4 mg |
| Application Type/Number: | NDA 22-037 |
| Applicant/Applicant: | Shire Pharmaceuticals |
| OSE RCM #: | 2009-257 |

**CONTENTS**

## EXECUTIVE SUMMARY

This review was written in response to a request from the Division of Psychiatry Products to evaluate the container labels, carton and package insert labeling for the product Intuniv (NDA# 22-037), for areas that could lead to medication errors.

Our evaluation noted areas where information on the container labels and carton labeling can be improved upon to provide increased readability and to ensure important drug information is retained with the product until the time of use. We also identified concerns with the proposed insert labeling. These concerns have been addressed by the Division of Psychiatry Products during the labeling meetings. We provide recommendations on how to improve the container labels in section 2 below. We request these revisions be implemented prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact, Abolade Adeolu, OSE Project Manager, at 301-796-4264.

# 1 MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA)[1] in our evaluation of the container labels, carton and insert labeling submitted for review. We reviewed the container labels submitted by the Applicant on January 26, 2009, as well as the physician sample container labels submitted on April 24, 2009. In addition we reviewed the most current revision of the package insert labeling submitted on April 22, 2009. (see Appendix A and B for images):

- Container labels for 1 mg, 2 mg, 3 mg, and 4 mg (100 tablet count)
- Container labels for 1 mg and 2 mg physician samples (7 tablet count)
- Prescribing Information (no image)

DMEPA also reviewed a working model of the physician sample packaging provided by the Applicant in response to our request dated April 22, 2009. Review comments are included in section 2.1.B below.

# 2 RECOMMENDATIONS

We provide the following recommendations for the Applicant.

## A. CONTAINER LABELS (100 tablet count)

You use a white font for your proprietary and established names, strength, and other text on the labels and labeling. However, as currently presented, the white font against a light colored background makes this information difficult to read. We recommend you use a darker font color to improve readability of important information on the principal display panel.

## B. PHYSICIAN SAMPLE CONTAINER LABELS (7 tablet count)

(b) (4)

[redacted]

[1] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

(b) (4)

Based on these concerns, we recommend the following:

**a.** The base container label must include the proprietary name, established name, dosage form, and strength statement. (b) (4)

**b.** Include the statement 'XX mg per tablet' or 'Each tablet contains XX mg' on the principal display panel of the 'peel back' and 'base' container labels. This will better inform patients that 1 mg or 2 mg is contained in each tablet. (b) (4)

**c.** Use a darker font color to improve the readability and presentation of the established name. As currently presented, the red font color against the white background gives the name a blurred appearance and makes it difficult to read.

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/s/
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Walter Fava
7/17/2009 04:42:07 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/17/2009 04:49:17 PM
DRUG SAFETY OFFICE REVIEWER

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

| | |
|---|---|
| Date: | July 15, 2009 |
| To: | Thomas Laughren, M.D. Division Director |
| | **Division of Psychiatry Products** |
| Through: | Jodi Duckhorn, MA, Team Leader |
| | **Division of Risk Management** |
| From: | LaShawn Griffiths, MSHS-PH, BSN, RN |
| | Patient Product Information Reviewer |
| | **Division of Risk Management** |
| Subject: | DRISK Review of Patient Labeling (Patient Package Insert) |
| Drug Name(s): | Intuniv (guanfacine) |
| Application Type/Number: | NDA 22-037 |
| Applicant/sponsor: | Shire Pharmaceuticals Inc. |
| OSE RCM #: | 2009-318 |

## 1 INTRODUCTION

Shire Pharmaceuticals Inc. submitted a New Drug Application (NDA 22-037) for Intuniv (guanfacine) extended-release tablets on August 24, 2006. The submission includes proposed Professional Information (PI) in PLR format, and Patient Labeling Information (Patient Package Insert). Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents 6-17 years of age. The Applicant references the NDA approvable letter dated June 7, 2007 from the FDA.

## 2 MATERIAL REVIEWED

- INTUNIV Patient Package Insert (PPI) submitted August 24, 2006
- INTUNIV Prescribing Information (PI) submitted August 24, 2006 and revised by the Review Division throughout the current review cycle

## 3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

Content and formatting revisions are made to ensure that the information is legible, clear, and patient-friendly. Patient Information that is well designed and clearly worded can help to maximize patient use and understanding of important safety information that is presented.

The draft PPI submitted by the Applicant has a Flesch Kinkaid grade level of 9.1, and a Flesch Reading Ease score of 53.9%. To enhance patient comprehension, materials should be written at a $6^{th}$ to $8^{th}$ grade reading level, and have a reading ease score of at least 60% (60% corresponds to an $8^{th}$ grade reading level). Our revised PPI has a Flesch Kinkaid grade level of 8.2 and a Flesch Reading Ease score of 58.5%.

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible,
- ensured that the PPI is consistent with the PI,
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have

reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI.

All future relevant changes to the PI should also be reflected in the PPI.

## 4 CONCLUSIONS AND RECOMMENDATIONS

1. The "Who should not take INTUNIV?" section was deleted. If the risk of hypersensitivity is theoretical with INTUNIV, hypersensitivity should not be listed as a contraindication to use.
2. In the "What should I tell my doctor before taking INTUNIV?" section
   - (b) (4) was removed because it is not listed in the PI. For consistency, if the Applicant wishes to add this to the PPI, it must first be added to the PI.
   - (b) (4) was removed because it is not listed in the PI. For consistency, if the Applicant wishes to add this to the PPI, it must first be added to the PI.
3. In the "How should I take INTUNIV?" section (b) (4) was removed. We recommend the Applicant clarify what a patient should do if there is a missed dose. For consistency, if the Applicant wishes to add this information to the PPI it must be added to the PI.
4. In the "Other Important Safety Information about INTUNIV" section (b) (4) was removed because it is not listed in the PI. For consistency if the Applicant wishes to add this to the PPI it must first be added to the PI.

Please let us know if you have any questions.

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/s/
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LaShawn Griffiths
7/15/2009 10:55:59 AM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
7/15/2009 10:57:21 AM
DRUG SAFETY OFFICE REVIEWER

# MEMORANDUM

**To:** **Sandy Chang, PharmD**
**Division of Psychiatry Products**

**From:** **Iris Masucci, PharmD, BCPS**
**Division of Drug Marketing, Advertising, and Communications**
**for the Study Endpoints and Label Development (SEALD) Team, OND**

**Date:** **July 10, 2009**

**Re:** **Comments on draft labeling for Intuniv (guanfacine) extended-release tablets**
**NDA 22-037**

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We have reviewed the proposed label for Intuniv (FDA version dated 7/2/09 and received by SEALD 7/6/09) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

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/s/
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Iris Masucci
7/14/2009 10:41:40 AM
DDMAC PROFESSIONAL REVIEWER

Laurie Burke
7/14/2009 05:04:51 PM
INTERDISCIPLINARY

# Interdisciplinary Review Team for QT Studies
## Response to a Request for Consultation: QT Study Review

| | |
|---|---|
| **IND or NDA** | 22037 |
| **Brand Name** | (b) (4)™ |
| **Generic Name** | Guanfacine (SPD503) |
| **Sponsor** | Shire Pharmaceuticals |
| **Indication** | Attention Deficit Hyperactivity Disorder |
| **Dosage Form** | Tablet |
| **Therapeutic Dose** | 1 to 4 mg per day |
| **Duration of Therapeutic Use** | Chronic |
| **Maximum Tolerated Dose** | Not determined |
| **Application Submission Date** | 24 August 2006 |
| **Review Classification** | Standard NDA |
| **Date Consult Received** | 07 March 2007 |
| **Date Consult Due** | 04 May 2007 |
| **Clinical Division** | DPP / HFD 130 |
| **PDUFA Date** | 24 June 2007 |

# 1 SUMMARY

## 1.1 BACKGROUND

Shire Pharmaceuticals submitted a NDA 22037 on 24 August 2006 for an extended release formulation

## 1.2 OVERALL SUMMARY OF FINDINGS

The concentration-QT analysis demonstrated that the guanfacine prolongs the QTc. However, the magnitude of QT prolongation can not be adequately quantified, since four out of the seven studies (Study 104, 106, 107 and 203) were open label studies and there were no controls in these studies. Also there was inadequate data for analyzing relationship between change from baseline, placebo and guanfacine concentrations. In two instances, subjects at 3 and 4 mg a day of (b) (4)™ were discontinued from study due to "ECG QT corrected interval prolonged". Hence for a clear delineation of the effect of guanfacine on the QTc the sponsor should conduct a "thorough QT study."

## 1.3 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

### 1.3.1 Is there enough of a QT effect to warrant including it in labeling?

The data the sponsor has submitted indicates administration of guanfacine prolongs the QTc but is not adequate to describe the relationship of guanfacine concentrations and QTc; i.e. the magnitude of the QTc effect. **The sponsor's proposed label "The mean** change in QTcF ranged from 1 to 10 msec in patients receiving 1 mg to 4 mg of (b) (4)™ **respectively" highlights the difficulty** in recommending labeling because mean changes in QTc less than 5 msec are not of regulatory concern while those exceeding this level are.

### 1.3.2 If so, where in the label would you recommend including it?

If the review division decides that the benefits of making (b) (4)™ available for patients outweighs any possible risk from its affect on QTc, we recommend that you state in the label that the effect of (b) (4) on the QTc has not been adequately studied. Prolongation of the QT interval can result in a type of ventricular tachycardia called Torsade de pointes, which may result in syncope, seizures, and death. Therefore, reasonable precautions should be taken to mitigate the possible effects of guanfacine on the QT interval, including:

1. Checking serum potassium and magnesium prior to initiating therapy and when appropriate thereafter since hypokalemia and hypomagnesemia can predispose to Torsade de pointes,
2. Avoiding concomitant use of other drugs known to prolong QTc,
3. Avoiding concomitant medications that tend to increase guanfacine levels (especially CYP3A4 inhibitors),
4. Avoid taking guanfacine with high fat meal as it increases the Cmax on the average by 77% and AUC by 40%,
5. Avoiding use in patients with liver impairment,
6. Careful screening to identify patients with Long QT syndrome and avoiding use in these patients, and
7. Checking QTc interval prior to initiating therapy and periodically thereafter.

### 1.3.3 If we expect that the QT effect is in the moderate range, would it be reasonable to consider labeling it now? Or would you strongly recommend requesting a QT study before making such a decision?

As stated in the ICH E14 guidelines "Drugs are expected to receive a clinical electrocardiographic evaluation…typically including a single trial dedicated to evaluating their effect on cardiac repolarization ('thorough QT/QTc study')." There do not appear to be any factors that reduce the need for such a study of guanfacine. Indeed, the information contained in NDA 22037 suggests that guanfacine is likely to prolong the QTc. Therefore, describing the relationship between guanfacine concentrations and QTc in the provider label may be important for the safe use of this product.

### 1.4 Reviewer's Comments

## 2 PROPOSED LABEL

*Effects on Heart Rate and QT Interval* – In short-term, controlled clinical studies of 662 patients with ADHD (513 on (b) (4)' and 149 taking placebo), a dose-dependent decrease in heart rate was observed in patients receiving (b) (4)™. The mean change in heart rate ranged from -2 to -15 bpm in patients receiving 1 mg to 4 mg of (b) (4)™ respectively, compared to -2 bpm in patients receiving placebo.

An increase in QTcF (QT corrected by Fridericia's formula) was also observed in patients receiving (b) (4). The mean change in QTcF ranged from 1 to 10 msec in patients receiving 1 mg to 4 mg of (b) (4) respectively, compared to 2 msec in patients receiving placebo. The mean changes in QT are likely related in part to limitations of the calculations to correct for decreases in heart rate that occur with (b) (4)'. (b) (4) and placebo treatment groups showed a similar number

of patients with outlier values for QT and QTc. The QTc increases in patients taking (b) (4)[*] were not associated with cardiovascular adverse events. No patients receiving (b) (4)[™] had a QTcF greater than 500 msec.

# 3 BACKGROUND

## 3.1 INDICATION

Attention Deficit Hyperactivity Disorder

## 3.2 DRUG CLASS

Selective alpha-2A-adrenoceptor agonist

## 3.3 MARKET APPROVAL STATUS

An immediate release formulation of guanfacine, Tenex, was approved for the treatment of systemic arterial hypertension in 1986. The extended release formulation is not approved for marketing.

## 3.4 PRECLINICAL INFORMATION

Cardiovascular safety pharmacology studies did not demonstrate that guanfacine hydrochloride prolonged ventricular repolarization.

In vitro

- Guanfacine (1 μg/ml or 3.54 μM) did not inhibit hERG current compared to vehicle, when evaluated in a whole cell voltage clamp study, with hERG expressed in a mammalian cell line (HEK293). E-4031 was utilized as a concurrent positive control.
- While there was no evidence of test substance related hERG inhibition, issues that limit this interpretation are listed below.
    - Test substance was evaluated at a single, relatively low concentration.
    - Current run-down was excessive (approximately 30%) in test substance and vehicle treated cells during the 15 minute incubation period.
    - While E-4031 was utilized as a positive control, only a supra-therapeutic concentration (100 nM) was evaluated. At this concentration, complete inhibition was not seen, which suggests that the assay lacked sensitivity (E-4031 inhibited hERG current by approximately 75%).

In vivo

- Guanfacine did not prolong QTc in conscious telemeterized dogs (n = 4 male Beagles) when given orally at single doses of 0.5 and 1.5 mg/kg. The QT interval was corrected for heart rate using Fridericia and individual correction methodologies. Dose related toxicity limited the highest dose tested to 1.5 mg/kg; 5.0 mg/kg producing emesis, piloerection accompanied by poor limb co-ordination, notable dragging of forelimbs and weakness of the hind limbs. Doses of 0.5 and 1.5 mg/kg increased PR interval and decreased heart rate in a dose-related fashon. Bradycardia was observed in 2 of 4 dogs at both doses tested.

The sponsor described ECG changes in the 2 dogs that exhibited bradycardia related arrhythmias as follows -

*"On inspection of all of the ECG waveforms from all 4 dogs on each day of telemetry recording, the following observations were made:- in dog 5941, administration of guanfacine caused a dose-dependent exacerbation of an underlying inherent brady-dysrhythmia characterized by sinus pauses and first- and second-degree heart block and associated supraventricular premature complexes. This occurred between 59 min-4 h and 31 min and 7 h 49 min following administration of 0.5 and 1.5 mg/kg guanfacine, respectively. In dog 4216 a similar brady-dysrhythmia, characterized by sinus pauses and first- and second-degree heart block and associated supraventricular premature complexes, was noted following the 0.5 mg/kg dose (1 h 50 min-1 h 53 min). The incidence of this dysrhythmia increased following 1.5 mg/kg guanfacine (53 min-5 h). No test substance related alterations of lead II ECG waveform or rhythm were noted in the remaining 2 animals."*

Plasma guanfacine concentrations at 2 hrs after administration of 1.5 mg/kg were 8.26, 34.03, 49.47 and 52.83 ng/ml.

Safety margins for QT effects based on in vivo QT telemetry data are shown below:

Safety margin based on dose multiple -

- animal dose, 1.5 mg/kg (HED, 0.75 mg/kg)
- maximum therapeutic human dose, 4 mg/day or 0.067 mg/kg/day
- dose ratio $_{\text{animal to human}}$, 0.75/0.067 or 11 fold.

Safety margin based on plasma concentrations -

- At 2 hrs, plasma concentrations ranged from 8.26 to 52.83 ng/ml. These concentrations are 2 to 15 times the human $C_{max}$ at the maximum human therapeutic dose of 4 mg/day.

| Animal | | Human | | Safety Margin |
|---|---|---|---|---|
| Dose (mg/kg) | 1.5 | Dose (mg) | 4 | --- |
| HED (mg/kg) | 0.75 | Dose (mg/kg) | 0.067 | 11 |
| Plasma $Conc_{2\ hrs}$ (ng/ml) | 8.26-52.83 | Plasma $C_{max}$ (ng/ml) | 3.58±1.39 | 2-15 |

HED, human equivalent dose

It should be noted that while an internal positive control was not evaluated in this *in vivo* QT study, an approximately 10% increase (or about 25-30 ms) is typically needed to capture a drug related effect on QT in these models.

### 3.5 Previous Clinical Experience (Dr. Ana Szarfman)

The QT-IRT requested Dr Ana Szarfman in DCRP review the cases that might indicate an association between guanfacine and QT prolongation and/or torsades de pointes in AERS and to assess the corresponding MGPS data mining signal scores or adjusted relative reporting ratios (ARRR) in AERS.

Guanfacine had a total of 702 adverse event reports in AERS as of January 2007.

The MGPS methodology identified the expected association between guanfacine and bradycardia with an ARRR of 5.61 (4.2, 7.42) for the bradycardia-guanfacine association. This signal was generated by 35 cases.

Although there were only four cases of QT prolongation identified, three in adults and one in a child, the ARRR was 2.35 (1.03,4.78). The adult cases were associated with diuretic use (which can result in hypokalemia) and myocardial infarction. There was no definite signal linking guanfacine to seizures (torsades de pointes can be confused with seizures, especially in children). There were no cases coded as torsades de pointes.

There was a signal of drug-drug interactions generated by 30 cases with an ARRR of 3.04 (2.24, 4.06). Of relevance, 3 of these cases documented increases in valproic acid blood levels when guanfacine was used concomitantly.

*Reviewer's comments:*

1. *There does appear to be an association between guanfacine and QT prolongation but the confidence intervals are wide due to the paucity of reports.*
2. *The QT prolongation and drug-drug interaction signals with guanfacine may deserve further monitoring. Although not documented with guanfacine in this analysis, some drug-drug interactions, including the ones associated with valproic acid use have the potential of exacerbating QT prolongation.*

### 3.6 CLINICAL PHARMACOLOGY

Table 1 summarizes the key features **of guanficine's clinical pharmacology.**

## Table 1 Highlights of Clinical Pharmacology (Data Compiled by the Sponsor)

| | | |
|---|---|---|
| Therapeutic dose | 1-4 mg | |
| Maximum tolerated dose | Not determined | |
| Principal adverse events | From Phase III studies: somnolence, sedation, fatigue and decreased heart rate and blood pressure based on most common adverse reactions. Also noted in proposed label's Warnings and Precautions | |
| Maximum dose tested | Single Dose | 4 mg |
| | Multiple Dose | Titrated up to 4 mg<br>Day 1 2mg , Days 9-15…2mg<br>Days 16-22…3 mg, Days 23-29…4mg<br>(Protocol SPD503-107) |
| Exposures Achieved at Maximum Tested Dose | Single Dose | 4 mg Single dose<br>$C_{max}$ 3.56 (37%) ng/mL<br>AUC 125 (41%) ng-h/mL<br>(Protocol SPD503-104) |
| | Multiple Dose | 4mg Multiple dose (QD dosing)<br>$C_{max}$ 10.1 (70%) ng/mL.. Pediatric<br>$AUC_{24}$ 162 (72%) ng-h/mL Pediatric<br>$C_{max}$ 7.01 (22%) ng/mL.. Adolescent<br>$AUC_{24}$ 117 (24%) ng-h/mL Adolescent<br>(Protocol SPD503-107) |
| Range of linear PK | 1-4 mg QD dosing | |
| Accumulation at steady state | $C_{max}$ 61%; AUC 69%<br>(Protocol SPD503-203) | |
| Metabolites | As discussed in NDA section 2.7.2.1, the glucuronide and sulfate conjugates of 3-OH guanfacine account for approximately 50% of the radioactivity excreted in the urine. The oxidized mercapturic acid derivatives are the only other compounds that account for a significant portion of the radioactivity.<br>(Literature reference:<br>Kiechel JR. Pharmacokinetics and metabolism of guanfacine in man: a review. Br J Clin Pharmacol. 1980; 10: 25S-32S) | |
| Absorption | Absolute/Relative Bioavailability | The absolute bioavailability of immediate release guanfacine (Tenex® ) is 80-100%,whilst the relative bioavailability of SPD503 compared to Tenex® is ~60%<br>Literature references:<br>Kiechel JR. Pharmacokinetics and metabolism of guanfacine in man: a review. Br J Clin Pharmac. 1980; 10: 25S-32S.<br>Carchman SH, Crowe JT Jr, Wright GJ. The bioavailability and pharmacokinetics of guanfacine after oral and intravenous administration to healthy volunteers. J Clin Pharmacol. 1987; 27: 762-767. |
| | $T_{max}$ | 5.01h (3-48h) in adults<br>(Protocol SPD503-104) |
| Distribution | Vd/F | 833 L (39%) in adults<br>11.1 L/kg (36%)<br>(Protocol SPD503-104) |
| | % bound | 64-72% bound to human plasma<br>(Literature references:<br>Same as for Absorption, Absolute/Relative Bioavailability) |
| Elimination | Route | Renal (~50%)<br>(Literature references:<br>Same as for Absorption, Absolute/Relative Bioavailability) |
| | Terminal $t_{½}$ | 16 (26%) h in adults<br>(Protocol SPD503-104) |
| | CL/F | 617 mL/min (38%) in adults<br>8.35 mL/min/kg (40%) in adults<br>(Protocol SPD503-104) |

| Table 1. Highlights of Clinical Pharmacology for SPD503 (guanfacine HCl) extended-release tablets | | |
|---|---|---|
| Intrinsic Factors | Age | **6-12 yrs multiple 4mg qd dose**<br>$C_{max}$ 10.1 (70%) ng/mL<br>$AUC_{24}$ 162 (72%) ng-h/mL<br>Cl/F 522 (41%) mL/min;<br>14.3 (26%) mL/min/kg<br>**13-17 yrs multiple 4 mg qd dose**<br>$C_{max}$ 7.01 (22%) ng/mL<br>$AUC_{24}$ 117 (24%) ng-h/mL<br>Cl/F 607 (27%) mL/min;<br>10.7(29%) mL/min/kg<br>(Protocol SPD503-107) |
| | Sex | **Male multiple 4 mg qd dose**<br>$C_{max}$ 7.5 (27%) ng/mL<br>$AUC_{24}$ 125 (27%) ng-h/mL<br>Cl/F 11.9 (30%) mL/min/kg<br>**Female multiple 4mg qd dose**<br>$C_{max}$ 10.6 (80%) ng/mL<br>AUC 170 (84%) ng-h/mL<br>Cl/F 13.8 (31%) ml/min/kg<br>(Protocol SPD503-107) |
| | Race | Not available |
| | Hepatic & Renal Impairment | Study not conducted for this program, however, see NDA 2.7.2.2.2.3: guanfacine is cleared to an equal extent by the kidney and liver<br>(Literature references:<br>Same as for Absorption, Absolute/Relative Bioavailability) |
| Extrinsic Factors | Drug interactions | %GMR (Combo/503)<br>**A. Vs. Rifampin**<br>$C_{max}$ GMR =45 (38-54 CI)<br>AUC GMR =37 (23-58CI)<br>(Protocol SPD503-108)<br>**B. Vs. Ketoconazole**<br>Cmax GMR =175 (145-209)<br>AUC GMR= 313 (251-390)<br>(Protocol SPD503-106) |
| | Food Effects | Fed/fast %GMR (90%CI)<br>$C_{max}$ 175 (161-189)<br>$AUC_{\infty}$ 137 (127-148)<br>(Protocol SPD503-104) |
| Expected High Clinical Exposure Scenario | As doses increase on a mg/kg basis efficacy increases however, there is a potential increase in dose related AE's such as somnolence, sedation and hypotension | |

*GMR is Geometric Mean Ratio

# 4 SPONSOR'S SUBMISSION

## 4.1 OVERVIEW

The sponsor did not conduct a thorough QT study. The sponsor collected information on the effects of guanfacine on QTc in 6 studies (a description of each study was provided by the statistical reviewer in Appendix 6.1). The sponsor assessed the relationship between guanfacine concentrations and QTcF by pooling data across studies. A review of the exposure response data by the clinical pharmacology review, Dr. Atul Bhattaram, is presented in Appendix 6.2.

# 5 REVIEWERS' ASSESSMENT

## 5.1 PHARMACOLOGY/TOXICOLOGY ASSESSMENTS

## 5.2 STATISTICAL ASSESSMENTS

The results presented by the sponsor showed a QTc prolongation signal. For example, in Study 106, for Group SPD503, the overall QTcF mean change from baseline was 8.2, 6.0, 11.5, 8.4 and 6.5 ms at hour 7, 8, 9, 10, and 96, respectively. In Study 206, for SPD

503 (three doses combined), the change in QTcF from baseline to visit 5 was 11.4 ms with standard deviation 13.49. In Study 301, for SPD 503 3 mg, the mean change in QTcF from baseline to Week 3 was 9.1 ms with standard deviation 16.20. However, the actual effect of administering (b) (4)™ on the QTc is unclear due to the following limitations of the studies:

- Four out of the seven studies (Study 104, 106, 107 and 203) were open label studies and there were no controls in these studies. Lack of controls maes I impossible to isolate the effect of drug from confounders.
- The study populations varied. Study 104 and 106 were conducted on healthy subjects aged 18-55. Study 107, 206, 302 and 304 were conducted on pediatric population (aged 6-17) with ADHD. Study 203 was conducted on children aged 6-12 with ADHD.
- The time points at which QT measurements were made varied widely among different studies. In Studies 104, 106 and 107 and 203, QT intervals were measured at several time points after dosing within a three day time frame. For example, in Study 104, the QT measurements were taken at hour -1, 0, 6, 7, 8, 10, and 96 after dosing. However, in Studies 206, 301, and 304, QT measurements were collected only once at certain visits. For example, in Study 206, QT measurements were collected on baseline, visit 5 (Study Day 28) and visit 8 (Study Day 45). No information was provided whether the QT intervals were collected before, at or after Cmax.

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The sponsor has not conducted a thorough QT study. The sponsor collected information on the effects of guanfacine administration on the QTc in 6 studies. These studies have several limitations presented in Table 2.

**Table 2: Study Description**

| Study | Positive Features of the Study | Negative Feature of the Study |
|---|---|---|
| 104 (N=48) | • Guanfacine concentrations were measured. | • No placebo group in the study.<br>• Study was not conducted in the patient population of interest (Food Effect Study in Adult Subjects)<br>• Data collected after single dose alone.<br>• Collected baseline measurements only for first 3 hours |
| 106 (N=20) | • Data collected after single and multiple doses.<br>• Guanfacine concentrations were measured. | • No placebo group in the study.<br>• Study was not conducted in the patient population of interest (Ketoconazole Drug-Drug Interaction Study)<br>• Collected baseline measurements only for first 3 hours |
| 107 (N=28) | • Study was conducted in the patient population of interest. | • No placebo group in the study.<br>• Collected baseline measurements only |

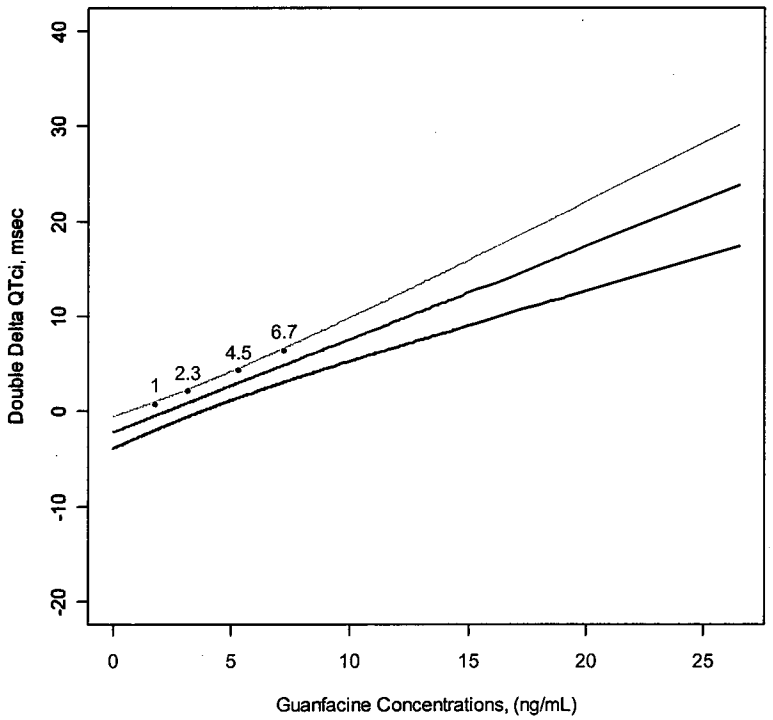
| | | |
|---|---|---|
| | • Data collected after single and multiple doses.<br>• Dose levels for approval are included in the study.<br>• Data collected for 4 weeks on treatment using a combination of measurements around peak concentrations and pre-dose (trough).<br>• Guanfacine concentrations were measured. | for first 3 hours. |
| 203 (N=20) | • Study was conducted in the patient population of interest.<br>• Dose levels for approval are included in the study.<br>• Data collected for 7 weeks during forced up titration as well as down titration (1-2-3-4-3-2-1 mg/day).<br>• Guanfacine concentrations were measured. | • No placebo group in the study. |
| 206 (N=182) | • Study was conducted in the patient population of interest.<br>• Placebo group was included.<br>• Dose levels for approval are included in the study.<br>• Data collected for 7 weeks during forced up titration as well as down titration (1-2-3-4-3-2-1 mg/day).<br>• Guanfacine concentrations were measured. | • Data collected only at one time point (5 hours) at steady state. |
| 301 (N=345) | • Phase-III study in the patient population of interest.<br>• Placebo group was included. | • Not clear when ECGs were acquired relative to the time of dosing. No serial sampling was done.<br>• Drug concentrations were not measured. |
| 304 (N=324) | • Phase-III study in the patient population of interest.<br>• Placebo group was included. | • Not clear when ECGs were acquired relative to the time of dosing. No serial sampling was done.<br>• Drug concentrations were not measured. |

The sponsor analyzed the relationship between guanfacine concentrations and QT prolongation in studies SPD503-107, SPD503-203, SPD503-206. The sponsor concluded that for every 1 ng/mL increase in guanfacine concentrations, the QTc is prolonged by

approximately 1 msec. This is derived based on the slope of concentration-QTc (Population corrected) effect which is 0.9 msec/ng/mL.

The pharmacometric reviewer conducted an independent concentration-QT analysis by analyzing the above mentioned studies along with studies SPD503-104, SPD503-106. **The reviewer's analysis is in agreement in the sponsor's findings. The mean** ΔΔQTci prolongation (**assuming** 2.5 msec for placebo effect) versus concentrations along with upper and lower 90% confidence intervals is shown below. The upper 90% confidence interval estimates of the ΔΔQTci prolongation are obtained at the Cmax of 1.76, 3.15, 5.28 and 7.23 ng/mL after multiple oral doses of 1, 2, 3, and 4 mg respectively.

**Figure 1: Upper, Mean and Lower 90% Confidence Intervals For ΔΔQTcI (Double-Delta; Baseline, Placebo Subtracted) Versus Guanfacine Concentrations.**




Note: The text in the graph refers to the upper 90% confidence interval estimates at the $C_{max}$ of 1.76, 3.15, 5.28 and 7.23 ng/ml after multiple oral doses of 1, 2, 3 and 4 mg respectively.

The main issue with the acceptability of the overall conclusions of the analysis is that studies SPD503-104, SPD503-106, SPD503-107 and SPD503-203 were open label studies and there were no controls in these studies.

### 5.4 MEDICAL ASSESSMENTS

The QT-IRT clinical reviewer reviewed SAE narratives from NDA 22037 provided by **the review division for syncopal or "syncopal- like" events and was unable to identify** any definite cases of torsade de pointes or other ventricular arrhythmias. However, the most current IB (1 Sep 2006) in table 14 page 57 states that one subject taking (b) (4)™ 3 mg qd and one taking (b) (4)™ 4 mg qd were discontinued due **to "ECG QT corrected prolonged."**

*Reviewer's comment: Not observing any cases of torsade de pointes is not reassuring because the total duration of observation is too brief to reliably detect an infrequent event. The premarketing studies of many drugs subsequently associated with QT prolongation and torsade were not remarkable.*

# 6 APPENDICES

## 6.1 STATISTICAL REVIEW

### 6.1.1 Study 104

A Phase 1 Study to Investigate the Effect of Food on the Pharmacokinetics of SPD503 in Healthy Volunteers

#### 6.1.1.1 Protocol Number

SPD503-104

#### 6.1.1.2 Objectives

The primary objective of this study was to assess the effect of food on the bioavailability of a single 4mg (1 x 4mg) dose of SPD503.

The secondary objectives of this study were to assess the bioequivalence of a single 4mg (1 x 4mg) tablet of SPD503 compared to four 1mg tablets of SPD503 and to evaluate the safety and tolerability of a 4mg dose of SPD503.

#### 6.1.1.3 Design

This research study utilized a randomized, open-label, single-dose, three-period crossover design. Forty-eight (48) subjects were enrolled in the study in two groups of 24 subjects each.

**During each period, subjects were admitted to the study center on Day –1 (at least 18** hours prior to dosing during Period 1 and at least 12 hours prior to dosing during Periods 2 and 3) to reconfirm eligibility. Following an overnight fast of at least 10 hours, subjects received a 4mg oral tablet dose of SPD503 on Day 1 (as either 4 x 1mg tablets fasted, a 1 x 4mg tablet fasted or a 1 x 4mg tablet following a standard high-fat breakfast). PK blood samples were collected and safety assessments were performed through 48 hours post-dose. Subjects were released from the unit following completion of the 48-hour post-dose procedures and were required to return to the clinic 72 and 96 hours post-dose for PK samples and safety assessments. Following a minimum 7-day washout, subjects returned for Periods 2 and 3 where they were crossed over to an alternate treatment (either 4 x 1mg tablets fasted, 1 x 4mg tablet fasted or 1 x 4mg tablet following a standard high-fat breakfast).

##### *6.1.1.3.1 Sponsor's Justification for Design*

The six-sequence crossover design allowed for evaluation of the effect of food on the pharmacokinetics of SPD503. Since subject plasma levels are not affected by blinding, this study was conducted with open-label dosing. The 7 days between the three study

periods allowed sufficient time for SPD503 washout, based on a minimum of five half-lives of the drug (~17 hours)17 in adults. Safety monitoring was conducted through 30 days following the final dose of study drug administration.

#### *6.1.1.3.2 Controls*

There were no controls in this study.

#### *6.1.1.3.3 Blinding*

This was an open-label study and no blinding was required.

### 6.1.1.4 Study Subjects

Forty-eight (48) healthy adult subjects (24 subjects per group) aged 18 to 55 inclusive who met all inclusion criteria were eligible to participate this study.

### 6.1.1.5 Sponsor's Results

QT intervals were corrected for HR using both Fridericia's and Bazett's formulas. Both QTcF and QTcB results are presented in the post text table and appendix (Section 12, Table 3.4.1 and Appendix 2.9.2.1). Only QTcF results are presented in the in-text tables (text Table 3 and text Table 4) and discussed in the text.

The sponsor states that all mean ECG parameters remained within normal limits. Although no marked changes from Baseline were noted, there was a trend for a small fall in HR over the 8-10 hour period in all three treatments.

**Table 3 Overall ECG Mean Change from Baseline**

| | Treatment A 4x1mg, Fasted (N=47) | | | | | | Treatment B 1x4mg, Fed (N=42) | | | | | | Treatment C 1x4mg, Fasted (N=44) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | -1 hour | 6 hour | 7 hour | 8 hour | 10 hour | 96 hour | -1 hour | 6 hour | 7 hour | 8 hour | 10 hour | 96 hour | -1 hour | 6 hour | 7 hour | 8 hour | 10 hour | 96 hour |
| HR Interval | -1.7 | 1.4 | -0.6 | -4.9 | -5.7 | -2.1 | -2.1 | -1.8 | -5.1 | -7.3 | -8.3 | -1.6 | -1.2 | 0.7 | -3.2 | -5.4 | -5.6 | -1.8 |
| PR Interval | 2.8 | 4.7 | 3.9 | 2.5 | 2.2 | 3.5 | 2.8 | 5.1 | 6.2 | 5.4 | 3.4 | 2.1 | 1.7 | 4.5 | 5.1 | 2.3 | 1.3 | 0.7 |
| QRS Interval | 3.1 | 2.1 | 2.8 | 3.4 | 3.7 | 2.5 | 2.2 | 4.8 | 4.1 | 3.6 | 2.7 | 1.4 | 2.3 | 3.3 | 3.9 | 3.6 | 4.3 | 0.9 |
| QT Interval | 5.7 | -0.2 | 6.1 | 10.0 | 15.3 | 3.1 | 6.2 | 9.5 | 14.4 | 19.0 | 19.1 | 2.8 | 5.6 | 1.5 | 9.0 | 12.0 | 13.9 | 2.9 |
| QTc Fridericia | 2.7 | 2.3 | 5.2 | 0.4 | 4.9 | -0.7 | 2.0 | 6.5 | 4.8 | 5.1 | 2.8 | 0.1 | 3.3 | 2.8 | 3.0 | 2.0 | 3.1 | 0.1 |

Source: Section 12, Table 3.4.1.
Note: Please note N refers to the number of subjects with at least a pre-dose ECG evaluation during that treatment.

**Source: Table 15 of sponsor's Clinical Study Report**

**Table 4: Summary of QTcF Increase from Baseline by Treatment**

| | | Increase from Baseline | | | | | |
|---|---|---|---|---|---|---|---|
| | | Treatment A 4x1mg, Fasted (N=47) | | Treatment B 1x4mg, Fed (N=42) | | Treatment C 1x4mg, Fasted (N=44) | |
| Measurement | Hour | 30 to <60 | >=60 | 30 to <60 | >=60 | 30 to <60 | >=60 |
| QTcF (msec) | Predose | 0 | 0 | 2 | 0 | 0 | 0 |
| | 6 | 1 | 0 | 0 | 0 | 1 | 0 |
| | 7 | 0 | 0 | 0 | 0 | 2 | 0 |
| | 8 | 0 | 0 | 3 | 0 | 1 | 0 |
| | 10 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 96 | 0 | 0 | 0 | 0 | 0 | 0 |

Source: Section 12, Table 3.4.1.
Note: Please note N refers to the number of subjects with at least a pre-dose ECG evaluation during that treatment.

**Source: Table 16 of sponsor's Clinical Study Report**

The maximum QTcF increase from Baseline in this study was 44msec; this increase occurred at Hour 6 following Treatment A administration. The maximum QTcF post-dose value in this study was 460msec; this value occurred at approximately Hour 10 following Treatment A.

The sponsor state that the Investigator considered all of the individual ECG abnormalities to be not clinically significant in the context of this study. No ECG AEs were reported in this study.

### 6.1.2 Study 106

A Phase 1, Open-Label, Single-Sequence, Crossover Study to Evaluate the Effect of Ketoconazole on the Pharmacokinetics of SPD503 in Healthy Adult Subjects

#### 6.1.2.1 Protocol Number

SPD503-106

#### 6.1.2.2 Objectives

The primary objective of this study was to assess the effect of ketoconazole on the pharmacokinetics of a single 4mg dose of SPD503.

The secondary objective of this study was to evaluate the safety and tolerability of a 4mg dose of SPD503 when given concurrently with ketoconazole.

#### 6.1.2.3 Design

This was a single-sequence crossover study that was conducted in healthy adult volunteers aged 18-55 at a single center in the United States.

##### *6.1.2.3.1 Sponsor's Justification for Design*

A previous study has shown that SPD503 is metabolized (*in vitro*) by CYP3A4 (Shire Study No. V00652-SPD503-IIIG). The potential for drug-drug interactions, therefore,

exists between SPD503 and CYP3A4 inhibitors and inducers. Ketoconazole was used in this study as a prototypic inhibitor of CYP3A4, which it is hypothesized, might increase plasma levels of SPD503 if the two compounds are coadministered.

The single-sequence crossover design allowed for evaluation of the effect of ketoconazole on the PK of SPD503. Since subject plasma levels are not affected by blinding, this study was conducted with open-label dosing. The 7 days between study periods allowed sufficient time for SPD503 washout, based on a minimum of five half-lives of the drug (~17 hrs) in adults. Safety monitoring was conducted through 30 days following the final dose of study drug administration.

#### *6.1.2.3.2 Controls*

There were no controls in this study.

#### *6.1.2.3.3 Blinding*

This was an open label study.

### 6.1.2.4 Study Subjects

Twenty (20) healthy adult male and female volunteers aged 18-55 years (yrs) inclusive were chosen to participate in this study.

### 6.1.2.5 Sponsor's Results

QT intervals were corrected for HR using both **Bazett's (QTcB) and Fridericia's (QTcF)** formulas. Both QTcB and QTcF results are presented in the post text tables and appendices (Table 3.4.1 and Appendix 2.9.2.1). Only QTcF results are presented in the text tables (Table 5 and Table 6) and discussed in the text.

Table 5 and Table 6 summarize overall ECG mean changes from Baseline and QTcF increases from Baseline by treatment, respectively.

The sponsor states that all mean ECG parameters remained within normal limits and no marked changes from Baseline were noted.

HR tended to decrease after SPD503 dosing. HR decreases from Baseline were somewhat greater with combination therapy compared to SPD503 alone.

**Table 5: Overall ECG Mean Change from Baseline**

| | SPD503 | | | | | | SPD503 + Ketoconazole | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | -1h | 7h | 8h | 9h | 10h | 96h | -1h | 7h | 8h | 9h | 10h | 96h |
| HR Interval | -4.8 | -4.7 | -9.7 | -11.8 | -8.9 | 0.2 | -4.6 | -9.1 | -13.1 | -15.1 | -12.6 | -4.1 |
| PR Interval | 6.8 | 3.7 | 4.5 | 5.0 | -0.4 | 5.9 | 6.0 | 5.2 | 5.0 | 1.7 | -0.5 | 2.8 |
| QRS Interval | 3.3 | 5.0 | 5.1 | 4.8 | 4.3 | 2.8 | 7.0 | 9.9 | 9.3 | 3.6 | 6.3 | 5.3 |
| QT Interval | 14.2 | 15.7 | 24.5 | 34.2 | 25.1 | 5.2 | 8.6 | 28.6 | 35.4 | 34.8 | 33.6 | 15.1 |
| QTc Fredericia | 5.9 | 8.2 | 6.0 | 11.5 | 8.4 | 6.5 | 1.2 | 11.9 | 9.3 | 4.0 | 8.5 | 8.3 |

Note: Baseline for each subject is the average of the three measurements taken on Study Day -1.
Pre-dose = -1 hr, Relative hr* = hrs from SPD503 dosing
SPD503 = 1 x 4mg SPD503 Alone (Study Day 1)
SPD503 + Ketoconazole = 1 x 400mg Ketoconazole (QD for 6 days) with 1 x 4mg SPD503 (Study Day 3)
**Source: Table 10 of sponsor's Clinical Study Report**

**Table 6: Qualitative QTcF Changes from Baseline**

| | Increase from Baseline | | | | |
|---|---|---|---|---|---|
| | | SPD503 | | SPD503 + Ketonazole | |
| **Measurement** | **Relative hr*** | **30 to <60** | **>=60** | **30 to <60** | **>=60** |
| QTcF (msec) | Pre-dose | 0 | 0 | 0 | 0 |
| | 7 | 1 | 0 | 1 | 0 |
| | 8 | 0 | 0 | 1 | 0 |
| | 9 | 2 | 0 | 0 | 0 |
| | 10 | 1 | 0 | 0 | 0 |
| | 96 | 1 | 0 | 1 | 0 |

Note: Baseline for each subject is the average of the three measurements taken on Study Day -1.
Pre-dose = -1 hr, Relative hr* = hrs from SPD503 dosing
**Source: Table 11 of sponsor's Clinical Study Report**

A total of seven subjects, five subjects following SPD503 therapy in Period 1 and three subjects following combination therapy in Period 2 (one subject is included for both periods), had at least one QTcF increase from Baseline >30msec. The maximum QTcF increase from baseline following SPD503 therapy was 41msec and the maximum QTcF increase from baseline following combination therapy was 47msec. All QTcFs were ≤ 444msec.

### 6.1.3 Study 107

A Phase I Study to Assess the Pharmacokinetics of SPD503 Administered to Children and Adolescents Aged 6-17 with Attention-Deficit/Hyperactivity Disorder (ADHD)

#### 6.1.3.1 Protocol Number

SPD503-107

#### 6.1.3.2 Objectives

The primary objective of the study was to determine the PK of SPD503 in plasma after a single dose of SPD503 2mg and multiple doses of 2 and 4mg.

The secondary objectives are to assess the contribution of demographic subgroups in the study population on the PK of guanfacine and to evaluate the relationship between guanfacine plasma concentrations and measurements of vital signs (e.g. blood pressure [BP] and heart rate) and ECGs.

#### 6.1.3.3 Description

This was a phase I, open-label, dose escalation study designed to assess the PK of SPD503 administered to children (ages 6-12) and adolescents (ages 13-17) with ADHD.

Eligible subjects were admitted to the clinic for three confinement periods over the course of the study. Subjects were confined at the start of the study to capture data on SPD503 2mg single dose and after reaching steady state at 2 and 4mg respectively. Blood samples were taken predose and at multiple time-points throughout the 24 hours postdose, with a high concentration of samples taken at the estimated time of peak plasma concentration (tmax is ~5 hours). Vital signs and ECGs were also taken at multiple time-points while subjects were confined, again performed within tmax of the study drug.

Subjects were titrated off SPD503 in 1mg decrements every 3 days beginning on Day 30. End of study assessments were conducted on Day 37, 2 days post discontinuation of study drug. Subjects were followed 30 days after discontinuation to document information about any ongoing adverse events (AEs) and collect information about any new related AEs or SAEs.

##### *6.1.3.3.1 Sponsor's Justification for Design*

An open-label, forced dose escalation study design allowed for the assessment of the PK and safety of SPD503 in doses up to 4mg/day. As SPD503 is being evaluated for the treatment of ADHD in pediatrics; a sample population of children and adolescents aged 6-17 years was appropriately selected. Although samples for PK assessments were taken at multiple time-points in the first 24 hours postdose, the majority of time-points were concentrated around the estimated peak plasma concentration time of 5 hours.

##### *6.1.3.3.2 Controls*

There were no controls in this study.

##### *6.1.3.3.3 Blinding*

This was an open label study.

### 6.1.3.4 Study Subjects

A number of PK studies have been conducted in healthy adult volunteers. This study was designed to evaluate the PK of SPD503 in the targeted patient population. Twenty-eight subjects aged 6 to 17 years inclusive who satisfied DSM-IV-TR□ criteria for a diagnosis of ADHD were eligible for participation. Since the study drug is being evaluated for use in children and adolescents with ADHD, an even distribution of subjects (14 aged 6-12, and 14 aged 13-17) were enrolled.

### 6.1.3.5 Sponsor's Results

A summary of ECG parameters is presented in Table 7. The sponsor states that although there were some changes in ECG parameters with some subjects moving from a normal predose result to an abnormal result at 5, 6, or 8 hours postdose; none of the changes were clinically significant.

**Table 7: Summary of Mean (SD) ECG Parameters**

| | 2mg Single Dose (N=28) | | | | | 2mg Multiple Dose (N=28) | | | | | 4mg Multiple Dose (N=28) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hour | | | | | Hour | | | | | Hour | | | | |
| Parameter | 0 | 5 | 6 | 8 | 24 | 0 | 5 | 6 | 8 | 24 | 0 | 5 | 6 | 8 | 24 |
| PR (msec) | 139.1 (19.69) | 140.0 (15.56) | 140.3 (15.02) | 138.0 (14.83) | 136.4 (17.01) | 145.9 (21.82) | 143.5 (18.48) | 142.0 (15.97) | 139.8 (16.59) | 137.5 (18.05) | 146.9 (21.06) | 143.3 (19.10) | 143.8 (15.99) | 139.4 (15.77) | 137.5 (18.08) |
| HR (bpm) | 73.7 (16.51) | 77.7 (10.99) | 75.9 (12.77) | 78.3 (15.72) | 71.3 (13.43) | 68.5 (12.97) | 72.7 (11.94) | 73.6 (10.50) | 68.8 (12.00) | 66.1 (10.84) | 65.4 (12.84) | 68.5 (8.27) | 66.2 (10.42) | 63.0 (11.33) | 64.5 (11.13) |
| QRS (msec) | 80.4 (6.01) | 84.3 (6.77) | 82.5 (7.04) | 83.1 (7.72) | 79.4 (6.91) | 82.2 (5.99) | 81.6 (6.78) | 82.0 (5.94) | 82.8 (7.58) | 81.1 (5.06) | 81.4 (6.37) | 82.5 (7.18) | 82.2 (7.71) | 82.9 (7.00) | 80.5 (5.69) |
| QT (msec) | 373.9 (36.72) | 373.1 (22.24) | 371.8 (32.70) | 367.8 (30.44) | 374.1 (28.29) | 394.2 (29.31) | 372.1 (30.92) | 373.3 (30.30) | 385.5 (30.21) | 379.1 (23.16) | 396.3 (31.28) | 391.3 (30.92) | 388.7 (33.53) | 396.5 (35.23) | 385.4 (28.53) |
| $QT_cB$ (msec) | 407.9 (24.52) | 422.3 (23.50) | 413.9 (18.92) | 415.1 (23.81) | 403.8 (26.40) | 417.0 (28.72) | 405.9 (23.03) | 410.1 (22.02) | 408.6 (21.33) | 394.4 (18.79) | 408.9 (24.16) | 416.1 (22.98) | 405.0 (24.03) | 402.1 (22.70) | 395.9 (22.82) |
| $QT_cF$ (msec) | 395.6 (18.71) | 405.1 (18.53) | 399.0 (19.45) | 398.3 (18.97) | 393.2 (21.06) | 408.7 (21.55) | 394.1 (21.24) | 397.2 (20.93) | 400.3 (18.39) | 388.9 (16.77) | 404.2 (18.80) | 407.4 (23.45) | 399.2 (23.57) | 399.8 (21.68) | 392.1 (19.46) |

Source: Section 12, Table 3.4.1

**Source: Table 18 of sponsor's Clinical Study Report**

A summary of quantitative changes in QTc intervals from predose is provided in Table 8. The incidence of subjects with a 30-60msec change from predose in QT or QTcB, or a 30-59msec change in QTcF was generally similar after the administration of single 2mg and multiple 2 and 4mg SPD503 doses. Subjects with a >60msec change from predose in QT or QTcB, or a ≥60msec change in QTcF was generally similar after the administration of single 2mg and multiple 2 and 4mg SPD503 doses. Subjects with a >60msec change from predose in QT or QTcB, or a ≥60msec change in QTcF after the administration of a single 2mg SPD503 did not have a similar change after the administration of multiple 2mg SPD503 doses. No subject had a >60msec change from predose in QT or QTcB, or a ≥60msec change in QTcF after the administration of multiple 4mg SPD503 doses. Additionally, no subject had a QTcF interval >480msec during the study.

**Table 8: Summary of Quantitative Changes in QT, QTcB and QTcF**

| | | | 2mg Single Dose (N=28) | | 2mg Multiple Dose (N=28) | | 4mg Multiple Dose (N=28) | |
|---|---|---|---|---|---|---|---|---|
| | Change from Hour 0 | Hour | n | % | n | % | n | % |
| QT (msec) | 30-60 | 5 | 1 | (3.6) | 0 | (0.0) | 2 | (7.1) |
| | | 6 | 3 | (10.7) | 0 | (0.0) | 2 | (7.1) |
| | | 8 | 1 | (3.6) | 0 | (0.0) | 2 | (7.1) |
| | | 24 | 3 | (10.7) | 0 | (0.0) | 0 | (0.0) |
| | >60 | 5 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | | 6 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | | 8 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | | 24 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| QTcB (msec) | 30-60 | 5 | 4 | (14.3) | 0 | (0.0) | 6 | (21.4) |
| | | 6 | 5 | (17.9) | 1 | (3.6) | 3 | (10.7) |
| | | 8 | 4 | (14.3) | 0 | (0.0) | 2 | (7.1) |
| | | 24 | 3 | (10.7) | 0 | (0.0) | 0 | (0.0) |
| | >60 | 5 | 2 | (7.1) | 0 | (0.0) | 0 | (0.0) |
| | | 6 | 0 | (0.0) | 1 | (3.6) | 0 | (0.0) |
| | | 8 | 1 | (3.6) | 0 | (0.0) | 0 | (0.0) |
| | | 24 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| QTcF (msec) | 30-59 | 5 | 3 | (10.7) | 0 | (0.0) | 2 | (7.1) |
| | | 6 | 2 | (7.1) | 1 | (3.6) | 3 | (10.7) |
| | | 8 | 1 | (3.6) | 0 | (0.0) | 2 | (7.1) |
| | | 24 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | ≥60 | 5 | 1 | (3.6) | 0 | (0.0) | 0 | (0.0) |
| | | 6 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | | 8 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | | 24 | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

**Source: Table 19 of sponsor's Clinical Study Report**

### 6.1.4 Study 203

A Phase II, Open-Label, Safety and Tolerability Dose Escalation Study of SPD503 Modified Release Tablets Administered To Children with Attention Deficit Hyperactivity Disorder (ADHD)

#### 6.1.4.1 Protocol Number

SPD503-203

#### 6.1.4.2 Objectives

The primary objective of the study was to assess, under controlled conditions, the safety and tolerability of SPD503 modified release (MR) formulation at doses of 1, 2, 3 and 4mg/day, administered to children with Attention Deficit Hyperactivity Disorder (ADHD).

The secondary objective of the study was to examine the pharmacokinetic profile of SPD503 after a 1mg single dose and multiple dosing of 1mg and 4mg/day.

#### 6.1.4.3 Description

This study was a Phase II, open-label, single center, forced dose titration of four doses of SPD503 in subjects who were diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR□) criteria [12].

The study consisted of three phases conducted over approximately 10 weeks. The screening period of up to one week allowed for the determination of appropriateness of each subject's inclusion in the study. The washout phase was approximately one week but could be up to 45 days depending on the half-life of the subject's current medication. During the washout phase subjects stopped all psychoactive medication. The open-label treatment phase consisted of 7 weeks in total: 4 weeks of open-label dose escalation and 3 weeks of downward titration. The children were followed for a final week of observation after study drug was discontinued.

##### *6.1.4.3.1 Sponsor's Justification for Design*

Not provided

##### *6.1.4.3.2 Controls*

Not applicable to this study.

##### *6.1.4.3.3 Blinding*

This was an open label study.

#### 6.1.4.4 Study Subjects

A total of 22 subjects aged 6-12 were enrolled into the screening and washout periods of this single center study. One subject (#018) withdrew consent before initiation of treatment and one subject (#008) was enrolled as a possible alternate participant but was later withdrawn prior to treatment, as participation was not required. Study treatment was given to a total of 20 subjects. All 20 subjects completed the study.

#### 6.1.4.5 Sponsor's Results

**Overall Mean and Mean Percent Changes in Dose Escalation Phase:** During the dose escalation phase (i.e., Weeks 1 through 4) analysis of variance showed statistical significance ($p<0.05$) for all ECG parameters overall (i.e., regardless of time point) for mean change and mean % change from overall baseline levels. These results must be interpreted with caution, as no adjustment was made for the effect of multiple comparisons. Overall mean change and overall mean percent change from baseline value, by treatment week, are provided in Table 9.

**Table 9: Overall ECG Mean Change and Mean Percent Change, Dose Escalation**

| | Overall Mean Change from Baseline | | | | | Overall Mean % Change from Baseline | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 (1mg) | Week 2 (2mg) | Week 3 (3mg) | Week 4 (4mg) | p-value[1] | Week 1 (1mg) | Week 2 (2mg) | Week 3 (3mg) | Week 4 (4mg) | p-value[1] |
| PR Interval | 0.05 | 2.20 | 3.01 | -1.63 | 0.0024 | 0.19 | 1.73 | 2.31 | -1.19 | 0.0026 |
| QRS Interval | 0.31 | 0.79 | 2.12 | 0.43 | 0.0025 | 0.42 | 1.02 | 2.62 | 0.63 | 0.0023 |
| QT Interval | -1.09 | 6.93 | 21.10 | 35.05 | <0.0001 | -0.30 | 2.00 | 5.94 | 9.85 | <0.0001 |
| QTc Bazett | -2.26 | -5.39 | -6.89 | -7.24 | 0.0378 | -0.54 | -1.29 | -1.64 | -1.74 | 0.0430 |
| QTc Fredericia | -1.90 | -1.07 | 2.89 | 7.37 | <0.0001 | -0.49 | -0.25 | 0.78 | 1.91 | <0.0001 |
| RR | 4.51 | 52.68 | 126.78 | 197.31 | <0.0001 | 0.81 | 7.1 | 16.58 | 25.70 | <0.0001 |

[1] ANOVA

Source: Table 27 of sponsor's Clinical Study Report

**Overall Mean and Mean Percent Changes in Dose Escalation Phase:** During the downward titration phase (i.e., Weeks 4 through 8) analysis of variance showed statistical significance ($p<0.05$) for all ECG parameters overall (i.e., regardless of time point) for mean change and mean % change from overall baseline levels. These results must be interpreted with caution, as no adjustment was made for the effect of multiple comparisons. Overall mean change and overall mean percent change from baseline value, by treatment week, are provided in Table 10.

**Table 10: Overall ECG Mean and Mean Percent Change, Downward Titration**

| | Overall Mean Change from Baseline | | | | | | Overall Mean % Change from Baseline | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 4 (4mg) | Week 5 (3mg) | Week 6 (2mg) | Week 7 (1mg) | Week 8 (0mg) | p-value[1] | Week 4 (4mg) | Week 5 (3mg) | Week 6 (2mg) | Week 7 (1mg) | Week 8 (0mg) | p-value[1] |
| PR Interval | -1.63 | -0.64 | 1.16 | -0.92 | -4.44 | 0.0026 | -1.19 | -0.37 | 0.93 | -0.45 | -3.11 | 0.0034 |
| QRS Interval | 0.43 | -0.51 | -1.10 | -1.51 | -1.61 | 0.0190 | 0.63 | -0.54 | -1.21 | -1.71 | -1.82 | 0.0169 |
| QT Interval | 35.05 | 25.10 | 4.84 | -9.53 | -16.29 | <0.0001 | 9.85 | 7.10 | 1.42 | -2.67 | -4.43 | <0.0001 |
| QTc Bazett | -7.24 | -2.36 | 5.08 | 9.04 | 5.42 | <0.0001 | -1.74 | -0.55 | 1.25 | 2.20 | 1.34 | <0.0001 |
| QTc Fredericia | 7.37 | 7.25 | 4.75 | 2.04 | -2.66 | 0.0001 | 1.91 | 1.88 | 1.22 | 0.50 | -0.65 | <0.0001 |
| RR | 197.31 | 124.68 | 6.60 | -72.50 | -87.27 | <0.0001 | 25.70 | 16.58 | 1.16 | -9.26 | -10.95 | <0.0001 |

[1] ANOVA

Source: Section 14 Tables 3.1.2C 3.1.3C 3.2.2C 3.2.3C 3.3.2C 3.3.3C 3.4.2C 3.4.3C 3.5.2C 3.5.3C 3.6.2C 3.6.3C

Source: Table 28 of sponsor's Clinical Study Report

### 6.1.5 Study 206

A Phase II Study to Assess the Safety, Tolerability and Efficacy of SPD503 Administered to Children and Adolescents Aged 6-17 with Attention-Deficit/Hyperactivity Disorder (ADHD)

#### 6.1.5.1 Protocol Number

SPD503-206

#### 6.1.5.2 Objectives

**Primary**

To assess the effect of SPD503 compared to placebo on tasks of sustained attention in children and adolescents aged 6-17 diagnosed with Attention Deficit Hyperactivity Disorder (ADHD), with particular reference to the 5-pt Choice Reaction Time (CRT) test in the Cambridge Neuropsychological Test Automated Battery (CANTAB).

**Secondary**

- To compare cognitive functioning effects of SPD503 and placebo in children and adolescents diagnosed with ADHD, with particular reference to the Digit Symbol Substitution Task/Coding Test (DSST/Coding) as well as the Spatial Working Memory (SWM) in the CANTAB assessment battery.
- To assess the effects of SPD503 and placebo in children and adolescents with ADHD using the Permanent Product Measure of Performance (PERMP), ability-adjusted math test administered at 1, 2, 3, 5, 6, and 8 hours post-dose in a controlled environment.
- To compare the sedative effects (measured by Pictorial Sleepiness Scale [PSS] self-report and observer rated) of SPD503 and placebo in children and adolescents diagnosed with ADHD at multiple time points throughout the day.
- To assess the efficacy of an optimal SPD503 dose compared to placebo in the treatment of children and adolescents with ADHD based on the reduction in symptom score on the ADHD-Rating Scale-IV (ADHD-RS-IV).
- To assess the effect of SPD503 compared to placebo on clinician-rated global impressions of ADHD severity and improvement (CGI-S and CGI-I).
- To assess the relationship between the plasma level of SPD503 (at 1, 2, 3, 5, 6, and 8 hours post-dose) and cognitive function, as measured by the PERMP, across the day.
- To evaluate the safety and tolerability of SPD503, including specific evaluation of daytime sleepiness using the Pediatric Daytime Sleepiness Scale (PDSS) and PSS.

#### 6.1.5.3 Description

This was a phase II, randomized, double-blind, multi-center, placebo-controlled, dose-optimization study, designed to assess the safety and tolerability of SPD503 (1mg, 2mg, and 3mg) in children and adolescents aged 6-17 diagnosed with ADHD. Subjects visited the study site approximately 11 times during the course of the 15-week study **(Screening/Washout – 4wks, Visit -1/Baseline – 0.5wks, Treatment – 6.5wks, Follow-up –4wks). During the treatment period, subjects** visited the sites on a weekly basis.

##### *6.1.5.3.1 Sponsor's Justification for Design*

The purpose of this study was to assess the effect of SPD503 compared to placebo on tasks of sustained attention in children and adolescents aged 6-17 diagnosed with ADHD. The protocol relied on repeated measures of objective and behavioral assessments that are recognized to be valid assessments of attention and psychomotor functioning. In addition to evaluating standard safety parameters, this study also evaluated sedative effects of SPD503 using the PDSS and PSS to further characterize similar sedative-like events observed in the SPD503 development program.

The use of a placebo arm as the control group in this study allowed the clinical efficacy and any sedative effects of SPD503 to be clearly defined.

#### *6.1.5.3.2 Controls*

Placebo control is used in this study.

#### *6.1.5.3.3 Blinding*

This is a double-blind study.

### 6.1.5.4 Study Subjects

Approximately 187 healthy pediatric subjects (aged 6-17 years) with ADHD were to be enrolled. All potential subjects must have been properly consented, met all inclusion/exclusion criteria, and undergone all Screening procedures to be eligible for participation in this study. No replacement subjects were to be used.

### 6.1.5.5 Sponsor's Results

Table 11 displays the mean changes in ECG parameters from Baseline to Visit 5 by randomized treatment group and optimal dose. The analyses of mean changes in ECG parameters were conducted using the Investigator selected ECG value for each timepoint if repeat ECGs were collected.

**Table 11: Changes in ECG Parameters from Baseline to Visit 5 by Randomized Treatment Group and Optimal Dose (Full Analysis Set/Safety Population)**

| ECG parameter<br>Statistic | Placebo<br>(N=57) | SPD503<br>total<br>(N=121) | SPD503<br>1mg<br>(N=14) | SPD503<br>2mg<br>(N=37) | SPD503<br>3mg<br>(N=70) |
|---|---|---|---|---|---|
| HR (bpm) | | | | | |
| n | 53 | 116 | 11 | 37 | 68 |
| Mean change (SD) | 0.0 (9.03) | -11.2 (9.66) | -3.5 (7.04) | -11.0 (7.71) | -12.5 (10.46) |
| PR (msec) | | | | | |
| n | 53 | 116 | 11 | 37 | 68 |
| Mean change (SD) | 2.6 (8.59) | 3.7 (9.89) | 2.8 (11.10) | 5.2 (10.39) | 3.0 (9.47) |
| QRS (msec) | | | | | |
| n | 53 | 116 | 11 | 37 | 68 |
| Mean change (SD) | 0.4 (4.32) | 0.1 (5.01) | 0.2 (4.95) | -0.5 (5.34) | 0.4 (4.87) |
| QT (msec) | | | | | |
| n | 53 | 116 | 11 | 37 | 68 |
| Mean change (SD) | 5.7 (16.12) | 31.5 (23.31) | 15.1 (18.82) | 31.6 (18.11) | 34.0 (25.55) |
| QTcP (msec) | | | | | |
| n | 53 | 116 | 11 | 37 | 68 |
| Mean change (SD) | 6.1 (10.44) | 11.6 (13.56) | 10.2 (13.19) | 13.5 (14.02) | 10.8 (13.46) |
| QTcB (msec) | | | | | |
| n | 53 | 116 | 11 | 37 | 68 |
| Mean change (SD) | 6.4 (15.38) | 0.7 (16.41) | 7.2 (13.94) | 3.3 (16.69) | -1.8 (16.33) |
| QTcF (msec) | | | | | |
| n | 53 | 116 | 11 | 37 | 68 |
| Mean change (SD) | 6.1 (10.49) | 11.4 (13.49) | 10.1 (13.47) | 13.2 (13.99) | 10.6 (13.32) |

Note: Baseline is the average ECG evaluation at the Baseline visit.
Note: QTcP is a population corrected QT which is calculated as $QTcP=QT/[(60/HR)^{0.33}]$.
Source: Table 28 of sponsor's Clinical Study Report

### 6.1.6 Study 301

A Phase III, Randomized, Multi-Center, Double-Blind, Parallel-Group, Placebo-Controlled Safety and Efficacy Study of SPD503 in Children and Adolescents Aged 6-17 with Attention Deficit Hyperactivity Disorder (ADHD)

#### 6.1.6.1 Protocol Number

SPD503-301

#### 6.1.6.2 Objectives

**Primary**

Assess, under controlled conditions, the safety and efficacy of SPD503 compared with placebo in the treatment of children and adolescents (aged 6-17 years) with attention deficit hyperactivity disorder (ADHD). The primary efficacy measurement was the ADHD rating scale IV (ADHD-RS-IV).

**Secondary**

- Assess the duration of action of SPD503 using parent and teacher rating scales. Parents assessed the subjects **using the Conners' Parent** Rating Scale-Revised: Short Form (CPRS-R) administered at approximately 12, 14, and 24 hours after **dosing and teachers used the Conners' Teacher Rating Scale-Revised: Short Form** (CTRS-R) at approximately 4 and 8 hours after dosing.
- Compare the safety and tolerability of the four randomized dose groups (SPD503 2, 3, and 4mg/day and placebo);
- Assess global impressions of ADHD severity and improvement from the clinician and parent or caregiver;
- Assess SPD503's effect on self-esteem, mental health, and family functioning based on the parent and child versions of the Child Health Questionnaire (CHQ).

#### 6.1.6.3 Description

This was a randomized, multi-center, double-blind, parallel-group, placebo-controlled, forced dose escalation study to assess the safety and efficacy of three doses of SPD503 (2, 3, and 4mg/day) compared with placebo in children and adolescents (aged 6-17) who have ADHD. The study was conducted in 48 centers in the United States.

##### *6.1.6.3.1 Sponsor's Justification for Design*

The study was designed to assess the efficacy and safety of SPD503 compared with placebo. The fixed dose escalation design was chosen to ensure that adequate numbers of subjects were included in each dosing group for safety and efficacy assessments. Placebo was chosen as the comparator group because there is a substantial placebo effect in controlled ADHD studies. Comparing the placebo group to active treatment allows for a better estimate of the true effect of drug in the study population.

##### *6.1.6.3.2 Controls*

Placebo controls were used in this study.

##### *6.1.6.3.3 Blinding*

This was a double-blind study.

#### 6.1.6.4 Study Subjects

A total of 345 subjects were enrolled and randomized; 86 subjects in the placebo group, 87 subjects in the SPD503 2mg group, 86 subjects in the 3mg group, and 86 subjects in the 4mg group.

#### 6.1.6.5 Sponsor's Results

No ECG abnormality was reported as an SAE. Seven (7) subjects discontinued from the study due to ECG abnormalities (6 reported as AEs and 1 reported as protocol violation): 2 in the placebo group, 1 in the randomized 2mg SPD503 group, 2 in the randomized 3mg group, and 2 in the randomized 4mg group (Section 8.3.4.1). No subject had a QRS interval ≥120msec, a QT interval ≥480msec, a QTcB or QTcF interval ≥500msec, or a

QTcF increase from Baseline ≥60msec at any ECG assessment. While on study drug, 13 subjects (1 on placebo and 12 on SPD503) had abnormal ECGs of clinical significance per Investigator; the Sponsor considered 5 of these ECGs to be of clinical interest.

Table 12 presents ECG results by actual dose at Week 3. Mean changes in PR and QRS intervals from Baseline were unremarkable. Uncorrected QT intervals were prolonged at all doses (placebo and all actual SPD503 doses) at Week 3 due to the slowing of heart rate observed; however, mean prolongations of QTcF and QTcB were numerically smaller (QTcF) or negligible (QTcB).

**Table 12: Summary of ECG Results by Actual Dose at Week 3 (Safety Population)**

| **Parameter** Statistic | Placebo (N= 70) | SPD503 2mg (N= 75) | SPD503 3mg (N= 142) |
|---|---|---|---|
| **Heart rate (bpm)** | | | |
| Mean actual (SD) | 77.5 (11.02) | 69.5 (10.82) | 63.8 (10.59) |
| Mean change (SD) | -0.3 (10.77) | -8.0 (10.26) | -13.6 (11.09) |
| **PR Interval (msec)** | | | |
| Mean actual (SD) | 141.6 (14.62) | 141.4 (16.35) | 140.3 (20.19) |
| Mean change (SD) | 1.3 (9.95) | 0.9 (10.98) | 1.1 (13.39) |
| **QRS interval (msec)** | | | |
| Mean actual (SD) | 81.1 (7.94) | 80.0 (9.39) | 82.4 (8.93) |
| Mean change (SD) | 0.1 (7.68) | 0.1 (7.98) | 1.7 (7.35) |
| **QT Interval (msec)** | | | |
| Mean actual (SD) | 365.4 (25.03) | 380.3 (29.60) | 393.4 (29.01) |
| Mean change (SD) | 3.9 (22.61) | 19.5 (20.58) | 33.5 (26.71) |
| **QTcF Interval (msec)** | | | |
| Mean actual (SD) | 396.0 (15.84) | 397.1 (20.94) | 398.9 (17.22) |
| Mean change(SD) | 3.7 (14.79) | 6.1 (12.96) | 9.1 (16.20) |
| **QTcB Interval (msec)** | | | |
| Mean actual (SD) | 412.4 (17.77) | 406.3 (23.03) | 402.2 (18.98) |
| Mean change (SD) | 3.5 (17.69) | -1.2 (17.26) | -3.9 (18.42) |

Source: Section 12.1 Table 3.5.1
Note: "Mean change" represents the mean change from Baseline.

**Source: Table 52 of sponsor's Clinical Study Report**

Table 13 shows a post-hoc analysis of QTcB and QTcF data by actual dose regardless of study week. SPD503 did not increase QTcB interval compared with placebo treatment.

QTcF changes from Baseline were 1.3, -3.3, 6.7, 9.1, and 8.2msec for subjects while taking 0 (placebo), 1, 2, 3, and 4mg SPD503, respectively. However, the small number of ECGs taken while subjects were on the 1mg and 4mg SPD503 doses limits any conclusions about the ECG findings seen with these two doses.

**Table 13: QTcB and QTcF Data by Actual Dose at the Time of the ECG Assessment (Safety Population)**

| Parameter<br>Statistic | Placebo | SPD503<br>1mg | SPD503<br>2mg | SPD503<br>3mg | SPD503<br>4mg |
|---|---|---|---|---|---|
| **Number of Subjects[a]** | 86 | 259 | 245 | 148 | 63 |
| **Number of Subjects with ECG[b]** | 76 | 16 | 189 | 144 | 6 |
| **QTcB Interval (msec)** | | | | | |
| Mean (SD) | 409.1 (17.97) | 407.2 (16.08) | 407.9 (20.33) | 402.1 (18.60) | 400.7 (19.06) |
| **QTcB Change from Baseline[c,d]** | | | | | |
| Mean (SD) | 0.0 (18.08) | -5.3 (18.70) | 1.1 (16.62) | -3.9 (17.96) | -10.2 (21.14) |
| **QTcF Interval (msec)** | | | | | |
| Mean (SD) | 393.5 (16.71) | 393.0 (12.41) | 397.1 (18.27) | 398.7 (17.08) | 401.5 (15.57) |
| **QTcF Change from Baseline[c,d]** | | | | | |
| Mean (SD) | 1.3 (15.28) | -3.3 (13.63) | 6.7 (13.57) | 9.1 (16.12) | 8.2 (17.45) |

a: Number of subjects who took the specified actual dose at any time during the study.
b: Number of subjects who had an ECG taken while receiving the specified actual dose.
c: For each subject, the Baseline ECG is the mean of multiple ECGs taken at Baseline.
d: Change from Baseline is derived from comparing the ECG taken while on study drug with the Baseline ECG of the same subject.
**Source: Table 53 of sponsor's Clinical Study Report**

### 6.1.7 Study 304

A Phase III, Randomized, Double-Blinded, Multi-Center, Parallel-Group, Placebo-Controlled Safety and Efficacy Study of SPD503 in Children and Adolescents Aged 6-17 with Attention-Deficit Hyperactivity Disorder (ADHD)

#### 6.1.7.1 Protocol Number

SPD503-304

#### 6.1.7.2 Objectives

**Primary** o

Assess, under controlled conditions, the efficacy of SPD503 (1mg, 2mg, 3mg, and 4mg/day) compared with placebo in the treatment of children and adolescents aged 6-17 years with ADHD.

**Secondary**

- Assess the duration of effect of SPD503 as determined via parent rating scales.
- Compare the safety and tolerability of placebo and the four treatment groups of 1mg, 2mg, 3mg, and 4mg/day SPD503 doses.
- Assess the effect of SPD503 on global impressions of ADHD severity and improvement from the clinician and parent or caregiver.
- Assess the effect of SPD503 on self-esteem, mental health, and family functioning based on the Child Health Questionnaire – Parent Form (CHQ-PF50).

#### 6.1.7.3 Description

This was a randomized, double-blind, parallel-group, multi-center, placebo-controlled, dose ranging study that assessed the safety and efficacy of four doses of SPD503 (1mg, 2mg, 3mg, and 4mg/day) compared with placebo in children and adolescents aged 6-17 years who were diagnosed with ADHD. The study design was a titration to a fixed randomized dose followed by dose tapering. The study was conducted at 51 centers in the United States. Three hundred and twenty-four subjects were randomized in this study. Once 300 subjects were randomized, enrollment remained open in order to recruit 25% females and 25% adolescents.

##### *6.1.7.3.1 Sponsor's Justification for Design*

This study was designed to assess the efficacy and safety of SPD503 compared with placebo. The fixed dose design was chosen to ensure that adequate numbers of subjects were included in each dosing group for efficacy and safety assessments. A placebo control was chosen as the comparator group because of the substantial placebo effect in controlled ADHD studies. A comparison of the placebo group with the active SPD503 treatment groups helped to better estimate the true effect of drug in the study population.

##### *6.1.7.3.2 Controls*

Placebo controls were used in this study.

##### *6.1.7.3.3 Blinding*

This is a double-blind study.

#### 6.1.7.4 Study Subjects

Approximately 300 subjects age 6 to 17 years inclusive, who satisfied DSM-IV-TR criteria diagnosis of ADHD, were eligible for participation. All subjects who participated were consented and assented, met all inclusion and no exclusion criteria, and underwent all procedures at Screening.

#### 6.1.7.5 Sponsor's Results

Table 14 presents a summary of ECG results by actual dose and by week in the Safety Population. No subject discontinued from the study due to an ECG abnormality, and no abnormality was reported as an SAE. Only two subjects had ECG findings that were considered by the investigator as abnormal and clinically significant. One subject had a first degree atrioventricular block, and another subject presented with symptomatic sinus bradycardia.

**Table 14: Summary of ECG Results by Actual Dose at the Time of Assessment (Safety Population)**

| | | Placebo | SPD503 1mg | SPD503 2mg | SPD503 3mg | SPD503 4mg |
|---|---|---|---|---|---|---|
| **Heart rate (bpm)** | | | | | | |
| Week 6 | n | 44 | 48 | 48 | 38 | 42 |
| | Mean actual (SD) | 75.0 (11.37) | 75.5 (8.39) | 68.1 (11.02) | 68.4 (10.44) | 64.7 (11.69) |
| | Mean change (SD) | -2.8 (9.61) | -3.7 (8.95) | -5.7 (11.89) | -5.8 (9.98) | -13.3 (12.26) |
| Week 9 / End-of-Study | n | 48 | 168 | 7 | 7 | 1 |
| | Mean actual (SD) | 74.6 (9.50) | 74.8 (11.71) | 77.3 (9.27) | 80.3 (12.27) | 55.0 (--) |
| | Mean change (SD) | -3.3 (8.59) | -1.6 (10.85) | -2.5 (13.67) | 1.1 (15.41) | -27.7 (--) |
| **PR Interval (msec)** | | | | | | |
| Week 6 | n | 44 | 48 | 48 | 38 | 42 |
| | Mean actual (SD) | 137.5 (19.85) | 140.9 (25.85) | 142.6 (19.39) | 139.4 (17.91) | 143.4 (17.14) |
| | Mean change (SD) | -2.2 (10.78) | 3.2 (18.48) | 2.6 (9.79) | -2.8 (10.48) | -3.4 (11.98) |
| Week 9 / End-of-Study | n | 48 | 168 | 7 | 7 | 1 |
| | Mean actual (SD) | 137.9 (17.55) | 139.5 (16.92) | 138.6 (12.25) | 136.7 (9.29) | 153.0 (--) |
| | Mean change (SD) | -1.8 (9.60) | -2.0 (11.46) | 2.0 (6.88) | 5.1 (8.68) | 23 (--) |
| **QRS Interval (msec)** | | | | | | |
| Week 6 | n | 44 | 48 | 48 | 38 | 42 |
| | Mean actual (SD) | 79.4 (9.63) | 78.6 (7.71) | 81.0 (8.39) | 82.0 (10.23) | 80.0 (9.18) |
| | Mean change (SD) | -1.0 (6.79) | 0.7 (7.19) | -0.3 (5.43) | 0.8 (7.12) | 0.1 (6.81) |
| Week 9 / End-of-Study | n | 48 | 168 | 7 | 7 | 1 |
| | Mean actual (SD) | 80.3 (8.85) | 80.6 (8.55) | 81.1 (4.34) | 76.3 (10.00) | 76.0 (--) |
| | Mean change (SD) | 0.6 (5.05) | 0.3 (6.74) | -0.1 (7.06) | 0.7 (4.75) | 4.3 (--) |

| | | Placebo | SPD503 1mg | SPD503 2mg | SPD503 3mg | SPD503 4mg |
|---|---|---|---|---|---|---|
| **QT Interval (msec)** | | | | | | |
| Week 6 | n | 44 | 48 | 48 | 38 | 42 |
| | Mean actual (SD) | 358.2 (24.49) | 360.1 (21.72) | 378.0 (24.87) | 379.3 (25.02) | 389.9 (29.21) |
| | Mean change (SD) | 4.4 (23.66) | 9.3 (18.59) | 12.9 (24.46) | 17.0 (25.67) | 31.6 (28.37) |
| Week 9 / End-of-Study | n | 48 | 168 | 7 | 7 | 1 |
| | Mean actual (SD) | 362.6 (21.00) | 362.3 (26.70) | 353.0 (21.52) | 359.0 (33.05) | 419.0 (--) |
| | Mean change (SD) | 9.1 (16.99) | 3.4 (22.95) | -3.0 (22.15) | 9.5 (30.95) | 65.7 (--) |
| **QTcF Interval (msec)** | | | | | | |
| Week 6 | n | 44 | 48 | 48 | 38 | 42 |
| | Mean actual (SD) | 383.7 (17.80) | 387.7 (16.16) | 392.2 (15.67) | 394.4 (12.79) | 397.1 (14.95) |
| | Mean change (SD) | -0.3 (16.31) | 4.3 (12.74) | 2.4 (12.32) | 7.1 (12.75) | 9.7 (15.92) |
| Week 9 / End-of-Study | n | 48 | 168 | 7 | 7 | 1 |
| | Mean actual (SD) | 388.5 (14.28) | 387.7 (17.28) | 383.1 (14.50) | 393.1 (18.59) | 407.0 (--) |
| | Mean change (SD) | 4.6 (14.49) | 1.0 (14.32) | -3.4 (15.23) | 11.6 (16.01) | 13.7 (--) |
| **QTcB Interval (msec)** | | | | | | |
| Week 6 | n | 44 | 48 | 48 | 38 | 42 |
| | Mean actual (SD) | 397.6 (21.31) | 402.4 (16.78) | 399.9 (19.38) | 402.5 (15.03) | 401.2 (17.76) |
| | Mean change (SD) | -2.7 (17.42) | 1.3 (15.29) | -3.1 (15.50) | 1.8 (13.28) | -2.2 (16.74) |
| Week 9 / End-of-Study | n | 48 | 168 | 7 | 7 | 1 |
| | Mean actual (SD) | 402.3 (16.39) | 401.4 (19.15) | 399.1 (16.40) | 411.4 (11.31) | 401.0 (--) |
| | Mean change (SD) | 2.1 (17.52) | -0.4 (16.77) | -4.4 (18.55) | 12.3 (16.77) | -13.7 (--) |

Source: Section 12.1, Table 3.6.1.

Note: "Mean change" represents the mean change from Baseline.

Note: (--) represents no SD due to n=1.

**Source: Table 49 of sponsor's Clinical Study Report**

Table 15 shows a post-hoc analysis of QTcB and QTcF data by actual dose regardless of study week. SPD503 did not increase the mean QTcB interval compared with placebo treatment. Mean QTcF changes from Baseline were 2.96, 1.79, 2.62, 7.35, and

10.28msec for subjects who received placebo, 1mg, 2mg, 3mg, and 4mg SPD503, respectively.

**Table 15: QTcB and QTcF Data by Actual Dose at the Time of the ECG Assessment (Safety Population)**

| Parameter Statistic | Placebo | SPD503 1mg | SPD503 2mg | SPD503 3mg | SPD503 4mg |
|---|---|---|---|---|---|
| **Number of subjects[1]** | 66 | 256 | 180 | 113 | 59 |
| **Subjects with a ECG assessment[1]** | 59 | 191 | 105 | 102 | 45 |
| | | | | | |
| **QTcB Interval (msec) (From subjects with an ECG assessment while on study drug)** | | | | | |
| Mean (SD) | 401.2 (15.38) | 401.6 (16.91) | 398.4 (17.46) | 401.5 (16.21) | 401.9 (17.15) |
| **QTcB Change from Baseline[2,3]** | | | | | |
| Mean (SD) | 1.69 (13.42) | 0.31 (15.01) | -3.15 (15.36) | -0.49 (14.89) | -1.84 (17.08) |
| | | | | | |
| **QTcF Interval (msec) (From subjects with an ECG assessment while on study drug)** | | | | | |
| Mean (SD) | 386.28 (14.00) | 387.73 (15.73) | 390.16 (15.10) | 394.14 (13.98) | 397.47 (15.00) |
| **QTcF Change from Baseline[2,3]** | | | | | |
| Mean (SD) | 2.96 (12.53) | 1.79 (12.89) | 2.62 (12.66) | 7.35 (13.23) | 10.28 (15.62) |

Source: Section 12.1 Table 3.6.7.1.

1 Subjects receiving active drug are counted in more than one column.
2 Baseline for each subject is the average ECG evaluation at Visit 0.
3 Change from Baseline statistics are calculated based on subject level change from Baseline values.

Source: Table 50 of sponsor's Clinical Study Report

## 6.2 CLINICAL PHARMACOLOGY REVIEW

Please refer to Dr. Atul Bhattaram's exposure-response analysis for QT in the Clinical Pharmacology Pharmacometrics Review (DFS date: 05-June 2007).

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

/s/

Christine Garnett
6/12/2007 08:27:30 AM
PHARMACOLOGIST
Atul Bhattaram was the clinical pharmacology reviewer.

Joanne Zhang
6/12/2007 10:51:40 AM
BIOMETRICS

Jingyu Luan
6/12/2007 11:15:17 AM
BIOMETRICS

Stephen Grant
6/12/2007 12:03:35 PM
MEDICAL OFFICER

Norman Stockbridge
6/13/2007 01:59:54 PM
MEDICAL OFFICER

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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## CLINICAL INSPECTION SUMMARY

DATE: May 17, 2007

TO: Felecia Curtis, Regulatory Project Manager
Robert Levin, M.D., Medical Officer
Thomas Laughren, M.D., Director
Division of Psychiatry Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H., Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Sheryl Gunther, Pharm.D.
Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-037

SPONSOR: Shire Pharmaceutical Development, Inc.

DRUG: SPD503 (guanfacine hydrochloride)

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Attention-Deficit Hyperactivity Disorder

CONSULTATION REQUEST DATE: December 4, 2006

DIVISION ACTION GOAL DATE: May 24, 2007

PDUFA GOAL DATE: June 24, 2007

## I. BACKGROUND

Clinical investigator inspections were conducted at three clinical sites that performed studies for which the sponsor submitted data in NDA 22-037. The clinical investigator inspections were conducted according to the Compliance Program 7348.811, the Inspection Program for Clinical

Investigators. The inspections covered work performed under protocols SPD503-301 and SPD503-304.

In this NDA, the sponsor has included results of protocols SPD503-301 and SPD503-304. Protocol SPD503-301 was a randomized, multi-center, double-blind, parallel-group, placebo-controlled, forced dose escalation study to assess the safety and efficacy of three doses of SPD503 (2, 3, and 4 mg/day) compared with placebo in children and adolescents (aged 6-17) who have ADHD. The primary measure of efficacy was the clinician-administered ADHD-rating scale (ADHD-RS-IV).

SPD503-304 was a randomized, double-blind, parallel-group, multi-center, placebo-controlled, dose ranging study that assessed the safety and efficacy of four doses of SPD503 (1mg, 2mg, 3mg, and 4 mg/day) compared with placebo in children and adolescents aged 6-17 years who were diagnosed with ADHD. The study design was a titration to a fixed randomized dose followed by dose tapering. The primary objective of this study was to assess, under controlled conditions, the efficacy of SPD503 (1mg, 2mg, 3mg, and 4 mg/day) compared with placebo in the treatment of children and adolescents aged 6-17 years with ADHD.

**Basis for Sites Selection**: Three clinical sites (Drs. Arnold, Harper, and Pai) were inspected. These sites were inspected due to enrollment of large numbers of study subjects. The goals of inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events.

## II. RESULTS (by site):

| Clinical Investigator/Site | Protocol(s) | Inspection Date | EIR Received Date | Final Classification |
|---|---|---|---|---|
| **Valerie K. Arnold, M.D.**<br>Clinical Neuroscience Solutions, Inc.<br>6401 Poplar Avenue<br>Suite 420<br>Memphis, TN 38119 | SPD503-301<br>SPD503-304 | 2/19/2007-<br>3/11/2007 | 5/8/2007 | NAI |
| **Linda Harper, M.D.**<br>Clinical Neuroscience Solutions, Inc.<br>77 West Underwood Street, 3rd Floor<br>Orlando, FL 32806 | SPD503-304 | 2/13/2007-<br>2/21/2007 | 3/27/2007 | NAI |
| **Kamalesh K. Pai, M.D.**<br>Clinical Neuroscience Solutions, Inc.<br>6867 Southpoint Drive North<br>Jacksonville, FL 32216 | SPD503-301 | 1/30/2007-<br>2/8/2007 | 4/4/2007 | VAI |

Key to Classifications
NAI - No deviation from regulations. Data acceptable.
VAI - No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI - Response Requested = Deviation(s) from regulations.
OAI - Significant deviations from regulations. Data unreliable.

(1) **Linda Harper, M.D.**
**Clinical Neuroscience Solutions, Inc.**

a. What was inspected?

There were 15 subjects who participated in protocol SPD503-304. The FDA investigator reviewed the records for all subjects enrolled in this protocol. The FDA investigator reviewed the source documents and case report forms (CRFs), and compared them with data listings provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary:

Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms. There were minor deficiencies related to protocol compliance and Institutional Review Board submissions. However, there were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted.

Recommendation: Data from this clinical site appear acceptable for use in support of this NDA.

(2) **Kamalesh K. Pai, M.D.**
**Clinical Neuroscience Solutions, Inc.**

a. What was inspected?

For protocol SPD503-301, there were 20 subjects screened, 17 subjects enrolled, and 12 subjects who completed the study. The FDA investigator reviewed the records for all 17 subjects enrolled in this protocol. The FDA investigator reviewed the source documents and CRFs, and compared them with data listings provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary:

Except for a deficiency related to obtaining study advertisement IRB approval, there were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

Recommendation: Data from this clinical site appear acceptable for use in support of this NDA.

(3) **Valerie K. Arnold, M.D.**
**Clinical Neuroscience Solutions, Inc.**

a. What was inspected?

The FDA investigator reviewed the records for all 28 subjects enrolled in protocols SPD503-301/304. The FDA investigator reviewed the source documents and CRFs, and compared them with data listings provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary:

Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms. There were minor deficiencies related to protocol compliance. No underreporting of adverse events was noted. There were no significant inspectional findings that would adversely impact data acceptability.

Recommendation: Data from this clinical site appear acceptable for use in support of this NDA.

## III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, for the three clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events was noted. Overall, data generated for protocols SPD503-301 and SPD503-304 at these clinical sites appear acceptable for use in support of NDA 22-037.

*{See appended electronic signature page}*

Sheryl Gunther, Pharm.D.
Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

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Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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

/s/
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Sheryl Gunther
5/17/2007 04:19:16 PM
BIOPHARMACEUTICS

Jose Tavarezpagan
5/17/2007 04:47:14 PM
CSO

Constance Lewin
5/17/2007 04:54:57 PM
MEDICAL OFFICER