CLINICAL PHARMACOLOGY REVIEW

NDA:	**22-037 N000**
Submission Dates:	8/24, 10/4, 2006, and 2/09, 3/06, 3/12, 3/16, 4/20, 5/25 2007
Brand Name:	(b) (4)
Generic Name:	**Guanfacine Hydrochloride**
Dosage Form & Strength:	Extended release Tablets 1 mg; 2 mg; (b) (4) 3 mg, (b) (4) and 4 mg
Indication:	ADHD
Applicant:	Shire Pharmaceuticals
Submission:	Original NDA
Divisions:	DPEI and Psychiatric Drug Products, HFD-130
Primary Reviewer:	Elena V. Mishina, Ph.D.
Team Leaders:	Patrick Marroum, Ph.D.
Pharmacometrics Consult:	Atul Bhattaram, Ph.D.
Pharmacometrics Team Leader:	Joga Gobburu, Ph.D.

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS:

The following recommendations and comments below should be properly addressed by the sponsor.

(b) (4)

2. (b) (4)

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3. Please see the detailed Labeling Recommendations as described and adopted in Section 3, p. 37.

1.2 COMMENTS:

Issues not addressed by the sponsor:

1. The risk for lowering of blood pressure, heart rate and prolongation of QTc needs to be incorporated in the label and appropriate follow-up measures for patients taking guanfacine need to be proposed.

2. Due to the nature of data collected on QT (No time matched placebo, baseline measurements, unknown food effects) prolongation, the sponsor should conduct a thorough QT study for a clear understanding of the drug effects.

3. In future clinical trials, the sponsor is recommended to collect blood samples for measuring guanfacine concentrations. Due to the wide range of body-weights of patients in the clinical trials, exposure derived based on guanfacine concentrations would be more informative to understand issues related to clinical benefit (ADHD-RS-IV scores) and safety (lowering of blood pressure, heart rate and prolongation of QTc) than actual dose. This could have greatly helped in understanding the risk-benefit ratio in this patient population.

4. Based on all the issues that have been noted in the review, it appears that the starting dose of 1 mg in all age groups and further up-titration would allow for a better management of safety and balancing with benefit. The Office of Clinical Pharmacology finds the proposed dosing regimen to be a safe starting schedule.

5. When (b) (4) was administered with ketoconazole, the exposure to guanfacine (AUC_{0-inf}) increased 3-fold. The concomitant administration of (b) (4) with potent CYP3A4/5 inhibitors should be avoided.

6. The administration of (b) (4) with a high fat breakfast in adults led to a 77% increase of the peak plasma concentrations. The Package Insert should recommend the drug administration with a light meal.

7. Published literature suggests that co-administration of guanfacine may result in higher concentrations of valproic acid. Since there is a possibility of coadministration (b) (4) with valproic acid derivatives, the sponsor is encouraged to study the interaction of these drugs. In the mean time, the monitoring of these patients for valproic acid dose adjustment is recommended.

8. The sponsor should provide a justification for the choice of dissolution media. The use of a high concentration of (b) (4) is not justified because guanfacine is soluble at the proposed pH 2.2. Moreover, the use of (b) (4) makes the dissolution test less discriminating.

9. (b) (4)

_____ Date_____
Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

_____
Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

CPB Briefing was held on May 31, 2007

Attendees: Drs. T. Laughren, M. Mehta, A. Rahman, C. Sahajwalla, K. Reynolds, R. Uppoor, R. Bawaja, P. Marroum, Ting Ong, A. Bhattaram, R. Levin, C. Garnett, S. Apparaju, F. Goodsaid, J. Vaidyanathan, M. Mathis.

cc list: NDA 22-037, MehulM, MarroumP, MishinaE, Bawaja, HFD 130 BIOPHARM

1.3 Summary of OCBP Findings

1.3.1 Background

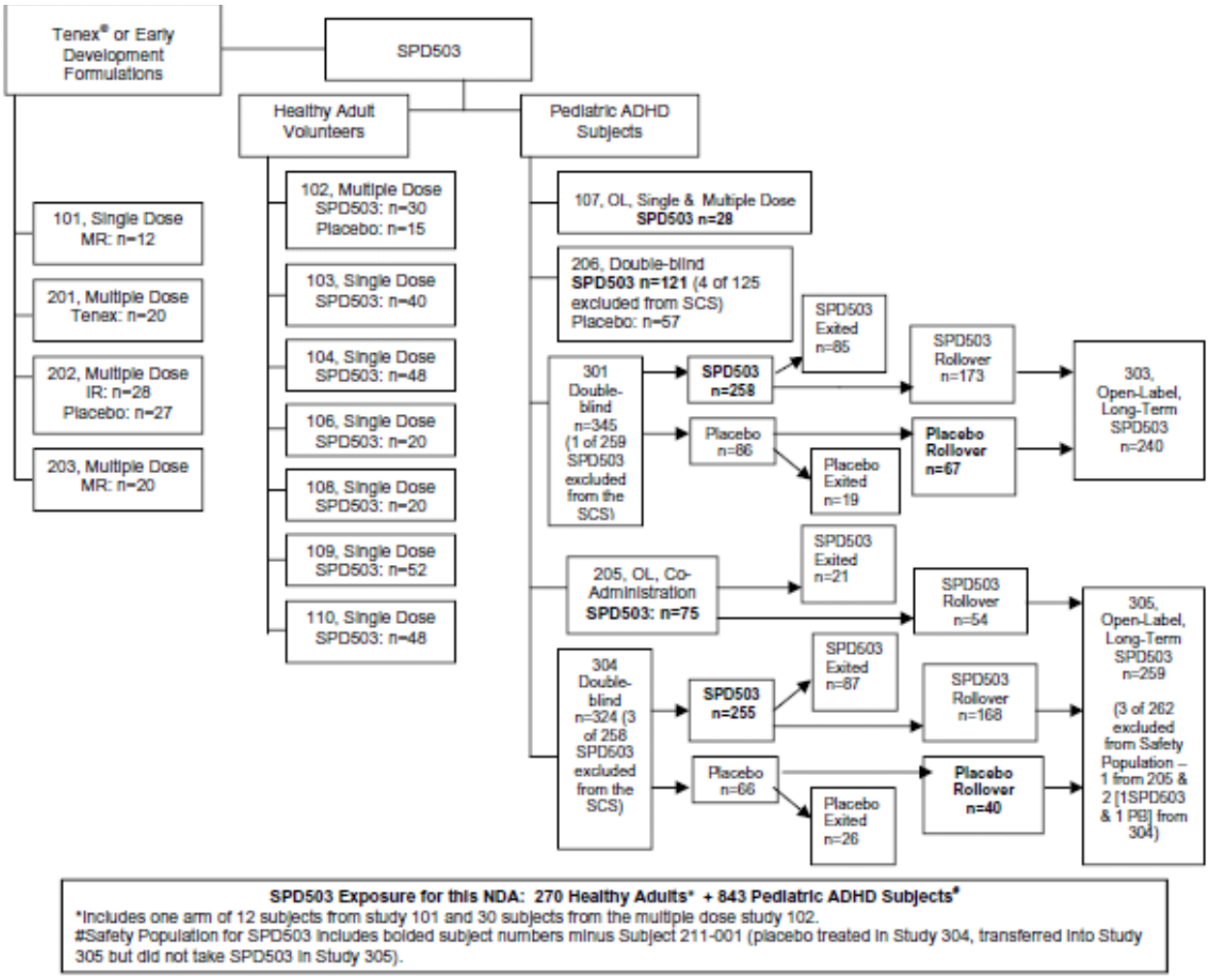
Shire Pharmaceuticals is seeking approval for [redacted] (b) (4) (guanfacine hydrochloride) extended release tablets for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents aged 6-17 years.

Approximately 8 percent of all school-age children, or about 4.4 million U.S. children aged 4 to 17 years, have been diagnosed with ADHD at some point in their lives, according to the U.S. Centers for Disease Control and Prevention. ADHD is one of the most common psychiatric disorders in children and adolescents that manifests as a persistent pattern of inattention and/or hyperactivity-impulsivity (more frequent and severe than is typically observed in individuals at a comparable level of development). The usual therapy for the treatment of attention-deficit hyperactivity disorder (ADHD) has been psychostimulants, such as methylphenidate and amphetamine. Nonstimulant medications (i.e. Strattera) are considered an alternative option offering a lower incidence of appetite suppression and minimal risk of abuse.

An immediate release Guanfacine hydrochloride (Tenex) was approved in 1986 for the treatment of hypertension as monotherapy or in combination with other antihypertensive agents. It has been used off label to treat the symptoms of ADHD as well as other α_2-adrenergic agonists (such as clonidine).

1.3.2 Current Submission

NDA 22-037 contains two pivotal trials (Phase-III, Double-Blind, Parallel-Group, Placebo-Controlled: 1, 2, 3, 4 mg/day) as evidence of effectiveness in addition to a flexible-dose finding study (Phase II: 1, 2, 3, 4 mg/day) for guanfacine. The sponsor also assessed the safety and tolerability of the co-administration of SPD503, dosed to maximum tolerability (1, 2, 3, or 4mg/day) and psychostimulants (methylphenidate or amphetamine) for the treatment of ADHD in patients who had suboptimal control on psychostimulants alone. All studies were conducted in children and adolescents 6 to 17 years old. In addition, the sponsor conducted Phase I studies in pediatric patients and adults to primarily understand the general pharmacokinetic characteristics of the extended release formulation (dose-proportionality, food effect, drug interaction studies) and tolerability issues. One bioavailability and three bioequivalence studies were performed; [redacted] (b) (4) The 5 new in vitro studies assessed the guanfacine's in vitro permeability and interaction with P-glycoprotein in Caco-2 cell monolayers; the hepatic metabolism by CYP450 and the potential for guanfacine to inhibit CYP450 enzymes, the binding to plasma protein and uptake by red blood cells. All these studies were reviewed. The scheme of the drug development program is shown below.



Pharmacokinetics

The extended release formulation was developed in order to minimize the fluctuation of the guanfacine plasma concentrations. The half-lives of both formulations are similar but the profiles are different: Tmax of SPD503 was delayed by about 3 hours, and the peak of guanfacine plasma concentration is shallower. The ratio of Cmax : C24 is decreased from 2.88 for Tenex to 1.85 for SPD503; therefore, the fluctuation of guanfacine plasma concentrations is indeed decreased. The PK parameters of guanfacine after the administration of SPD503 are dose proportional over the proposed dose range of 1 mg/day to 4 mg/day. Dose adjustment for the accumulation of guanfacine with once daily doses is not necessary because its PK was dose proportional at steady state as was tested in clinical studies, and chronic administration was not associated with an increase of the incidence of adverse events.

Absorption, Distribution, Metabolism, Excretion

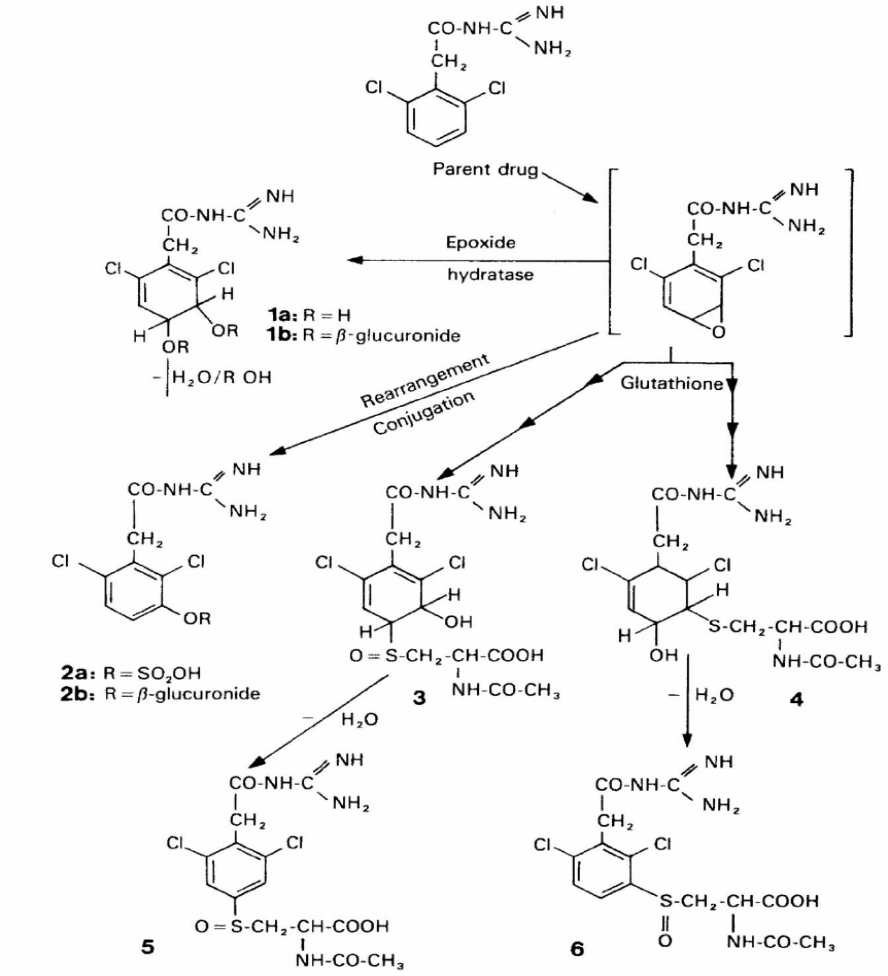
Guanfacine is not a substrate or a potent inhibitor of the P-gp pump. It is primarily transported by a passive transcellular pathway; and therefore, it exhibits a significant absorption in vivo. The absolute bioavailability (BA) of immediate release guanfacine is about 80%, and relative BA of SPD503 is 55%. When administered as an extended release formulation, guanfacine is absorbed with a Tmax of about 6 hours.

The volume of distribution of guanfacine was estimated as 804 L, indicating intracellular distribution. The plasma protein binding of guanfacine in human plasma has been studied by equilibrium dialysis and ranges from 64% to 72% (publications, 1980, 1987). Approximately 60% of guanfacine in the blood is bound to red blood cells.

The guanfacine immediate release in adults is cleared both by the liver and the kidney, and approximately 50% of the clearance of guanfacine is hepatic. The total clearance (CL) of guanfacine was about 11 L/h both after an intravenous (3mg) and after oral administration (2.3mg) of [14C]-guanfacine, and 30% of which was renal clearance (2.7 L/hr). After oral and intravenous administration, the ratio of renal clearance (CLR) to creatinine clearance (CLCR) averaged 2.3 ± 0.5 and 2.2 ± 0.5, respectively. As these ratios are greater than 1, guanfacine is excreted by the kidney by filtration and active secretion, although reabsorption by the tubule cannot be ruled out.

Guanfacine has a low hepatic extraction ratio (<0.3), therefore, alterations in hepatic blood flow (i.e. due to the liver disease) should not have a significant effect on its pharmacokinetics. However, the extended release formulation of guanfacine was not studied in hepatically and renally impaired patients.

The scheme of the guanfacine metabolic pathway is shown in the following scheme.



Cytochrome P450 3A4 is the predominant enzyme involved in the oxidative metabolism of guanfacine. The inhibitory potential of guanfacine was very weak for CYP450 1A2, 2C8, 2C9,

2C19, 2D6, and 3A4/5. After in vitro incubation of human hepatic microsome with various concentrations of guanfacine, the remaining activities of all isoenzymes were >93%, and for 2C8 it was >73%. The in vitro studies suggested that guanfacine is neither a reversible nor irreversible inhibitor of the above mentioned cytochromes.

Drug-drug interaction information
Coadministration of ketoconazole significantly increased the exposure to guanfacine: its Cmax increased 1.7 fold, AUC0-t increased 2.8 fold and AUC0-∞ increased 3.1 fold. Since the increased exposure to guanfacine may cause greater adverse events, the reviewer recommends avoiding the concomitant administration of guanfacine with the CYP3A4/5 inhibitors.
Coadministration with rifampin significantly decreased exposure to guanfacine with a decrease in Cmax by more than 50%, AUC0-t by 60% and $AUC_{0-\infty}$ by 70%. Guanfacine is always titrated in the clinic to the desirable effect (the dose range covers 4-fold); therefore, the reviewer recommends to up-titrate the guanfacine dose up to highest dose of 4 mg QD.

Pediatric Patients
The pharmacokinetics of guanfacine in children and adults are similar. The differences in the guanfacine exposure can be predicted by the subject's body weight. The exposure to guanfacine was higher in children (6-12 years old) compared with adolescents (13-17 years old). That can be explained by the lower body weight of the younger group of patients.

Parameter*	Multiple Dose 2mg		Multiple Dose 4mg	
	Children (6-12 years)	Adolescents (13-17 years)	Children (6-12 years)	Adolescents (13-17 years)
C_{max} (ng/mL)	4.4 ± 1.66	2.9 ± 0.77	10.1 ± 7.09	7.0 ± 1.53
t_{max} (h)	4.98 (3.95-7.97)	4.53 (2.93-7.98)	5.02 (3.97-10.3)	4.97 (1.00-7.97)
AUC_{0-24} (h•ng/mL)	70.0 ± 28.33	48.2 ± 16.06	162.1 ± 115.56	116.7 ± 28.37
CL/F				
(mL/min)	552 ± 215	826 ± 486	522 ± 212	607 ± 166
(mL/min/kg)	15.3 ± 4.11	14.4 ± 8.34	14.3 ± 3.70	10.7 ± 3.11

Weight was shown to be the main predictor for guanfacine exposure according to the population PK model in pediatric patients. The effect of sex, age, and race would not be expected to be clinically important due to the estimated precision of these effects and their lack of effect on inter-individual variability.

Exposure-Response Relationships
Effectiveness
There is a dose-response (ADHD-RS-IV) relationship for effectiveness in the studied patient population. The sponsor is proposing a fixed dose for all weight groups. However, the drug effects in the adolescents (13-17 years) are not different from those treated with placebo. This is due to higher placebo effects and lower Cmax (30%), AUC (30%) in adolescents (13-17 years) due to differences in bodyweights compared to children (6-12 years).

Safety

There is a relationship between dose/concentration-response relationship for safety measures such as QT, diastolic/systolic blood pressure, heart rate, somnolence etc. For every 1 unit increase in guanfacine concentrations, a 1 msec increase in QTcI (Individual Corrected by FDA) or QTcP (Population Corrected by Sponsor) from baseline would be observed.
Patients with lower bodyweights will be at more risk for changes in QT compared to those with heavier bodyweights. For labeling purposes, the exact risk of QT prolongation is not clear due to the absence of good quality data (time matched placebo, baseline etc). There are few cases of QT prolongation greater than 30 msec in the clinical studies. However, this is based on Fredericia's correction method which could be incorrect since the drug has effects on heart rate.

Benefit-Risk Ratio/ Dosage Regimen
The drug has not demonstrated additional benefit over placebo in patients who are 13 years or older (who tend to be heavier), the risk outweighs the benefit in this age group. In patients who are 6-12 years of age, the benefit-risk ratio is probably greater than unity.The sponsor is proposing to market dosage form strengths of 1, 2, (b) (4) 3, (b) (4) and 4 mg. All patients will start at a dose of 1 mg and subsequent dose adjustments would be 1 mg/week. The recommended dose range for maintaining patients on stable therapy is between 1 to 4 mg. For discontinuation, tapering off the dose in decrements up to 1 mg every 3 to 7 days is advised to avoid possible elevations in blood pressure.
Overall, the proposed dosing regimen would be adequate if the risk of QT prolongation, lowering of blood pressure, heart rate, somnolence issues can be managed. One additional factor that can help reduce the risk for adverse events is the delay between intake of food and the administration of (b) (4) Due to increased exposure with high fat breakfast, guanfacine should be taken preferably on a fasted stomach.

Biopharmaceutics

(b) (4)

The current method should only be accepted on an interim basis until the sponsor will develop a new dissolution method and specification for the guanfacine extended release tablets.

Biowaiver:

(b) (4)

The sponsor should submit the required documentation on the dissolution profiles.

2 QUESTION BASED REVIEW

2.1 General Attributes

History of Guanfacine Development

Immediate release Guanfacine hydrochloride (Tenex) was approved in 1986 for the treatment of hypertension as monotherapy or in combination with other antihypertensive agents.

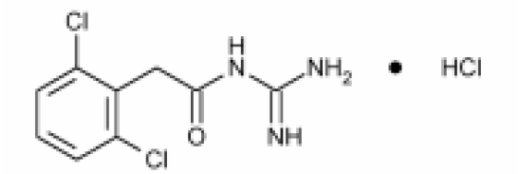
The usual therapy for the treatment of attention-deficit hyperactivity disorder (ADHD) has been psychostimulants, such as methylphenidate and amphetamine. Nonstimulant medications are considered an alternative option offering a lower incidence of appetite suppression and minimal risk of abuse. Recently, Strattera (atomoxetine HCL, a selective norepinephrine reuptake inhibitor) was approved as a first-line treatment for ADHD.

An immediate-release formulation of guanfacine and other α_2-adrenergic agonists (such as clonidine) is used off label to treat the symptoms of ADHD. In order to minimize the fluctuations between peak and trough concentrations and to have a convenient once daily dosing, an extended-release formulation (SPD503) of guanfacine hydrochloride was developed and studied.

The sponsor is seeking the approval of Guanfacine hydrochloride extended-release tablets for the treatment of ADHD in children and adolescents 6-17 years of age.

Highlights of chemistry and physical-chemical properties of the drug substance and product

Guanfacine hydrochloride (N-amidino-2-(2,6)-dichlorophenyl acetamide monohydrochloride) is a weakly basic drug, which has pH dependent solubility, with higher solubility at acidic pH conditions than at basic pH conditions. Guanfacine has relatively low solubility in water (~ 1mg/mL) and in most organic solvents. The only organic solvent in which guanfacine hydrochloride has relatively high solubility is methanol (>30mg/mL). Its structural formula is



Its empirical formula is C9H9CL2 N3O.HCl, molecular weight: 282.56.

The tablet formulations were designed to optimize the drug release from the dosage form over the pH range of the gastrointestinal tract. SPD503 is an extended-release formulation containing 1mg, 2mg, (b) (4) 3mg, (b) (4) or 4mg of guanfacine hydrochloride. The dosage form is comprised of the active ingredient, guanfacine hydrochloride, and inactive ingredients: (b) (4)

Fumaric acid, together with none or one of the following pigments: PB-1763, (b) (4)

What are the proposed mechanisms of action and therapeutic indication?

Guanfacine is a selective postsynaptic agonist of α_2-adrenergic receptors. It has high (b) (4) affinity for the human α_2A-adrenoceptor subtype with 15- to 20-fold selectivity over the α_2B-and α_2C-subtypes. By stimulating alpha-2A-adrenergic receptors, guanfacine reduces sympathetic

nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate. SPD503, an extended-release formulation provides the desired reduction in ADHD.

SPD503 (guanfacine hydrochloride) Extended-Release Tablets is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

What are the proposed dosages and route of administration?

The sponsor recommends that a once daily dose of (b) (4) begin at a dose of 1 mg and adjust in increments up to 1 mg/week. Tablets should not be crushed, chewed or broken before swallowing. The dose of (b) (4) should be maintained within the range of 1mg to 4 mg per day, depending on clinical response. During the discontinuation the doses should be tapered off in decrements up to 1 mg every 3 to 7 days to avoid possible elevations in blood pressure.

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

This submission includes an assessment of SPD503 for the treatment of ADHD in children and adolescents 6-17 years, using doses between 1 and 4mg once daily. To support this proposed indication, and to evaluate the compound's safety, including CNS and cardiovascular effects, a total of 18 clinical studies in pediatric populations (safety/PK/efficacy) and in adults (safety/PK) were performed, including two fixed-dose placebo-controlled studies treating ADHD in children and adolescents.

The ADME studies as well as the PK of guanfacine immediate release formulation in subjects with impaired renal function, the elderly, and patients with hypertension have been described previously (see review of Tenex, NDA 19-032, 1986). These finding and early publications were summarized by the sponsor.

For the extended release formulation (SPD503), the PK was assessed in adults (Study 102), and PK, dose-proportionality, and food effect of guanfacine after single- and multiple dose administration have been examined in children (6-12 years) and adolescents (13-17 years) with ADHD (Studies 104, 107, 203, and 206). In vivo drug interaction studies of guanfacine with ketoconazole and rifampin were conducted in adults (Studies 106 and 108). The Phase 3 safety and efficacy study 305 also included sparse plasma sampling and the results were included in the population PK/PD report.

In addition, one bioavailability and three bioequivalence studies (103, 109, and 110) were performed. (b) (4) .

The 5 new in vitro studies assessed the guanfacine's in vitro permeability and interaction with P-glycoprotein in Caco-2 cell monolayers; the hepatic metabolism by CYP450 and the potential for guanfacine to inhibit CYP450 enzymes, the binding to plasma protein and uptake by red blood cells.

The review of 11 clinical pharmacology/biopharmaceutics and 5 in vitro studies were performed by E. Mishina. The pharmacometric review (exposure –response and exposure safety data was performed by A Bhattram.

Were the correct moieties identified and properly measured to assess clinical pharmacology?

Yes. The sponsor measured the concentration of guanfacine in plasma. The major metabolite, guanfacine glucuronide, is inactive moiety,. Therefore, the measurements of the parent drug is acceptable for the assessment of the pharmacokinetics of this product.

EXPOSURE-RESPONSE

Were the relationship between efficacy endpoints and safety endpoints and drug plasma concentration described?

Yes. Please see the PM review for details.

Dose/Exposure-Effectiveness Relationship

The relationship between the time course of plasma concentrations of guanfacine or overall exposure (AUC) and various measures of drug effects from Phase II studies were examined through graphical and regression techniques. The sponsor did not collect plasma concentrations in the double-blind phase of the two Phase III trials. Hence, a description of the exposure-effectiveness relationship is not possible. The sponsor explored the relationship between time matched guanfacine concentrations and primary/secondary endpoints such as Choice Reaction Time (CRT), Permanent Product Measure of Performance (PERMP) in a Phase II study (SPD503-206). These analyses are useful in understanding the time course of drug effects.
In addition, the reviewer explored the time course of drug effects on Conners' Parent Rating Scale-Revise (CPRS-R) and Conners' Teaching Rating Scale-Revised (CTRS-R) in Phase III using graphical techniques. For greater details of the various clinical scores used in Phase II and Phase III trials, please refer to Appendix-I of the PM review.

Dose/Exposure-Safety Relationship

The relationship between dose/plasma concentrations of guanfacine or overall exposure (AUC) and safety related events from Phase II and Phase III studies were examined through graphical and regression techniques. If guanfacine concentrations were not measured, then dose-safety relationships were explored using graphical methods. The safety measures of interest were:

- QT prolongation
- Systolic and diastolic blood pressure
- Heart rate (pulse)
- Dizziness
- Somnolence
- Fatigue

Is there a Dose/Exposure-response (ADHD-RS-IV) relationship for effectiveness?

Yes, overall there is a dose-response relationship for effectiveness in the studied patient population. The sponsor is proposing a fixed dose for all weight groups. However, the drug effects in the adolescents (13-17 years) are not different from those treated with placebo. This is

due to higher placebo effects and lower Cmax (30%), AUC (30%) in adolescents (13-17 years) due to differences in body weights compared to children (6-12 years).

Is there a Dose/Exposure-response relationship for safety? Does the drug prolong the QT/QTc interval?

Yes, there is a relationship between dose/concentration-response relationship for safety measures such as QT, diastolic/systolic blood pressure, heart rate, somnolence etc. For every 1 unit increase in guanfacine concentrations, a 1 msec increase in QTcI (Individual Corrected by FDA) or QTcP (Population Corrected by Sponsor) from baseline would be observed.
Patients with lower bodyweights will be at more risk for changes in QT compared to those with heavier body weights.

Do the proposed dosing guidelines maximize benefit-risk ratio?

The sponsor is proposing to market dosage form strengths of 1, 2, (b) (4) 3, (b) (4) and 4 mg. All patients will start at a dose of 1 mg and subsequent dose adjustments would be 1 mg/week. The recommended dose range for maintaining patients on stable therapy is between 1 to 4 mg.
Overall, the proposed dosing regimen would be adequate if the risk of QT prolongation, lowering of blood pressure, heart rate, somnolence issues can be managed. One additional factor that can help to reduce the risk for safety events is the delay between intake of food and medication. Due to increases in Cmax (77%) and AUC (40%) with high fat breakfast, guanfacine should be taken preferably 1 hour prior to food.
Also since the drug has not demonstrated additional benefit over placebo in patients who are 13 years or older (who tend to be heavier), the risk outweighs the benefit in this age group. In patients who are 6-12 years of age, the benefit-risk ratio is probably greater than unity.

Are the pharmacokinetics of guanfacine in children and adults similar?

Yes. The differences in the guanfacine exposure can be predicted by the subject's body weight.
The effects of gender, age, and body weight on the pharmacokinetics of guanfacine using data from one study in 14 children (107) and 5 studies in adults (182 subjects). The reviewer shows the relationship between age and body weight and the dose-normalized Cmax and body weight below.

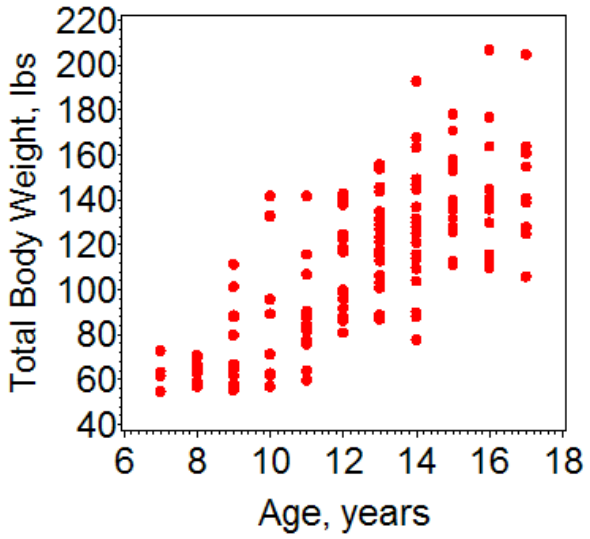


Figure 1 Relationship between body weight and age

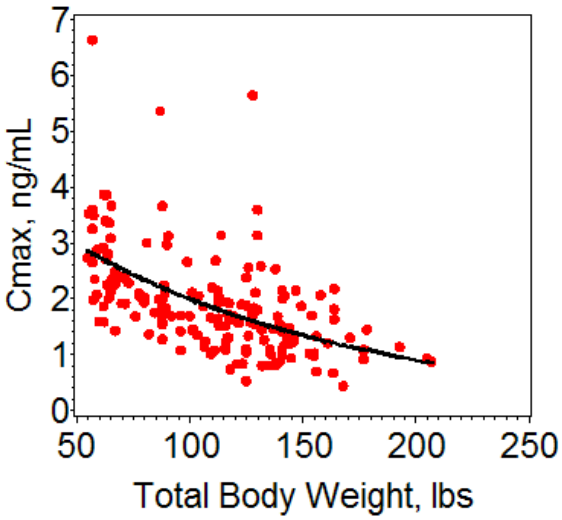


Figure 2 Relationship between dose-normalized Cmax and body weight

Figure 1 shows the relationship between bodyweight and age in the clinical studies. Figure 2 shows the relationship between dose-normalized Cmax and bodyweight in the clinical studies. Since all patients irrespective of their body weight were given fixed doses, patients with lower bodyweight have higher Cmax compared to those with higher body weight.

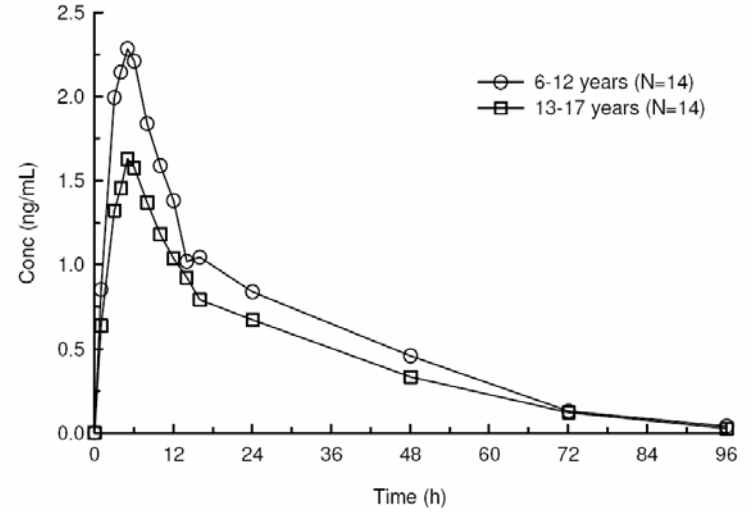


Figure 3. Mean plasma concentrations of guanfacine after oral administration of 2mg on Day 1 to pediatric (6-12 years) and adolescent (13-17 years) patients

The sponsor used the data from three clinical trials (SPD503-107, SPD503-203, and SPD503-206) to describe the population pharmacokinetics of SPD503. A variety of linear and nonlinear compartmental PK models were explored to describe guanfacine concentration-time data. Covariate effects were investigated with the primary focus of covariate effects on clearance (CL/F). A population PK model was successfully developed to describe guanfacine plasma concentrations in children (ages 6 to 17 years) with ADHD receiving therapeutic dosages of oral

guanfacine (SPD503; 1 to 4 mg/day). The population PK of guanfacine was described by a one-compartment model with first order absorption and a lag time. The estimates of the parameters are shown below.

Parameter	Fixed Effect Parameter Estimate (%SE)	Bootstrap 95% CI
CL/F (L/hr) = θ1	33.1 (5%)	30.2, 36.4
*$(WT/50)^{0.75}$	NA	NA
*$\theta5^{SEX}$	0.960 (8%)	0.824, 1.10
*$\theta6^{RACE}$	1.05 (8%)	0.878, 1.23
*$(AGE/12)^{\theta7}$	0.0358 (347%)	-0.240, 0.329
V/F (L/kg) = θ2	804 (6%)	703, 900
*$(WT/50)^{1}$	NA	NA
Ka (hr^{-1}) = θ3	0.552 (10%)	0.437, 0.670
Lag Time (hr) = θ4	0.651 (3%)	0.608, 0.697
Interindividual Variance (%SE)		
$\Omega_{1.1CL/F}$	0.180 (14%) CV%=42.4	0.134, 0.227
$\Omega_{1.2}COV_{CL/F-V/F}$	-0.000722 (3470%) r=-0.003	-0.0466, 0.0515
$\Omega_{2.2V/F}$	0.308 (17%) CV%=55.5	0.216, 0.427
$\Omega_{1.3}COV_{CL/F-Ka}$	-0.0473 (87%) r=-0.125	-0.128, 0.0373
$\Omega_{2.4}COV_{V/F-Ka}$	0.440 (16%) r=0.890	0.311, 0.628
$\Omega_{3.3Ka}$	0.793 (15%) CV%=89.1	0.573, 1.12
Residual Variance (%SE)		
σ^2_{pro}	0.0464 (10%) CV%=21.5	0.0377, 0.0552
σ^2_{add}	0.0205 (24%) SD=0.143	0.0125, 0.0340

%SE = percent standard error
CI = confidence interval
CL/F = apparent clearance
WT = weight
V/F = apparent central compartment volume of distribution
Ka = absorption rate constant
hr = hour
COV = covariance
CV% = percent coefficient of variation
SD = standard deviation
r = correlation
pro = proportional error
add = additive error

Typical population PK parameters (95% CI) given the reference covariates (Caucasian, male, 12 years, 50 kg) were CL/F, 33.1 (30.2, 36.4) L/hr; V2/F, 804 (703, 900) L; Ka 0.552 (0.437, 0.670) hr-1; and ALAG, 0.651 (0.608, 0.697) hr. Weight was shown to be the main predictor for guanfacine exposure. The effect of sex, age, and race would not be expected to be clinically important due to the estimated precision of these effects and their lack of effect on inter-individual variability. Model evaluation results indicated the observed guanfacine concentration data are well described by the model, and the PK parameters can be properly predicted based on the patient' body weight.

Was the dosage regimen recommended based on the data obtained for the pediatric population, and are there any unresolved issues of dosing or administration?

The sponsor recommends once daily dose of [redacted] (b) (4) beginning at a 1 mg dose which can be adjusted in increments up to 1 mg/week up to a dose of 4 mg per day, depending on

clinical response. For discontinuation, tapering off the dose in decrements up to 1 mg every 3 to 7 days is advised to avoid possible elevations in blood pressure.

The dosing recommended by the sponsor is not based directly on the body weight of the child. The actual doses that correlated with the clinical improvements were in the range of 0.05-0.08 mg/kg/day. That dose range corresponds to 1 mg in a 20 kg patient and 4 mg in a 50 kg patient. These weights represent respectively the average values for a 6 and a 14 years old child according to the National Center for Health Statistics. The lower 5% bound of the 6 years old subjects weight is 16 kg. The dosing recommendation should include the patient's weight limitation because guanfacine was not studied in patients weighing less than 20 kg. Doses up to 0.12 mg/kg/day (4 mg in 33 kg patient) may provide additional benefit; however, doses above 4 mg per day have not been studied.

The once daily dose will maintain the guanfacine plasma concentrations in the relevant therapeutic range.

PK characteristics of the drug and its major metabolite(s)

How does the PK of the immediate (Tenex) and extended (SPD503) release formulations of guanfacine differ?

The data for comparison are obtained from study 101, for Tenex, and 109, for SPD503. Mean guanfacine plasma concentration profiles after the 1 mg single doses of Tenex and SPD503 are shown in the Figure below.

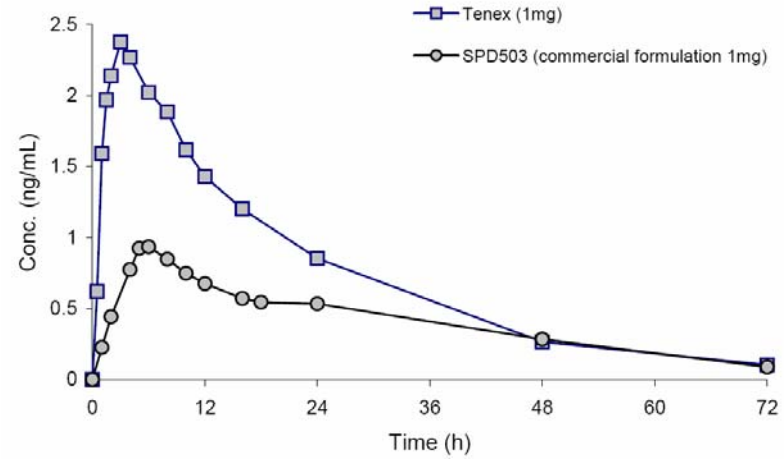


Figure 4. Mean plasma concentrations of guanfacine after oral administration of 1mg of Tenex or SPD503 under fasting conditions in healthy adult subjects.

Table 1. Guanfacine PK parameters (Tenex vs. SPD503)

PK parameter *		Tenex (n=12)	SPD503 commercial formulation (n=52)
C_{max}	(ng/mL)	2.45 ± 0.63	0.98 ± 0.26
t_{max}	(h)	3.0 (1.5-4.0)	6.0 (4.0-8.0)
AUC_{0-t}	(h.ng/mL)	53.0 ± 13.9	29.3 ± 8.8
$AUC_{0-\infty}$	(h.ng/mL)	56.0 ± 15.0	32.4 ± 8.8 †
$t_{½}$	(h)	15.7 ± 3.0	17.5 ± 3.8 †
C_{24}	(ng/mL)	0.85 ± 0.24	0.53 ± 0.17
F(rel)	(%)	-	55 (58)

The extended release formulation was developed in order to minimize the fluctuations of guanfacine plasma concentration. The half-lives of both formulations are similar but the profiles are different: Tmax of SPD503 was delayed by about 3 hours, and the peak of guanfacine plasma concentration is shallower. The ratio of Cmax : C24 is decreased from 2.88 for Tenex to 1.85 for SPD503; therefore, the fluctuations of guanfacine plasma concentration are indeed decreased. The relative bioavailability of the extended release vs. immediate release formulation at steady state was not assessed by the sponsor.

What are the single and multiple dose PK parameters?

The PK of guanfacine after single and multiple doses of SPD503 in the clinical dose range of 1 mg to 4 mg QD are dose proportional in adult healthy volunteers and pediatric patients.
The PK of guanfacine after single dose of 1, 2, and 4 mg, in healthy adults are shown in Figure 25 and Table 39. The dose-normalized PK parameters after single dose are summarized in the Table below:

Table 2. Dose-normalized PK parameters of Guanfacine after the single dose administration

Parameter/1 mg	**Pediatric (N=14)**	**Adolescents (N=14)**	**Children 6-17 y.o. (N=20)**
Cmax	1.25 (0.51)	0.84 (0.22)	1.95 (0.55)
AUCinf	32.6 (11.9)	23.8 (6.8)	29.7 (7.8)*
Tmax (h)	5	5	5
T1/2 (h)	14.4 (2.4)	17.9 (5.8)	11.0 (0.8)**

*AUC0-24
**MRT

The PK profiles and PK parameters of guanfacine after multiple doses of 1mg and 4 mg of SPD503 once daily in children with ADHD are shown in Figure 5 and in Table 3.
At steady state, after administration of 4mg of SPD503 once daily for 14 days the mean Cmax and AUC0-24 of guanfacine were twice those after administration of 2mg once daily for 14 days.

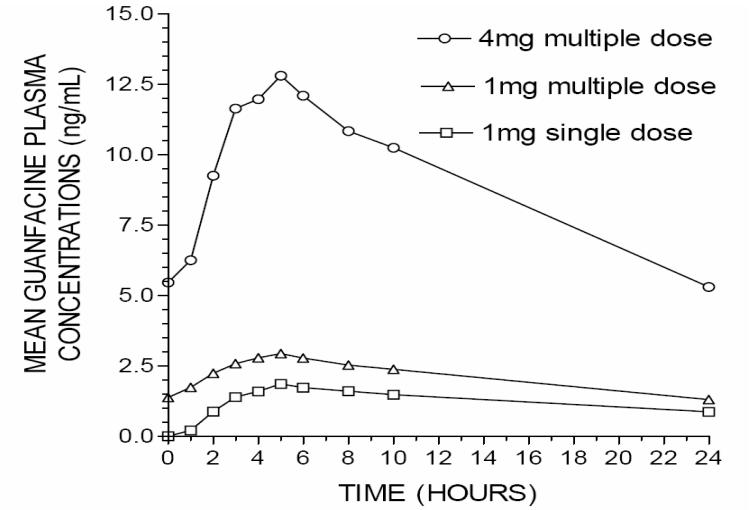


Figure 5. Mean guanfacine plasma concentration vs. time values

Table 3. Summary of Pharmacokinetic Parameters for Guanfacine After Repeated Oral Administration of 2 and 4mg SPD503 Doses Once Daily to Children (6-12 years) and Adolescents (13-17 years) with ADHD

Parameter*	Multiple Dose 2mg		Multiple Dose 4mg	
	Children (6-12 years)	Adolescents (13-17 years)	Children (6-12 years)	Adolescents (13-17 years)
C_{max} (ng/mL)	4.4 ± 1.66	2.9 ± 0.77	10.1 ± 7.09	7.0 ± 1.53
t_{max} (h)	4.98 (3.95-7.97)	4.53 (2.93-7.98)	5.02 (3.97-10.3)	4.97 (1.00-7.97)
AUC_{0-24} (h•ng/mL)	70.0 ± 28.33	48.2 ± 16.06	162.1 ± 115.56	116.7 ± 28.37
CL/F				
(mL/min)	552 ± 215	826 ± 486	522 ± 212	607 ± 166
(mL/min/kg)	15.3 ± 4.11	14.4 ± 8.34	14.3 ± 3.70	10.7 ± 3.11

Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The PK parameters of guanfacine are dose proportional over the proposed dose range of 1 mg/day to 4 mg/day.

How do the PK parameters change with time following chronic dosing?

The guanfacine half-life is about 17 hours; therefore, drug accumulation is expected with once a day dosing. The comparison of Cmax at steady state (Day 14) and after single dose (Table 8 and Table 9**,** Appendix) showed an accumulation of 72% and 69% in children and adolescent subjects with ADHD, respectively. Dose adjustment for the accumulation of guanfacine with once daily doses is not necessary because its PK was dose proportional at steady state as was tested in clinical studies, and chronic administration was not associated with an increase of the incidence of adverse events.

What are the characteristics of drug absorption (possible transporters and pH impact)?

Guanfacine is efficiently transported through the Caco-2 cell monolayers and was not considered a substrate or a potent inhibitor of the P-gp pump. It is primarily transported by a passive transcellular pathway; and therefore, it exhibits a significant absorption in vivo.
The absolute bioavailability (BA) of immediate release guanfacine is about 80%, and relative BA of SPD503 vs. Tenex is 55%. When administered as an extended release formulation, guanfacine is absorbed with a Tmax of about 6 hours.
Guanfacine is a weakly basic drug, with higher solubility at acidic pH conditions. The extended release formulation is formulated to optimize the release of guanfacine over the gastrointestinal pH range.

What are the characteristics of drug distribution (including plasma protein binding?)

The volume of distribution of guanfacine was estimated as 804 L, indicating intracellular distribution. The plasma protein binding of guanfacine in human plasma has been studied by equilibrium dialysis and ranges from 64% to 72% (publications, 1980, 1987). Approximately 60% of guanfacine in the blood is bound to red blood cells. The concentration of guanfacine was higher in red blood cells than in plasma and greater than that predicted by the hematocrit.

Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study was not performed for SPD503. The extended release formulation of guanfacine was not studied in hepatically and renally impaired patients.
The early studies (Kiechel, 1980) indicate that guanfacine immediate release is cleared both by the liver and the kidney, and approximately 50% of the clearance of guanfacine is hepatic. The total clearance (CL) of guanfacine was about 11 L/h both after an intravenous (3mg) and after oral administration (2.3mg) of [14C]-guanfacine, and 30% of which was renal clearance (2.7 L/hr). In renally impaired patients, the cumulative urinary excretion of guanfacine and renal clearance decreased as renal function decreased (Table 4). However, plasma guanfacine concentrations did not increase as renal function decreased. In patients with renal failure (GFR <5mL/min), only 2.4% of the oral dose was eliminated in the dialysate and the dialysis clearance was 53mL/min, about 15% of the total clearance. The authors (Kirsch, 1980) suggested that as renal function decreases, an increase in hepatic metabolism occurs. This is a possible explanation; however it has not been directly studied.

Table 4. Cumulative urinary excretion and total and renal clearances of guanfacine in subjects with normal and impaired renal function.

Glomerular Filtration Rate (mL/min)*	Cumulative Urinary Excretion (% Dose)	CL (mL/min)	CL_R (mL/min)
> 90	57 ± 32	360 ± 262	233 ± 245
10-30	14 ± 9	308 ± 274	34 ± 22
< 10	7.5 ± 2.4	257 ± 187	18 ± 15

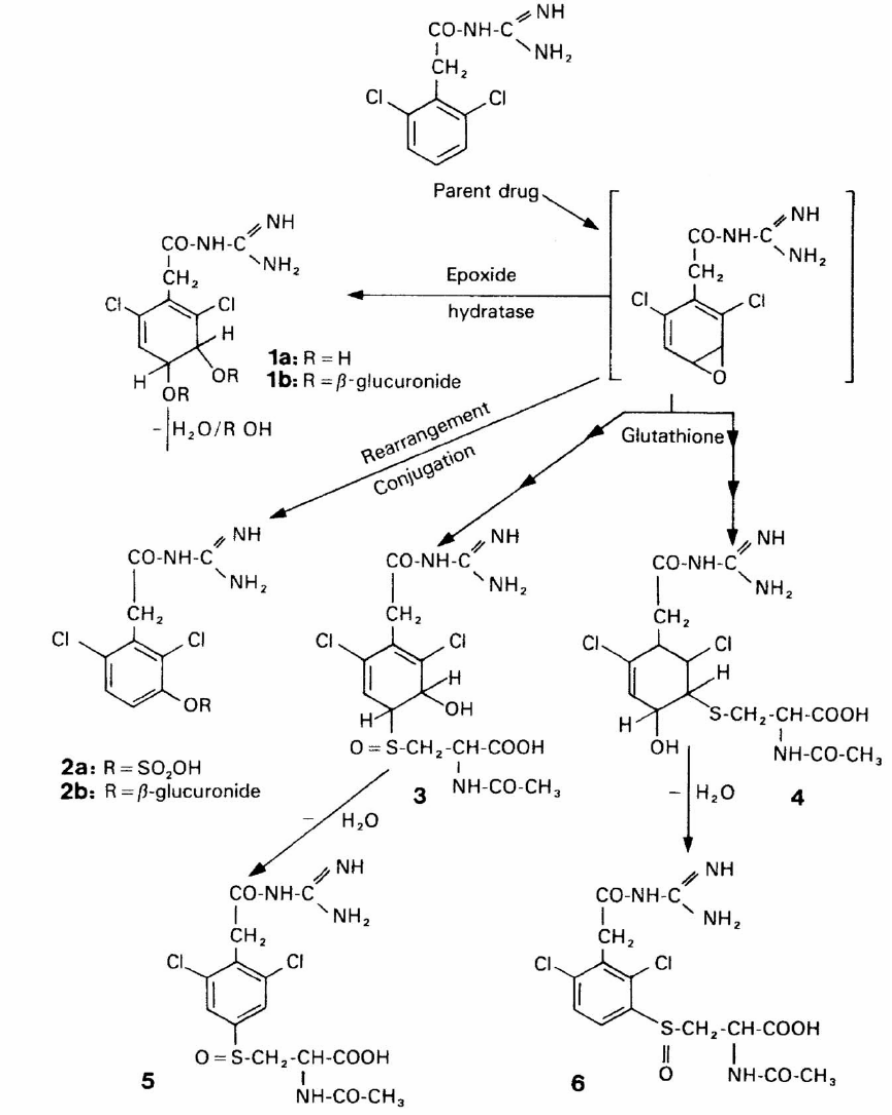
*>90 = normal; 10-30 = moderate; <10 = preuremic.

After oral and intravenous administration, the ratio of renal clearance (CLR) to creatinine clearance (CLCR) averaged 2.3 ± 0.5 and 2.2 ± 0.5, respectively. As these ratios are greater than

1, guanfacine is excreted by the kidney by filtration and active secretion, although reabsorption by the tubule cannot be ruled out.

What are the characteristics of drug metabolism? (extraction ratio, metabolic scheme, enzymes responsible, fractional clearances)

Guanfacine has a low hepatic extraction ratio (<0.3), therefore, alterations in hepatic blood flow (i.e. due to the liver disease) should not have a significant effect on its pharmacokinetics.
The scheme of the guanfacine metabolic pathway is shown in the following scheme.



Cytochrome P450 3A4 is the predominant enzyme involved in the oxidative metabolism of guanfacine. If CYP3A4 activity would be diminished by the coadministration of a potent inhibitor, it could result in an increase in guanfacine exposure. The involvement of CYP2E1 in the metabolism of guanfacine cannot be completely ruled out; however, in the *in vitro* study microsomes containing recombinant CYP2E1 did not metabolize the drug.

The inhibitory potential of guanfacine was very weak for CYP450 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4/5. After in vitro incubation of human hepatic microsomes with various concentrations of guanfacine, the remaining activities of all isoenzymes were >93%, and for 2C8 it was >73%. The in vitro studies suggested that guanfacine is neither a reversible nor irreversible inhibitor of the above mentioned cytochromes.
The guanfacine induction potential of the enzyme activities was assessed in vitro using hepatocytes obtained from 3 donors. There was no induction of the enzyme activities associated with the following cytochromes: 1A2, 2B6 and 3A4. In one donor's hepatocytes, the activity of CYP2C9 and 2C19 increased at the guanfacine concentration of 4mcM (~ 100-fold of Cssmax in a child who received 4 mg/day of guanfacine). Since this study involved hepatocytes only from 3 subjects, with one subject' data being different, the extrapolation of the results to the whole population was not feasible. The induction potential of guanfacine in vivo cannot be confirmed from this study.

What is the inter- and intra-subject variability of the PK parameters, and what are the major causes of variability?

Guanfacine is a moderately variable drug. Inter-individual variability for clearance was estimated as 14% (CV 42%), and for volume of distribution as 17% (CV 56%). The variabilities of the PK parameters of the immediate release formulation of guanfacine are similar to the same parameters of the extended release formulation (Table 1): For the Cmax values, variabilities (CV) were 26% and 27%, and for AUCinf 27% and 28%, respectively.

2.3 Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses? Based on what is known about exposure-response relationships, what dosage regimen adjustments, if any, are recommended for each subgroup listed below?

Age

The population PK model predicts that age would not be expected to be clinically important due to the estimated precision of its effect and lack of effect on interindividual variability. The differences in guanfacine exposure observed between the children (6-12 years old) and adolescents (13-17 years old) can be explained by body weight differences.

Race, in particular differences in exposure and/or response in Caucasians, African Americans, and/or Asians

The impact of race on guanfacine PK in children was not studied. The epidemiology of ADHD suggests a prevalence of approximately 4-7% in children, with a ~3:1 male:female ratio. Hispanic and African American children compared to white children are less likely to have a parent report a diagnosis of ADHD for the child. Approximately 1% of Hispanic children and 2% of African American children have parents report that the child has a diagnosis of ADHD compared to 4% of white children. These findings may represent either true racial differences in the prevalence of ADHD, or differential access or preferences for psychiatric care.
The population PK model predicts that race would not be expected to be clinically important due to the estimated precision of its effect and lack of effect on interindividual variability.

Gender

The population PK model predicts that gender would not be expected to be clinically important due to the estimated precision of its effect and lack of effect on interindividual variability.

Renal Impairment

The impact of renal impairment on the PK of guanfacine in children was not assessed. In adult patients with impaired renal function the cumulative urinary excretion of guanfacine and in renal clearance diminished as renal function decreased (Kirsch, 1980). In patients on hemodialysis, the dialysis clearance was about 15% of the total clearance. The low dialysis clearance suggests that the hepatic elimination (metabolism) increases as renal function decreases. The label recommendations should indicate that the PK of SPD503 was not assessed in renally impaired pediatric patients, and there is no information on dose adjustment for renally impaired children.

Hepatic Impairment

The impact of hepatic impairment on the PK of guanfacine in children was not assessed. Guanfacine in adults is cleared both by the liver and the kidney, and approximately 50% of the

clearance of guanfacine is hepatic. Hepatic impairment in children is rare and the evaluation of mild, moderate and severe hepatic impairment in the pediatric population cannot be estimated. The overall prevalence of co-morbid ADHD and hepatic impairment in children (since the two disorders appear to be unrelated) can be estimated to be very rare.
No recommendation on dose adjustment can be done.

What pharmacogenetic information is reported and is it important or not?

No pharmacogenomic information has been reported. Since guanfacine is metabolized by CYP3A4, and polymorphic enzymes are not involved in its metabolism, it is not expected that the metabolism of guanfacine would be influenced by genetics.

2.4 Extrinsic Factors

What extrinsic factors (herbal products, smoking, and alcohol use) influence dose-exposure and/or- response and what is the impact of any differences in exposure on response?

None of the above extrinsic factors were tested in this application.

Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. Guanfacine is metabolized by CYP3A4. If this enzyme activity will be decreased by coadministration of CYP3A4 inhibitors, the exposure to guanfacine is expected to increase. On the other hand, if the activity of CYP3A4 would increase by coadministration of CYP3A4 inducers, the exposure to guanfacine is expected to decrease. The sponsor performed two studies to assess the drug-drug interaction of guanfacine with ketoconazole (CYP3A4 inhibitor) and rifampin (CYP3A4 inducer).
Coadministration of ketoconazole significantly increased the exposure to guanfacine: its Cmax increased 1.7 fold, AUC0-t increased 2.8 fold and AUC0-∞ increased 3.1 fold. The concomitant intake of guanfacine with other drugs that inhibit CYP3A4/5 activity may likely result in increase in plasma levels of guanfacine, potentially leading to unwanted pharmacodynamic effects. In the label, the sponsor proposed to reduce the dose of (b) (4) when it is concomitantly administered with the CYP3A4/5 inhibitors. How to adjust the dose of guanfacine in the presence of either a CYP3A4/5 inducer or a CYP3A4/5 inhibitor is not clear since a dose adjustment scheme was not proposed by the sponsor. Since the elevation of plasma concentrations of guanfacine may cause greater prolongations in QT and decreases in blood pressure and heart rate, the reviewer recommends to avoid the concomitant administration of guanfacine with CYP3A4/5 inhibitors.
Coadministration with rifampin significantly decreased exposure to guanfacine with a decrease in Cmax by more than 50%, AUC0-t by 60% and $AUC_{0-\infty}$ by 70%. Therefore, in the case of coadministration of guanfacine with other drugs that induce CYP3A4/5 activity, it is likely that plasma levels of guanfacine would be lower than normal, potentially leading to a decrease in pharmacodynamic effects. The sponsor proposed in the label to increase the dose of (b) (4) within the recommended dose range when patients are taking (b) (4) concomitantly with a CYP3A4 inducer. Since the dose of guanfacine is always titrated in the clinic to a desirable effect (the dose range covers 4-fold), the reviewer considers that the up titration of guanfacine dose is reasonable up to highest dose of 4 mg QD.

What other co-medications are likely to be administered to the target population?

Psychostimulants and derivatives of valproic acid may be coadministered with guanfacine. There are no prospectively designed studies involving guanfacine and stimulant co-administration: nevertheless, it is known that in some children co-administration does occur. No formal interaction studies have been conducted with SPD503 coadministered with psychostimulants. Guanfacine, like other active central α2-adrenergic agonists, can cause sedation or drowsiness, especially at the inception of therapy. When SPD503 is used with other centrally active depressants, the potential for additive sedative effects should be considered. Subjects should be advised to avoid alcohol while taking SPD503.

Two pediatric subjects dosed with valproate concurrently with guanfacine experienced rapid significant increases in valproate levels. There have also been reports of interactions with tricyclic antidepressants and antipsychotics, which may cause unforeseen changes including the potential for additive or synergistic effect on decreasing blood pressure.
Guanfacine has been approved as a drug lowering blood pressure and heart rate. The sponsor proposed to exercise caution when it is co-administered with other antihypertensive drugs.

Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Yes. The sponsor performed a safety study in 75 children and adolescents aged 6-17 years with ADHD who were receiving a stable dose of amphetamine or methylphenidate (with sub-optimal response) and an adjunctive, maximum tolerated guanfacine dose up to 4 mg/day for 9 weeks. There was no clinical evidence of additive or unique adverse effects with this drug combination relative to what is observed with either medication alone. There were no serious adverse events in this study.
Coadministration of guanfacine and valproic acid was documented in the literature, indicating an increase of exposure to valproic acid. The mechanism of this interaction is unknown, although both guanfacine (via a Phase I metabolite, 3-hydroxy guanfacine) and valproic acid are metabolized by glucuronidation, possibly resulting in competitive inhibition. Although the interaction between guanfacine and valproic acid was not prospectively evaluated, the sponsor properly proposed in the label to monitor patients for dose adjustment when guanfacine is taken with other medications containing valproic acid.

Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Caco2-cell data indicate that guanfacine is neither a substrate nor an inhibitor of P-gp.

Are there other metabolic/transporter pathways that may be important?

No

2.5 General Biopharmaceutics

Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Guanfacine is a weakly basic drug, which has pH dependent solubility, exhibiting higher solubility at acidic pH conditions than at basic pH conditions.

Table 2: Solubility of Guanfacine Hydrochloride at 37°C as a Function of pH

Media	pH	Solubility (mg/mL) [b]
0.1N HCl		
Hydrochloric Acid Buffer [a]		
Acetate Buffer		
Phosphate Buffer		
Phosphate Buffer		

It's solubility in water and in organic solvents is low. The permeability of guanfacine is high, therefore, guanfacine belongs to BCS class 2 drugs.

What is the quantitative and qualitative composition of SPD503 formulation?

Table 57 (Appendix) provides the quantitative and qualitative composition of guanfacine sustained release formulations. Guanfacine free-base formulated as guanfacine hydrochloride (the active pharmaceutical ingredient, API) at strengths of 1, 2, (b) (4) 3, (b) (4) or 4mg. The formulations are manufactured using (b) (4)

pivotal clinical supplies and batches were made. Later in the development, the primary stability batches of SPD503 were manufactured using the same process and equipment at another site, Shire US Manufacturing, Inc. (SUMI).

What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Absolute bioavailability (BA) of the immediate release guanfacine is high (about 80%). The relative BA of SPD503 (to-be-marketed formulation) after single dose is about 56%. The SPD503 tablet (commercial formulation) was used in four studies, SPD503-103, SPD503-104, SPD503-109, and SPD503-110, and at doses ranging from 1mg to 4mg. In addition, the 2mg, (b) (4) and 4mg tablets were manufactured at two sites, (b) (4) SUMI. The sponsor performed several BA/BE studies. The following comparisons: 1mg and 4 mg (b) (4) formulations (Study 104),

2 mg SUMI, and 4 mg (b) (4) formulation (Study 109), and 2mg (b) (4) formulations (Study 110) were proven to be bioequivalent both by comparison of Cmax and AUC in each of these studies.

What data support a waiver of in vivo BE data?

(b) (4)

What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The sponsor assessed the food effect following a single dose oral administration of a 4mg tablet in fasted vs. fed condition. Food had a significant effect on the pharmacokinetics of guanfacine. The administration of SPD503 with a standard high-fat meal resulted in a 75% increase in Cmax and 38% increase in AUC. This change in exposure to guanfacine could lead to the increase in side effects (the incidence of fatigue and dizziness was significantly higher in the fed group). However, since the difference of Cmax of the extended release formulation administered with food (75%) is less that the difference Cmax of the immediate release formulation (150%) the drug administration is recommended independent of the meal.

Is the IVIVC model developed acceptable and can it be used to predict in vivo concentrations based on in vitro dissolution?

(b) (4)

Is the proposed dissolution method and specification acceptable?

No. The sponsor proposed a dissolution method which employs a USP Apparatus II with a speed of 75rpm and HCL pH 2.2 medium (b) (4) The dissolution method and specifications proposed by the sponsor are not acceptable at this time.

(b) (4)

(b) (4)

The Agency recommends the following dissolution specifications maintaining the basis until a new method and specifications are proposed.
The new method and specifications should be submitted within one year of the receipt of the action letter.

What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

(b) (4)

2.6 Analytical section

How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The concentration of guanfacine in human plasma was determined by HPLC coupled to a tandem mass spectrometry (LC/MS/MS) detector. Plasma containing guanfacine and the internal standard, (b) (4) was extracted using liquid-liquid extraction, concentrated, and analyzed by LC/MS/MS. The mobile phase was a gradient composed of (b) (4) l over a 4.1 minute period; the flow rate was 0.4mL/min. Guanfacine and (b) (4) were monitored by MRM at m/z transitions of 246 to 60 and 231 to 172, respectively.

What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?
The method was validated in the range of 0.05 to 2.5ng/mL based on the analysis of 0.5mL of human plasma. The plasma concentrations measured exceeded the ULOQ of 2.5 ng/mL. A dilution procedure was used.

Were the validation characteristics of the assay acceptable?
Yes.
All assays have their validation reports, see individual study reviews.

What is the overall conclusion regarding NDA 22-037?

Overall the Clinical Pharmacology and Biopharmaceutics section is acceptable.

3 DETAILED LABELING RECOMMENDATIONS

GENERAL

The Agency considered that the information provided in the original NDA 22-037 tablets was appropriate.

CLINICAL PHARMACOLOGY COMMENTS

Labeling Comments:

CLINICAL PHARMACOLOGY Section should have the following changes:

The following paragraph under Metabolism and Elimination:
"In individuals with normal renal function, guanfacine and its metabolites are excreted primarily in the urine. Approximately 50% (40-75%) of the dose is eliminated in the urine as unchanged drug; the remainder is eliminated mostly as conjugates of metabolites produced by oxidative metabolism of the aromatic ring. In individuals with normal renal function, the average elimination half-life is approximately 17 hr (range 10-30 hr). Steady state blood levels were attained within 4 days in most subjects. The guanfacine-to-creatinine clearance ratio is greater than 1.0, which would suggest that tubular secretion of drug occurs."

And the following section:

8.6 Use in Patients with Renal or Hepatic Impairment
Guanfacine is cleared to an equal extent by the kidney and liver 45 [see Pharmacokinetics (12.3)]. The pharmacokinetics of guanfacine have been studied in patients with moderately to severely impaired renal function. The pharmacokinetics of guanfacine has not been studied in patients with hepatic impairment.
The clearance of guanfacine in patients with renal insufficiency is reduced, but plasma levels of drug are only slightly increased compared to patients with normal renal function. The clearance of guanfacine in patients with hepatic impairment is also likely to be reduced, and plasma levels increased by an estimated 2- to 3-fold compared to patients with normal liver function. The dose in patients with renal or hepatic impairment is expected to be lower than in patients without impairment. Therefore, it is recommended that the rate and dose increment used during titration of (b) (4). in these patients be reduced, with closer monitoring for dose-dependent adverse effects such as hypotension or sedation.

Should be substituted with:

Renal Impairment
The impact of renal impairment on PK of guanfacine in children was not assessed. In adult patients with impaired renal function the cumulative urinary excretion of guanfacine and in renal clearance diminished as renal function decreased (Kirsch, 1980). In patients on hemodialysis, the dialysis clearance was about 15% of the total clearance. The low dialysis

clearance suggests that the hepatic elimination (metabolism) increases as renal function decreases. There is no information on dose adjustment in renally impaired children.

Hepatic Impairment
The impact of hepatic impairment on PK of guanfacine in children was not assessed. Guanfacine in adults is cleared both by the liver and the kidney, and approximately 50% of the clearance of guanfacine is hepatic. No recommendation on dose adjustment can be made."

In the Section DRUG INTERACTION:

7.1 CYP3A4/5 Inhibitors
There was a substantial increase in the rate and extent of guanfacine exposure when administered with ketoconazole, a CYP3A4/5 inhibitor. The Cmax for guanfacine doubled in the presence of ketoconazole, while AUC0-t and AUC0-inf increased by approximately 3-fold. When patients are taking (b) (4) concomitantly with a CYP3A4/5 inhibitor, the dose of (b) (4) should be reduced as appropriate.

The last sentence should be substituted with the following:

Since the elevation of plasma concentrations of guanfacine may cause greater prolongations in QT and decreases in blood pressure and heart rate, the reviewer recommends to avoid the concomitant administration of guanfacine with potent CYP3A4/5 inhibitors

The following paragraph should be added to the section:

Caution should be exercised when (b) (4) is administered concomitantly with the anti-hypertensive drugs.

In the Section DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

(b) (4) is an extended-release tablet and should be dosed once daily. Tablets should not be crushed, chewed or broken before swallowing because this will increase the rate of guanfacine release.

Should be amended with the following:

The drug may be administered either fasted or with a light meal.

4 APPENDICES

4.1 Individual Study Reviews

4.1.1 A Phase 1, Double-blind, Placebo-controlled, Randomized Safety Study of SPD503 in Young Healthy Adult Volunteers Aged 19-24 (102)

Study No: SPD503-102 Phase I
Investigators: (b) (4) **MD**
Study center(s): (b) (4)
Dates: 03 June 2004 - 21 September 2004

<table>
<tr><td>Objectives</td><td>Primary: to assess the rebound of systolic (SBP) and diastolic (DBP) blood pressure (BP) and other safety parameters, under controlled conditions, following the abrupt cessation versus dose tapering of SPD503 at a dose up to 4mg/day.
Secondary: to assess systolic and diastolic BP and pulse at Baseline (Day -1: 1 day prior to first dose) compared to Days 17 and 18 (abrupt cessation) and Days 31 and 32 (taper); to compare the safety and tolerability of the three groups: Treatment A, Treatment B and placebo.</td></tr>
<tr><td>Study Design</td><td>A double-blind, placebo-controlled, randomized, dose-escalation study evaluating the safety and tolerability of abrupt cessation and taper down of SPD503 compared to placebo with a forced dose-escalation design. All doses were given in the morning. Randomization in a 1:1:1 ratio (Treatment A: Treatment B: Placebo).
Phase I. Screening/Baseline:
Phase II. Double-Blind Treatment
<table>
<tr><th>Group #</th><th></th><th>Days 1-4</th><th>Days 5-8</th><th>Days 9-12</th><th>Days 13-16</th><th>Days 17-20*</th><th>Days 21-24</th><th>Days 25-30</th><th>Days 31-32*</th></tr>
<tr><td>1</td><td>Treatment A</td><td>1mg</td><td>2mg</td><td>3mg</td><td>4mg</td><td>P</td><td>P</td><td>P</td><td>P</td></tr>
<tr><td>2</td><td>Treatment B</td><td>1mg</td><td>2mg</td><td>3mg</td><td>4mg</td><td>3mg</td><td>2mg</td><td>1mg</td><td>P</td></tr>
<tr><td>3</td><td>Placebo</td><td>P</td><td>P</td><td>P</td><td>P</td><td>P</td><td>P</td><td>P</td><td>P</td></tr>
</table>
* On Days 17-18 and 31-32, there was a 48-hour period of confinement to monitor and document any potential rebound elevations in BP. The former focused primarily on the comparison between Treatment A vs. Treatment B, while the latter focused primarily on the comparison between Treatment B vs. Placebo. Placebo is presented as Treatment C in the tables, listings and figures.
Day 1, Treatment A and B 1mg of SPD503, doses increased in 1mg increments every 4 days until the subject reached the 4mg dose.
Days 17 and 18, ECGs, BP and HR obtained at multiple time points.
Day 17, Treatment B decreased daily dose in 1mg increments every 4 days until Day 31.
Day 17 Treatment A stopped the active treatment and initiated placebo through Day 32.</td></tr>
<tr><td>Population</td><td>Subjects male and female healthy adults, N=45, aged 19-24 years</td></tr>
<tr><td>Investigational Drug</td><td>SPD503, guanfacine hydrochloride, extended-release tablets:
<table>
<tr><th>Dose</th><th>Lot Number</th><th>Shape/Color</th></tr>
<tr><td>1mg</td><td>2026.001E</td><td>Round/White</td></tr>
<tr><td>2mg</td><td>2027.002E</td><td>Oval/White</td></tr>
<tr><td>3mg</td><td>2029.001B</td><td>Round/Green</td></tr>
<tr><td>4mg</td><td>2030.001F</td><td>Oval/Green</td></tr>
<tr><td>Placebo</td><td>*</td><td>Matched</td></tr>
</table></td></tr>
<tr><td>Placebo</td><td>Matched in shape/color to the treatment. Batches 2020.001 (1mg) 2021.001 (2mg) 2023.001 (3mg) 2024.001 (4mg)</td></tr>
</table>

Dosage	1, 2, 3 and 4mg QD
Duration	8 weeks
PD Assessment	NA
Safety Assessment	Measurements of vital signs (BP and pulse) were performed at all study visits. BP and HR were determined after the subject had been in a supine position for 10 minutes. The primary outcomes for this study were mean SBP and DBP measured on Days 17 and 18 and Days 31 and 32. Secondary outcomes are pulse rate measured at the same times and continuous ECG parameters, such as PR, QRS, HR, QT and QTc. Pulse rate and ECG parameters were analyzed in a corresponding manner to that described for the primary outcomes. 12-lead ECGs were performed at the Screening Visit (Visit 1) and all subsequent visits. Additionally, ECGs were performed every 30 minutes for 8 hours at the Baseline Visit (Visit 2) and multiple ECGs were performed during the two 48-hour periods of confinement (Visits 6 and 9).

RESULTS

There were no statistically significant differences in LSM DBP decreases or percent decreases from Baseline to the Day 17/18 endpoint between the abrupt cessation group (-6.17mmHg, -9.14%) and the group that tapered (-6.59mmHg, -9.94%).

LSM pulse rate decreases (p=0.0026) and percent decreases (p=0.0025) from Baseline to the Day 17/18 endpoint were significantly larger for the group that tapered (-12.79bpm, -18.95%) compared to the abrupt cessation group (-7.01bpm, -10.33%).

Table 5. Ambulatory Mean (SD) Change From Baseline – Days 17-18

		Treatment					
		A Abrupt Cessation		B Taper Down		Placebo	
		(N=15)		(N=12)		(N=11)	
Measurement	Study Day	Morning	Afternoon	Morning	Afternoon	Morning	Afternoon
Diastolic Blood Pressure (mmHg)	17	-8.13 (4.57)	-6.97 (3.77)	-7.35 (9.01)	-7.76 (7.78)	-2.97 (4.06)	-2.42 (3.97)
	18	-5.33 (5.10)	-4.02 (5.42)	-7.53 (7.97)	-6.52 (5.51)	-2.49 (4.01)	-3.19 (4.50)
Pulse (bpm)	17	-9.59 (7.39)	-6.43 (6.64)	-12.33 (4.44)	-11.83 (5.37)	-1.00 (3.96)	3.81 (4.60)
	18	-6.76 (6.78)	-3.14 (6.73)	-12.10 (5.71)	-12.83 (5.72)	-2.64 (5.32)	2.99 (3.86)
Systolic Blood Pressure (mmHg)	17	-11.01 (6.05)	-10.11 (4.62)	-8.98 (9.68)	-10.29 (7.39)	-2.99 (4.08)	-3.52 (3.28)
	18	-7.62 (7.60)	-6.18 (6.47)	-10.76 (6.81)	-8.99 (4.95)	-3.53 (4.17)	-3.41 (4.33)

Table 21 Treatment-Emergent Adverse Events by Number and Percent of Subjects Reporting Each Event (Safety Population)

Adverse Event	A (Abrupt Cessation) (N=15)		B (Taper Down) (N=15)		Placebo (N=15)		Total (N=45)	
Number of Subjects With Adverse Event	14	(93%)	8	(52%)	7	(47%)	29	(64%)
Cardiac disorders	1	(7%)	0		0		1	(2%)
Sinus tachycardia	1	(7%)	0		0		1	(2%)
Eye disorders	1	(7%)	0		0		1	(2%)
Eye pain	1	(7%)	0		0		1	(2%)
Gastrointestinal disorders	6	(40%)	4	(27%)	3	(20%)	13	(29%)
Constipation	0		1	(7%)	0		1	(2%)
Dry mouth	6	(40%)	4	(27%)	0		10	(22%)
Nausea	0		1	(7%)	0		1	(2%)
Toothache	0		0		2	(13%)	2	(4%)
Vomiting	0		0		1	(7%)	1	(2%)
General disorders and administration site conditions	8	(53%)	3	(20%)	2	(13%)	13	(29%)
Asthenia	1	(7%)	0		0		1	(2%)
Energy increased	1	(7%)	0		0		1	(2%)
Fatigue	6	(40%)	1	(7%)	1	(7%)	8	(18%)
Feeling abnormal	0		1	(7%)	0		1	(2%)
Feeling cold	0		1	(7%)	0		1	(2%)
Feeling hot	0		0		1	(7%)	1	(2%)
Pain	1	(7%)	0		0		1	(2%)
Pyrexia	1	(7%)	0		0		1	(2%)
Investigations	2	(13%)	2	(13%)	1	(7%)	5	(11%)
Blood pressure diastolic increased	1	(7%)	0		0		1	(2%)
Blood pressure systolic decreased	1	(7%)	1	(7%)	1	(7%)	3	(7%)
Blood pressure systolic increased	1	(7%)	0		0		1	(2%)
Electrocardiogram QT prolonged	0		1	(7%)	0		1	(2%)
Musculoskeletal and connective tissue disorders	0		1	(7%)	1	(7%)	2	(4%)
Arthralgia	0		0		1	(7%)	1	(2%)
Back pain	0		1	(7%)	0		1	(2%)
Nervous system disorders	9	(60%)	5	(33%)	4	(27%)	18	(40%)
Disturbance in attention	0		1	(7%)	0		1	(2%)
Dizziness	4	(27%)	2	(13%)	2	(13%)	8	(18%)
Headache	7	(47%)	3	(20%)	2	(13%)	12	(27%)
Hypoaesthesia	1	(7%)	0		0		1	(2%)
Psychomotor hyperactivity	0		0		1	(7%)	1	(2%)
Psychiatric disorders	3	(20%)	3	(20%)	1	(7%)	7	(16%)
Hallucination	0		0		1	(7%)	1	(2%)
Insomnia	3	(20%)	3	(20%)	0		6	(13%)
Restlessness	0		1	(7%)	0		1	(2%)
Respiratory, thoracic and mediastinal disorders	5	(33%)	2	(13%)	0		7	(16%)
Cough	1	(7%)	0		0		1	(2%)
Hoarseness	1	(7%)	0		0		1	(2%)
Nasal congestion	3	(20%)	1	(7%)	0		4	(9%)
Pharyngolaryngeal pain	2	(13%)	1	(7%)	0		3	(7%)
Respiratory tract congestion	1	(7%)	0		0		1	(2%)
Skin and subcutaneous tissue disorders	5	(33%)	0		0		5	(11%)
Dermatitis contact	5	(33%)	0		0		5	(11%)
Vascular disorders	1	(7%)	1	(7%)	1	(7%)	3	(7%)
Petechiae	1	(7%)	1	(7%)	1	(7%)	3	(7%)

There were statistically significant differences between the abrupt cessation and taper groups for QT changes and percent changes from Baseline to the Day 17/18 endpoint. The abrupt cessation group had an LSM increase of 20.70msec and the group that tapered had an LSM increase of 33.48msec (p=0.0094). The abrupt cessation group had an LSM percent increase of 5.43% and the group that tapered had an LSM percent increase of 8.81% (p=0.0075).

None of the subjects in this study exhibited QTcF increases from Baseline >60msec. However, eleven (33%) of the 30 subjects treated with guanfacine exhibited QTcF increases from Baseline >30msec.

	Treatment		
	A Abrupt Cessation	B Taper Down	Placebo
	N=15	N=12	N=11
Heart Rate (bpm)	-10.69 (4.55)	-13.46 (3.63)	-1.59 (4.73)
PR (msec)	-1.55 (6.50)	4.87 (8.60)	0.85 (5.14)
QRS (msec)	1.07 (2.88)	0.12 (3.21)	1.08 (2.59)
QT (msec)	20.92 (12.23)	32.95 (12.37)	1.68 (11.20)
QTcF (msec)	-1.20 (8.89)	2.08 (6.16)	-0.79 (6.79)

Results were first averaged by subject and day before summarization

REVIEWER COMMENTS:

1. In this study only PD measurements (ECGs, HR and blood pressure) were performed, and therefore, the PK/PD relationship could not be directly established. A prolongation of QTcF larger than 30 msec was observed in 30% of treated subjects. The sponsor's analysis of the QT data is not conclusive and the assumptions regarding the safety of guanfacine cannot be validated.
2. On the Day 17 of dosing with guanfacine, the decrease in DBP/SBP was 7-8/9-11mmHg at through measurement and pulse rate decreased by 10-12 bpm. This effect is normal for a drug which is approved for the treatment of hypertension but in the case of ADHD that may be the reason of dizziness (27%), headache (47%) and fatigue (40%) reported in adults participating in this study
3. Please see the pharmacometric (PM) review regarding the analyses of the drug safety.

4.1.2 A Phase I Study to Assess the Pharmacokinetics (PK) of SPD503 administered to Children and Adolescents aged 6-17 with Attention-Deficit/Hyperactivity Disorder (ADHD) (107)

Study number: SPD503-107
Study drug: SPD503, Guanfacine hydrochloride
Principal Investigator: Samuel W Boellner, MD
Study center: Clinical Study Centers, LLC Baptist Medical Towers One 9601 Lile Drive, Suite 900 Little Rock, AR 72205-6370
Study period: 01 Nov 2004 to 27 Dec 2004
Phase of development: Phase I

Objectives	Primary: To determine the PK of guanfacine in plasma after a single dose of 2mg and multiple doses of 2 and 4mg. Secondary: To assess the contribution of demographic subgroups in the study population on the PK of guanfacine. To evaluate the relationship between guanfacine plasma concentrations and measurements of vital signs (eg blood pressure and heart rate) and electrocardiograms (ECGs).
Study Design	An open-label, dose escalation PK study of SPD503 in children and adolescents diagnosed with ADHD. 1.*Screening/washout; 2. Check-in (Baseline);* *3.Open-label Treatment:* Single 2 mg dose of SPD503 on Day 1, PK collection up to 96 hours Multiple 2 mg doses of SPD503 from Day 5 on: PK (Day 13 to Day 15) Multiple 3mg doses of SPD503 daily on Days 16-22. PK trough sample on Day 23 Multiple 4mg doses of SPD503 daily on Days 23-29. PK samples on Day 28 *4.Down-Titration:* Multiple 3mg doses of SPD503 daily on Days 30 - 32. Multiple 2mg doses of SPD503 daily on Days 33 - 35.
Study Population	28 subjects were enrolled (14 children, aged 6-12 and 14 adolescents, aged 13-17, males and females).
Diagnosis and main criteria for admission	ADHD. Subjects with existing cardiac conditions (or a family history of significant cardiac conditions) or a history of seizures were excluded.
Investigational Drug	SPD503 (guanfacine hydrochloride) tablets manufactured by (b) (4) SPD503 1mg tablets Bulk Lot No.: 2026.001 Packaged Lot No.: FOB0001 SPD503 4mg tablets Bulk Lot No.: 2030.001 Packaged Lot No.: FOA0001 (A03055-014B01)
Dosage and Administration	Treatment A: a single oral dose of four (4) SPD503 1mg tablets administered with 240mL of water following a 10-hour fast. Treatment B: a single oral dose of one (1) SPD503 4mg tablet administered with 240mL of water following a high fat breakfast:
Sampling:	Predose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 48, 72, and 96 hours after

Blood	drug administration on Day 1. On Days 14 and 28: predose and 1, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hours after drug administration. An additional sample was collected on Day 23 (trough concentration for the 3 mg period). No PK samples during the downward titration.
Assay	HPLC with LS/MS/MS detection, chromatograms were shown.
PK Assessment	Cmax(ng/mL), Cmax/dose, Tmax (hr), AUC0-24(ng·hr/mL), AUC0-24/dose (ng·hr/mL/mg), CL/F, Vz/F
Safety (PD) Assessment	Systolic and diastolic BP, pulse, and sitting respiratory rate at all study visits. Twelve-lead ECGs were performed at Screening, the first Check-in (Day 0, for confirmation), predose, 5, 6, 8, and 24 hours postdose for each confinement period, on Day 23, and End of Study/Early Termination.
Statistical methods	Statistical analyses were performed on plasma data and PK parameters for each treatment condition and for subgroups of age, gender, and body weight. Changes in SBP, DBP, HR, and ECG (the QT interval was corrected using Fridericia's [QTcF] and Bazett's [QTcB] correction factors) vs plasma concentrations were explored graphically. The relationship between intensity of treatment-emergent sedative AEs and parameters of systemic exposure (Cmax and AUC0-t) was explored using Spearman's correlation coefficients. Rank statistics were applied to Cmax and AUC0-t and these ranks were correlated with the greatest intensity the subject experienced for the given treatment-emergent sedative AE.

Results

Demographics: A total of 28 subjects completed the study.

Table 6. Demographic Summary by Age and Overall for all Enrolled Subjects

		Children (N=14)	Adolescents (N=14)	Total (N=28)
Age (years)	n	14	14	28
	Mean (SD)	9.3 (1.82)	14.2 (1.05)	11.8 (2.90)
	Median	9.0	14.0	12.5
	Min, Max	7.0, 12.0	13.0, 16.0	7.0, 16.0
Gender	Male – n (%)	7 (50.0)	12 (85.7)	19 (67.9)
	Female – n (%)	7 (50.0)	2 (14.3)	9 (32.1)
Race	White – n (%)	9 (64.3)	12 (85.7)	21 (75.0)
	Black or African-American – n (%)	4 (28.6)	1 (7.1)	5 (17.9)
	Other – n (%)	1 (7.1)	1 (7.1)	2 (7.1)
Weight (lbs)	n	14	14	28
	Mean (SD)	76.6 (23.78)	125.9 (20.87)	101.2 (33.34)
	Median	64.5	125.0	108.0
	Min, Max	55.5, 132.0	86.5, 162.0	55.5, 162.0
Weight (lbs) Male	n	7	12	19
	Mean (SD)	79.5 (26.39)	127.6 (22.06)	109.9 (33.12)
	Median	75.0	126.0	115.0
	Min, Max	55.5, 132.0	86.5, 162.0	55.5, 162.0
Weight (lbs) Female	n	7	2	9
	Mean (SD)	73.6 (22.57)	115.5 (7.78)	82.9 (27.02)
	Median	64.0	115.5	65.0
	Min, Max	56.0, 116.0	110.0, 121.0	56.0, 121.0

Assay:

Plasma samples were analyzed for guanfacine using a validated liquid chromatograph-tandem mass spectrometry (LC/MS/MS) method.

Table 7: Assay Characteristics for Guanfacine

Parameter	Measure	Reviewer Comment
Linearity	0.05 ng/mL to 25ng/mL	Satisfactory
Precision (CV %)	≤ 8.6%	Satisfactory
Accuracy Between day	between -2.0% and 4.5%	Satisfactory
LLOQ	0.02ng/mL	Satisfactory
Specificity		Satisfactory

Pharmacokinetics of Pediatric vs. Adolescent Patients

After administration of a single 2mg dose on Day 1, mean exposure (Cmax and AUC0-∞) to guanfacine was higher in children (6-12 years) than in adolescents (13-17 years).

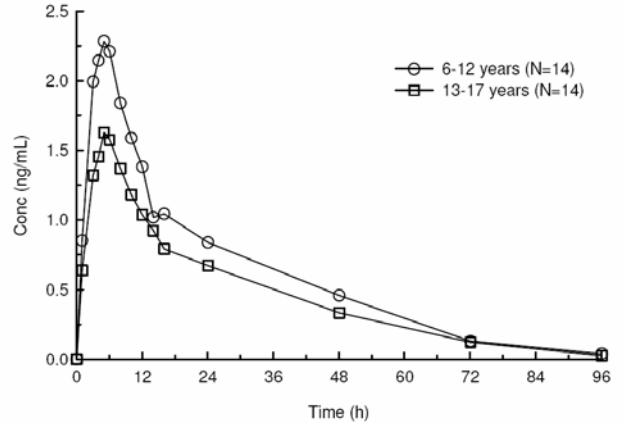


Figure 6. Mean plasma concentrations of guanfacine after oral administration of 2mg on Day 1 to pediatric (6-12 years) and adolescent (13-17 years) patients

The pediatric patients had about 30% lower CL/F and about 60% lower Vz/F.

Table 8. Summary of pharmacokinetic parameters for guanfacine after oral administration of 2mg on Day 1 to pediatric and adolescent patients

Parameter*	Pediatric (6-12 yrs) (N = 14)	Adolescents (13-17 yrs) (N = 14)
C_{max} (ng/mL)	2.55 ± 1.03	1.69 ± 0.43
t_{max} (h)	4.98 (2.93 - 8.43)	4.96 (3.97 - 6.00)
AUC_{0-t} (h•ng/mL)	56.9 ± 22.0	42.7 ± 12.9
$AUC_{0-\infty}$ (h•ng/mL)†	65.2 ± 23.9	47.3 ± 13.7
λ_z (h^{-1})†	0.0496 ± 0.0093	0.0428 ± 0.0153
$t_{½}$ (h)†	14.4 ± 2.39	17.9 ± 5.77
CL/F†		
(mL/min)	578 ± 215	754 ± 190
(mL/min/kg)	19.0 ± 8.08	13.3 ± 2.85
V_z/F†		
(L)	722 ± 326	1134 ± 343
(L/kg)	23.7 ± 11.9	19.9 ± 5.42

*Arithmetic mean ± standard deviation except for Tmax for which the median and range are reported.
†n for AUC_{∞}, λ_z, $t_{½}$, CL/F, and V_z/F = 9 for children 6-12 years and 12 for adolescents 13-17 years, respectively, due to the lack of a log-linear decay

Similar differences between pediatric an adolescent patients were observed after administration of 2mg and 4mg multiple doses. Mean plasma concentrations were higher in the younger patients, as were mean values for Cmax and AUC0-24.

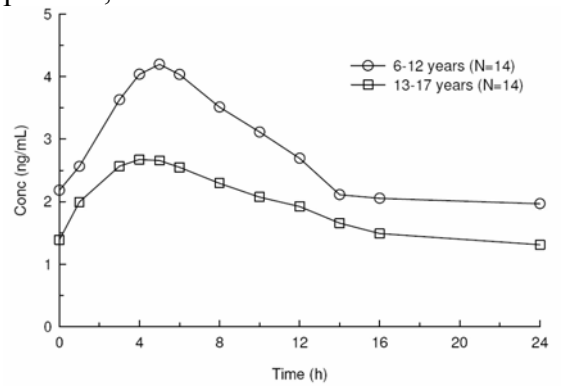


Figure 7. Mean plasma concentrations of guanfacine on Day 14 after oral administration of 2mg once daily to pediatric (6-12 years) and adolescent (13-17 years) patients

Table 9. Summary of pharmacokinetic parameters for guanfacine on Day 14 after oral administration of 2mg once daily to pediatric and adolescent patients.

Parameter*	Pediatric (6-12 yrs) (N = 14)	Adolescents (13-17 yrs) (N = 14)
C_{max} (ng/mL)	4.39 ± 1.66	2.86 ± 0.77
t_{max} (h)	4.98 (3.95 - 7.97)	4.53 (2.93 - 7.98)
AUC_{0-24} (h•ng/mL)	70.0 ± 28.3	48.2 ± 16.1
CL/F		
(mL/min)	552 ± 215	826 ± 486
(mL/min/kg)	15.3 ± 4.11	14.4 ± 8.34

The PK parameters calculated after the 4mg multiple doses of guanfacine were about twice higher than after the 2mg dose of drug confirming the linearity of guanfacine pharmacokinetics.

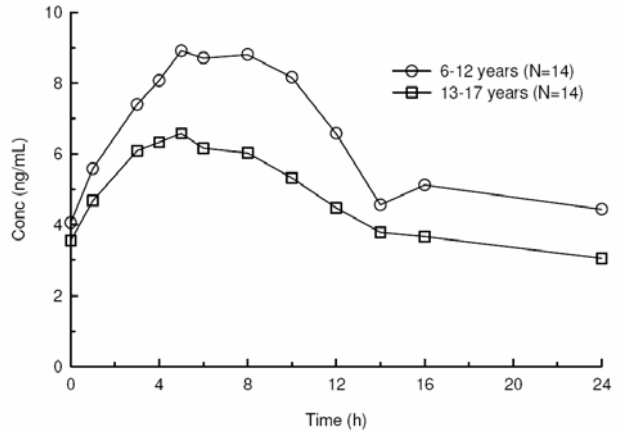


Figure 8. Mean plasma concentrations of guanfacine on Day 28 after oral administration of 4mg once daily to pediatric and adolescent patients.

Table 10. Summary of pharmacokinetic parameters for guanfacine on Day 28 after oral administration of 4mg once daily to pediatrics and adolescents

Parameter*	Pediatric (6-12 yrs) (N = 14)	Adolescents (13-17 yrs) (N = 14)
C_{max} (ng/mL)	10.1 ± 7.09	7.01 ± 1.53
t_{max} (h)	5.02 (3.97 - 10.3)	4.97 (1.00 - 7.97)
AUC_{0-24} (h•ng/mL)	162 ± 116	117 ± 28.4
CL/F (mL/min)	522 ± 212	607 ± 166
(mL/min/kg)	14.3 ± 3.70	10.7 ± 3.11

Effect of Gender on Guanfacine Pharmacokinetics

The mean plasma concentrations, Cmax and AUC values of guanfacine were about 30% higher in female patients than in male patients in the younger age group (Figure 9, Figure 10, and Figure 11). The differences in exposure were probably due to lower body weight in females compared with males (about 9% in this pediatric group). The gender differences in the older age group could not be evaluated because the distribution of males (n=12) vs. females (n=2) was not equal.

Table 11. Mean body weight by gender of the pediatrics and adolescents

Age Group	Weight (lb)*	
	Males	Females
6-12 years	83.0 ± 28.5 (7)	75.3 ± 22.3 (7)
13-17 years	129 ± 21.0 (12)	119 ± 8.84 (2)

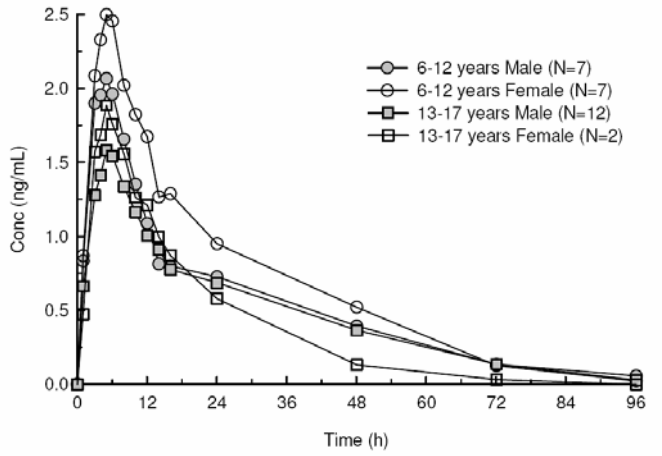


Figure 9. Mean.plasma concentrations of guanfacine by gender after oral administration of 2mg on Day 1 to pediatric and adolescent patients

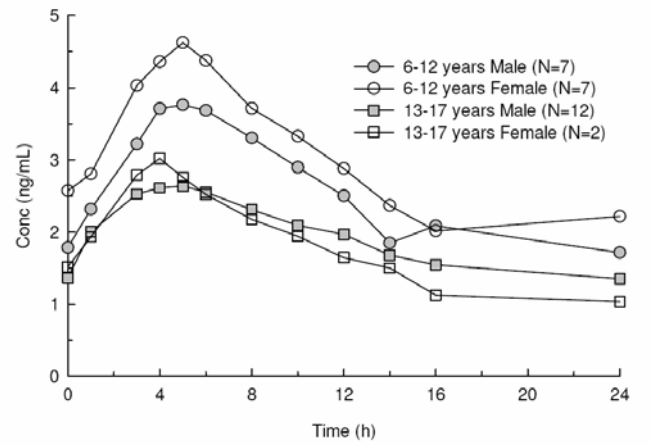


Figure 10. Mean plasma concentrations of guanfacine by gender on Day 14 after oral administration of 2mg once daily to pediatric and adolescent patients.

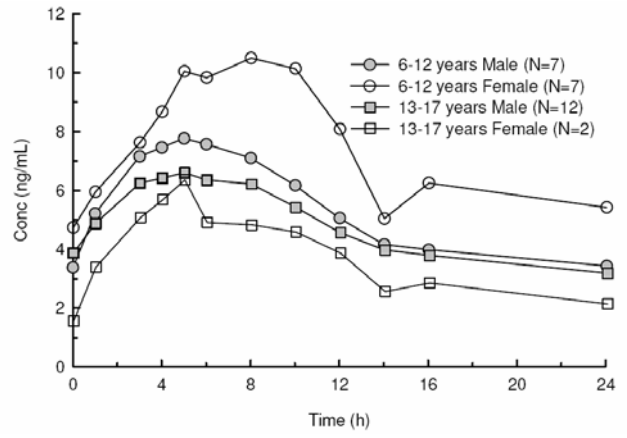


Figure 11. Mean plasma concentrations of guanfacine by gender on Day 28 after oral administration of 4mg once daily to pediatric and adolescent patients.

The effect of body weight on Cmax and AUC are shown in Figures below.

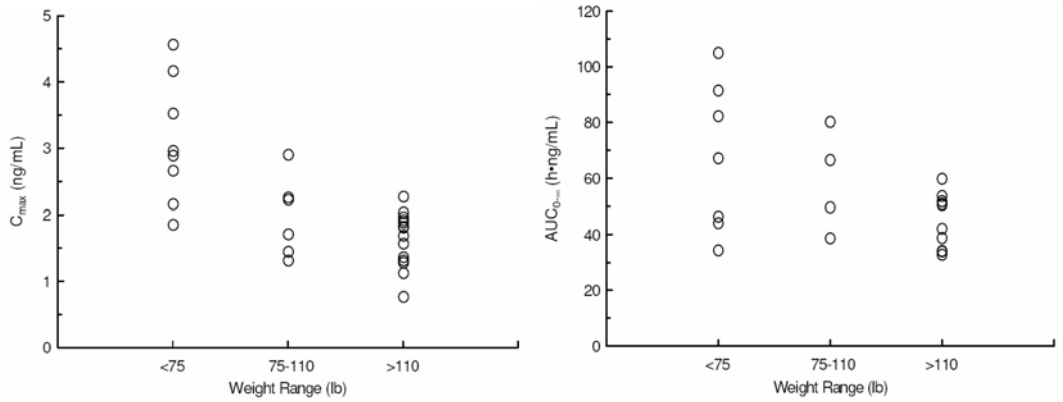


Figure 12. Individual patient SPD503 Cmax and AUC values after oral administration of 2mg on Day 1 to pediatric and adolescent patients.

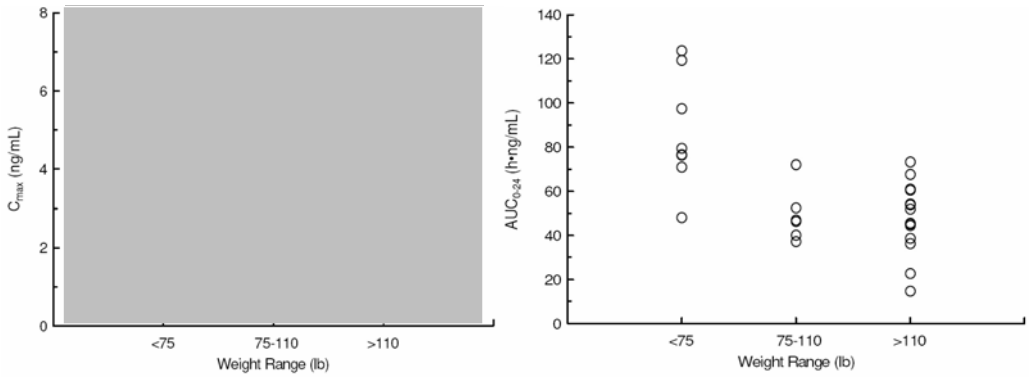


Figure 13. Individual patient SPD503 Cmax and AUC values after oral administration of 2mg on Day 14 to pediatric and adolescent patients

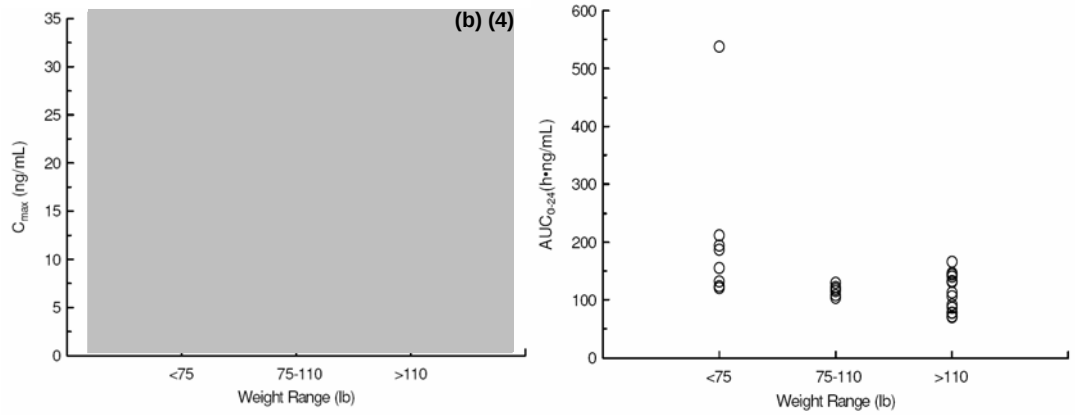


Figure 14. Individual patient SPD503 Cmax and AUC values after oral administration of 4mg on Day 28 to pediatric and adolescent patients

The graphic exploration of the data from all 3 periods of the study indicates that there is a trend to a decrease of exposure to guanfacine with the increase of body weight.

The correlations between guanfacine plasma concentrations and pharmacodynamic measurements (blood pressure, ECGs, QT, QTc Fridericia or Bazett and adverse events), were evaluated graphically.

COMMENTS:

1. The sponsor did not attempt to perform any analysis of the PK data in order to evaluate the statistical significance of the influence of body weight and/or gender on the pharmacokinetics of guanfacine.
2. Based on the information from the plots of the changes in blood pressure (systolic and diastolic), QT measurements (QT and Fridericia or Bazett corrected QT) vs. guanfacine plasma concentrations, the sponsor concluded that there were no apparent correlations. No data analyses were performed.
3. The time course of the effect (change of BP and QTc) was not evaluated.
4. Please see the PM review for the safety vs exposure evaluations.

4.1.3 A Phase 1 Study to Investigate the Effect of Food on the Pharmacokinetics of SPD503 in Healthy Volunteers (104)

Study number: SPD503-104
Study drug: SPD503, Guanfacine hydrochloride
Investigator(s): Investigator: (b) (4)
Study center: (b) (4)
Study period: 25 October 2004 to 15 December 2005
Phase of development: Phase I

Objectives	Primary: to assess the effect of food on the bioavailability of a single 4mg (1 x 4mg) dose of SPD503. Secondary: to assess the bioequivalence of a single 4mg (1 x 4mg) tablet of SPD503 compared to four 1mg (4 x 1mg) tablets of SPD503 and to evaluate the safety and tolerability of a 4mg dose of SPD503.
Study Design	A randomized, open-label, single-dose, 3-period crossover design. Following an overnight fast of at least 10 hours, subjects received a 4mg 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). After the PK and safety assessments (48 hours post-dose) subjects were to return at 72 and 96 hours post-dose. Following a minimum 7-day washout, subjects returned for Periods 2 and 3 when they were crossed over to an alternate treatment (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).
Study Population	Forty-eight healthy male and female subjects (18-55 years old), two groups of 24 each.
Investigational Drug	SPD503 (guanfacine hydrochloride) tablets manufactured by (b) (4) SPD503 1mg tablets Bulk Lot No.: 2026.001 Packaged Lot No.: FOB0001 SPD503 4mg tablets Bulk Lot No.: 2030.001 Packaged Lot No.: FOA0001 (A03055-014B01)
Dosage and Administration	Treatment A: a single oral dose of four (4) SPD503 1mg tablets administered with 240mL of water following a 10-hour fast. Treatment B: a single oral dose of one (1) SPD503 4mg tablet administered with 240mL of water following a high fat breakfast:
Sampling: Blood	Blood draws were taken at pre-dose (0 hour), 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 18, 24, 48, 72 and 96 hours post-dose.
Assay	HPLC with LS/MS/MS detection (Table), chromatograms were shown.
PK Assessment	Cmax(ng/mL), Cmax/dose, Tmax (hr), AUC0-24(ng·hr/mL), AUC0-24/dose (ng·hr/mL/mg), Cmin (ng/mL), Cmin/dose (ng/mL/mg), Cavg (ng/mL), Cavg/dose (ng/mL/mg), FL, MRT0-24 (hr)
PD Assessment	NA
Statistical methods	Summary statistics were presented for SPD503 plasma concentration data and the derived PK parameters by dose group and dietary status. The derived PK parameters, AUC0-t, AUC0-8 and Cmax, were statistically analyzed. The log-transformed AUC0-t, AUC0-8 and Cmax data from all

	three periods were analyzed using a general linear model in order to assess if the pharmacokinetics of SPD503 are affected by dietary status and if 4 x 1mg SPD503 was dose equivalent to 1x 4mg SPD503. The model included terms for sequence, subject within sequence, period and dose group and dietary status (1 x 4mg fasted, 1 x 4mg fed and 4 x 1mg fasted). All terms were fitted using fixed effects. Point estimates and 90% confidence intervals (CI) for the ratios of the 1 x 4mg fed/1 x 4mg fasted means were provided. Dose equivalence was assessed using the same model outlined above. Point estimates and 90% CI for the ratios of the 4 x 1mg fasted/1 x 4mg fasted means were provided.
Safety Assessment	Vital signs were taken pre-dose (0 hour), 6, 7, 8, 10, 24, 48, 72 and 96 hours post-dose. ECGs were also collected pre-dose (0 hour), 6, 7, 8, 10 and 96 hours post-dose.

Results

Demographics: A total of 42 subjects completed the study.

Table 12. Demographic Characteristics

Age (yr)	N	48	
	Mean (SD)	35.1	(11.6)
	Median (Min, Max)	34.0	(19, 55)
Frame, n(%)	Small	8	(17%)
	Medium	27	(56%)
	Large	13	(27%)
Race, n(%)	Black	2	(4%)
	Caucasian	10	(21%)
	Hispanic	35	(73%)
	Mixed	1	(2%)
Sex, n(%)	Female	32	(67%)
	Male	16	(33%)
Weight (lb)	N	48	
	Mean (SD)	163.8	(35.5)
	Median (Min, Max)	158.5	(111, 269)
Height (in)	N	48	
	Mean (SD)	65.5	(3.8)
	Median (Min, Max)	65.5	(58, 73)

Assay: Determination of the plasma concentration of guanfacine in the clinical samples following liquid-liquid extraction was performed by HPLC with detection by tandem mass spectrometry (MS/MS).

Table 13: Assay Characteristics for Guanfacine

Parameter	Measure	Reviewer Comment
Linearity	0.05 ng/mL to 25 ng/mL	Satisfactory
Precision (CV %)	$\leq$ 5.0%	Satisfactory
Accuracy Between day	between -3.6% and 2.7%	Satisfactory
LLOQ	0.05ng/mL	Satisfactory
Specificity		Satisfactory

Effect of food on bioavailability of SPD503

The coadministration of the 4mg SPD503 tablet with food significantly increased of exposure to guanfacine (Figure 15).

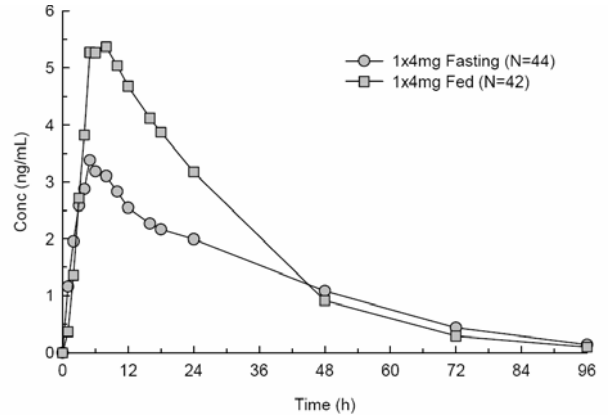


Figure 15. Mean Plasma Concentrations of Guanfacine After Oral Administration of Single 4mg Doses as 1x4mg Tablets Under Fed and Fasting Conditions to Healthy Subjects.

The pharmacokinetic parameters for guanfacine for two treatments compared in Table below.

Table 14. Summary of Pharmacokinetic Parameters for Guanfacine After Oral Administration of Single 4mg Doses as 1x4mg Tablets Under Fed and Fasting Conditions to Healthy Subjects

Parameter*	1x4mg Fed (N = 42)	1x4mg Fasting (N = 44)
C_{max} (ng/mL)	5.92 ± 1.42	3.56 ± 1.32
t_{max} (h)	6.02	5.01
	(4.00 - 24.1)	(3.00 - 48.0)
AUC_{0-t} (h•ng/mL)	161 ± 48.4	120 ± 47.1
$AUC_{0-\infty}$ (h•ng/mL)†	164 ± 50.1	125 ± 51.0
λ_z (h^{-1})†	0.0489 ± 0.0083	0.0456 ± 0.0098
$t_{½}$ (h)†	14.6 ± 2.43	16.0 ± 4.15
CL/F†		
(mL/min)	445 ± 141	617 ± 234
(mL/min/kg)	5.98 ± 1.94	8.35 ± 3.31
VZ/F†		
(L)	557 ± 195	833 ± 322
(L/kg)	7.40 ± 2.25	11.1 ± 4.04

*Arithmetic mean ± standard deviation except for t_{max} for which the median and range are reported.
†n for $AUC_{0-\infty}$, λ_z, $t_{½}$, CL/F and Vz/F = 41 for 1×4mg Fasting due to the lack of a log-linear decay

The geometric mean ratio, fed-to-fasting, was 175% for Cmax and 138% for AUC.

Table 15. Statistical Comparison of Pharmacokinetic Parameters for Guanfacine After Oral Administration of Single 4mg Doses as 1x4mg Tablets Under Fed and Fasting Conditions to Healthy Subjects

Parameter	Geometric Mean Ratio (%)*			
	Estimate	90% Confidence Interval		
C_{max}	174.57	161.56	→	188.62
AUC_{0-t}	138.94	129.09	→	149.54
$AUC_{0-\infty}$	137.27	127.02	→	148.34

*Ratio of fed to fasting. Based on analysis of natural log-transformed data.

Bioequivalence of 1mg and 4mg tablets

The mean plasma concentrations of guanfacine after administration of 4 x 1mg and 1 x 4mg tablets were very similar (Figure 16) and the statistical assessment concluded that these treatments are bioequivalent.

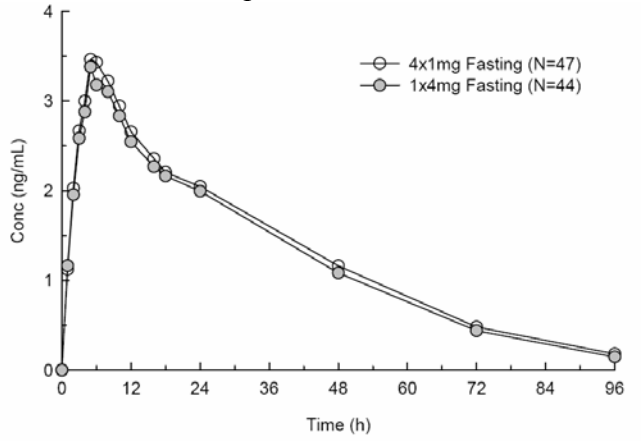


Figure 16. Mean Plasma Concentrations of Guanfacine after Oral Administration of Single 4mg Doses as 4x1mg and 1x4mg Tablets Under Fasting Conditions to Healthy Subjects

Table 16. Pharmacokinetic Parameters for Guanfacine After Oral Administration of Single 4mg Doses as 4x1mg and 1x4mg Tablets

Parameter*	4x1mg Fasting (N = 47)	1x4mg Fasting (N = 44)
C_{max} (ng/mL)	3.63 ± 1.15	3.56 ± 1.32
t_{max} (h)	5.01 (3.01 - 10.0)	5.01 (3.00 - 48.0)
AUC_{0-t} (h•ng/mL)	126 ± 43.8	120 ± 47.1
$AUC_{0-\infty}$ (h•ng/mL)†	133 ± 55.5	125 ± 51.0
λ_z (h^{-1})†	0.0430 ± 0.0097	0.0456 ± 0.0098
$t_{½}$ (h)†	17.4 ± 6.26	16.0 ± 4.15
CL/F†		
(mL/min)	564 ± 176	617 ± 234
(mL/min/kg)	7.63 ± 2.34	8.35 ± 3.31
VZ/F†		
(L)	803 ± 246	833 ± 322
(L/kg)	10.8 ± 2.90	11.1 ± 4.04

Table 17. Statistical Comparison of Pharmacokinetic Parameters for Guanfacine After Oral Administration of Single 4mg Doses as 4x1mg and 1x4mg Tablets Under Fasting Conditions to Healthy Subjects.

Parameter	Geometric Mean Ratio (%)*			
	Estimate	90% Confidence Interval		
C_{max}	101.59	94.08	→	109.70
AUC_{0-t}	106.11	98.65	→	114.14
$AUC_{0-\infty}$	106.97	98.83	→	115.77

REVIEWER COMMENTS:

1. Food had a significant effect on the pharmacokinetics of guanfacine. Administration of SPD503 with a high-fat meal resulted in a 75% increase in Cmax and 38% increase in AUC. The patients should be cautioned in the label to take medication at least 1hour prior to breakfast. The same conclusion was drawn in the pharmacometric review in order to minimize the risk of greater prolongations in QT and decreases in blood pressure, heart rate.
2. The mean values for Cmax, AUC0-t and AUC0-∞ were similar, the 90% CI for the geometric mean ratios, 4 x 1mg-to-1 x 4mg, were within the 80% -125% equivalence window. Thus, SPD503 given as 1 x 4mg tablet is bioequivalent to 4 x 1mg tablets.

4.1.4 A Phase 1, Open-Label, Single-Sequence, Crossover Study to Evaluate the Effect of Ketoconazole on the Pharmacokinetics of SPD503 in Healthy Adult Subjects (106)

Study number: SPD503-106
Name of active ingredient: SPD503, Guanfacine hydrochloride
Investigator: (b) (4)
Study center(s) (b) (4)
Study period: 08 July 2004 to 20 August 2004
Phase of development: Phase I

Objectives	Primary: to assess the effect of ketoconazole on the pharmacokinetics of a single 4mg dose of SPD503. Secondary: to evaluate the safety and tolerability of a 4mg dose of SPD503 when given concurrently with ketoconazole.
Study Design	A one-sequence crossover design. The study consisted of the following phases: screening, baseline, treatment Periods 1 and 2. Study Day -1 (Period 1) baseline assessments: vital signs, urine samples, blood for pregnancy test, and concomitant medications, ECGs. Day 1, Period 1: a single 4mg dose of SPD503 with PK blood sampling through 96 hrs. Days 8-14, Period 2: ketoconazole 400mg QD for a total of 6 days. A single 4mg dose of SPD503 was coadministered on Day 10.
Study Population	Twenty healthy male and female subjects (18-55 years old)
Investigational Drug Reference Drug	SPD503 (guanfacine hydrochloride) tablets manufactured by (b) (4) SPD503 4mg tablets Lot No.: 2030.001 Ketoconazole 200mg tablets, USP, immediate release manufactured by (b) (4). Lot No.: 51681
Sampling: Blood	SPD503: pre-dose (0 hour), 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 18, 24, 48, 72 and 96 hours post-dose on Day 1 and Day 10. Ketoconazole: trough Days 10, 11, 12.
Assay	HPLC with LS/MS/MS detection (Table), chromatograms were shown.
PK Assessment	Cmax(ng/mL), Cmax/dose, Tmax (hr), AUC0-24(ng·hr/mL), AUC0-24/dose (ng·hr/mL/mg), Cmin (ng/mL), Cmin/dose (ng/mL/mg), Cavg (ng/mL), Cavg/dose (ng/mL/mg), FL, MRT0-24 (hr)
Statistical methods	The $\log_e$-transformed AUC0-t, AUC0-8 and Cmax data were analyzed using a general linear model. The model included terms for period and subject. Point estimates and 90% confidence intervals (CIs) for the ratios of the treatment means (SPD503 with ketoconazole/SPD503 alone) were provided.

Assay:
Determination of the plasma concentration of guanfacine in the clinical samples following liquid-liquid extraction was performed by HPLC with detection by tandem mass spectrometry (MS/MS).

Table 18. Assay for Guanfacine

Parameter	Measure	Reviewer Comment
Linearity	0.05 to 25 ng/mL	Satisfactory
Precision (CV %)	≤ 4.9%	Satisfactory
Accuracy Between day	between -2.4% and 1.1%	Satisfactory
LLOQ	0.05ng/mL	Satisfactory
Specificity		Satisfactory

Plasma ketoconazole concentrations were determined by (b) (4) using a validated HPLC method with solid phase extraction and fluorescence detection.

Table 19. Assay for Ketoconazole

Parameter	Measure	Reviewer Comment
Linearity	0.04 to 8.0 mcg/mL	Satisfactory
Precision (CV %)	≤ 6.9%	Satisfactory
Accuracy Between day	Between -7.57 and -2.25%	Satisfactory
LLOQ	0.04mcg/mL	Satisfactory
Specificity		Satisfactory

Results:

Demographics: Twenty (20) subjects enrolled into and completed the study.

Table 20. Subject Demographics

Characteristic		All Subjects Treated (N=20)
Age (yr)	N	20
	Mean (SD)	29 (8)
	Median (Min, Max)	27 (19, 50)
Race, n(%)	Black	2 (10.0%)
	Caucasian	4 (20.0%)
	Hispanic	14 (70.0%)
Sex, n(%)	Female	13 (65.0%)
	Male	7 (35.0%)
Weight (lb)		
	Mean (SD)	162 (35.2)
	Median (Min, Max)	160 (99.5, 229)
Height (in)		
	Mean (SD)	65 (4.4)
	Median (Min, Max)	64 (57, 73)

Pharmacokinetics

The individual subject plasma ketoconazole concentrations on Study Days 10 through 12 are illustrated in Figure 17.

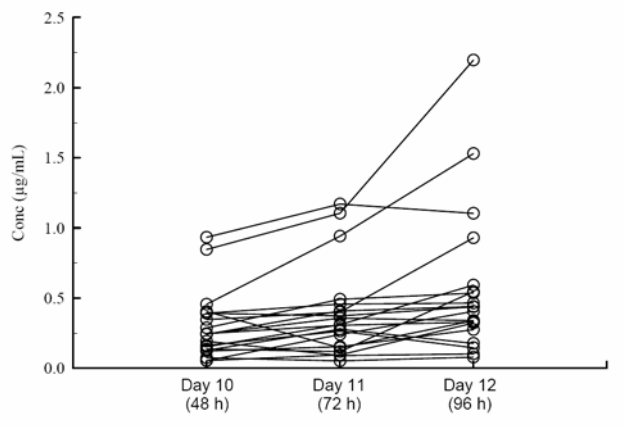


Figure 17. Individual Subject Plasma Concentrations of Ketoconazole on Study Days 10, 11, And 12 After Oral Administration of 400mg Once Daily (QD) On Study Days 8 Through 13

For the majority of subjects, plasma concentrations were consistent within each subject, indicating that steady state had been reached.

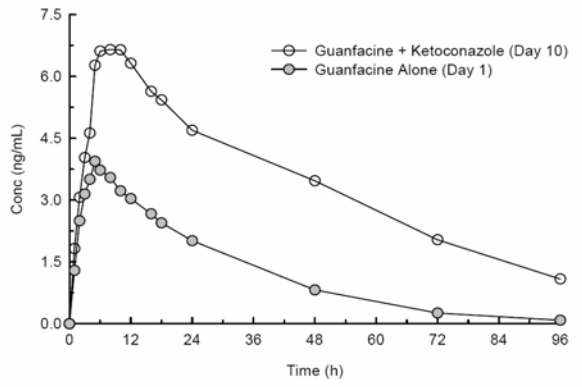


Figure 18. Mean Plasma Concentrations of Guanfacine. Closed circles – Guanfacine alone. Open circles - Guanfacine coadministered with ketoconazole.

Table 21. Summary of Guanfacine PK parameters

Parameter*	Guanfacine Alone (N=20)	Guanfacine + Ketoconazole (N=20)
C_{max} (ng/mL)	4.14 ± 1.58	7.29 ± 2.90
t_{max}	5.00	7.00
AUC_{0-t} (h•ng/ml)	117 ± 43.3	330 ± 134
$AUC_{0-\infty}$ (h•ng/mL)	120 ± 44.9	367 ± 158
λz (h^{-1})	0.0509 ± 0.0101	0.0270 ± 0.0051
$t_{1/2}$ (h)	14.2 ± 3.31	26.7 ± 5.72
CL/F (mL/min)	654 ± 251	242 ± 112
Vz/F (L)	775 ± 249	554 ± 269

*Arithmetic mean ± standard deviation except for t_{max} for which the median is reported.
N=18 for $AUC_{0-\infty}$, λ_z, $t_{1/2}$, CL/F and Vz/F

Table 22. Statistical Comparison of Pharmacokinetic Parameters for Guanfacine Administered Alone and Coadministered with Ketoconazole

Parameter	Ratio (%)*		
	Estimate	90% Confidence Interval	
		Lower Limit	Upper Limit
C_{max}	174.54	145.65	209.17
AUC_{0-t}	278.59	227.53	341.11
$AUC_{0-\infty}$	313.13	251.69	389.56

*Geometric mean ratio of guanfacine along to guanfacine plus ketoconazole. Based on analysis of natural log-transformed data.

CONCLUSION:

Coadministration of ketoconazole significantly increased the exposure to guanfacine: its Cmax increased 1.7 fold, AUC0-t increased 2.8 fold and AUC0-∞ increased 3.1 fold.

REVIEWER COMMENTS:

1. Concomitant intake of guanfacine with other drugs that inhibit CYP3A4/5 activity will likely to result in an increase of plasma levels of guanfacine, potentially leading to unwanted pharmacodynamic effects.
2. In the label, the sponsor proposed to reduce the dose of (b) (4) when it is concomitantly administered with CYP3A4/5 inhibitors. However, no dose adjustment scheme was proposed by the sponsor. Since the elevation of plasma concentrations of guanfacine may cause greater prolongations in QT and decreases in blood pressure and heart rate, the reviewer recommends to avoid the concomitant administration of guanfacine with the CYP3A4/5 inhibitors.

4.1.5 A Phase 1, Open-Label, Single-Sequence, Crossover Study to Evaluate the Effect of Rifampin on the Pharmacokinetics of SPD503 in Healthy Adult Subjects (108)

Study number: SPD503-108
Study drug SPD503, Guanfacine hydrochloride
Investigator: (b) (4)
Study center(s): (b) (4)
Study centers: 1
Study period: 13 August 2004 to 1 September 2004
Clinical phase: I

Objectives	Primary: to assess the effect of rifampin on the pharmacokinetics of a single 4mg dose of SPD503. Secondary: to evaluate the safety and tolerability of a 4mg dose of SPD503 when given concurrently with rifampin.
Study Design	A single-sequence crossover study. Screening: two weeks prior to entry. Baseline: Day -1 (Period 1). Treatment Periods 1, Days 1-7: a single 4mg dose of SPD503 on Day 1 with PK blood sampling through Day 5. Period 2, Days 8-19: dose of rifampin 600mg/day in the morning for a total of 11 consecutive days. A single 4mg dose of SPD503 was coadministered on the eighth day of rifampin dosing (Study Day 15). Blood samples for rifampin trough concentration determination were collected predose on Study Days 13-16. PK blood sampling for SPD503 was collected on Study Days 15-19. Subjects were released from the clinic on Study Day 19 after the 96-hr blood sample collection and study completion procedures were completed.
Study Population	Healthy adult males and females aged 18-55 years (yrs) inclusive, Planned: 20 subjects, 19 subjects completed the study.
Diagnosis and main criteria for admission	Screening blood pressure within normal range (<140mmHg systolic/<90mmHg diastolic) and a screening ECG within normal range. Subjects with any cardiac conditions or family history were excluded.
Investigational Drug	SPD503, Guanfacine hydrochloride, extended-release (XR) 4mg tablets manufactured by (b) (4) Lot No.: EOA0001
Reference therapy	Rifampin, USP, 300 mg capsules; manufactured by (b) (4); Lot No. 030997, expiration date: October 2006 and Lot No. 031552, expiration date March 2007.
Dosage and Administration	SPD503 was administered at Hour 0 on Day 1 and Day 15 after an overnight fast of not less than 10hrs (4 mg tablet). Subjects continued to fast for 4hrs following SPD503 dosing. Rifampin was administered at Hour 0 (approximately 0700) on Days 8-18 after a fast of not less than 2hrs (2 x 300mg capsules). Subjects continued to fast for one hour following rifampin dosing.
Sampling: Blood	Guanfacine HCL Day 1 and Day 8, respectively): Hour 0 (predose) and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 18, 24, 48, 72 and 96hrs postdose. Days 15-19 for plasma concentrations of guanfacine HCL. Rifampin trough plasma samples were obtained on Study Days 13-16.
Assay	Guanfacine HCl: HPLC with LS/MS/MS detection.

	Rifampin and desacetyl rifampin: HPLC with LC/MS/MS method after solid phase extraction, LLOQ 50.0ng/mL. Chromatograms were shown.
PK Assessment	AUC0-t, AUC0-∞, Cmax, Cmin, t1/2, Tmax, FI CL/F, Vz/F computed using non-compartmental analysis
PD Assessment: 12 lead ECG measurements	Visits 1, 3, and 11: pre-dose and prior to blood sample collection at hours 3, 4, 6, 8 and 10 hours post-dose, Visits 2, 4, 6, 9, and 12: pre-dose, Visits 5, 7, 8, 10, 13 -16: pre-dose and 3, 4, 6, 7, and 8 hours post-dose
Statistical methods	The log-transformed AUC0-t, AUC0-8 and Cmax data were analyzed using a general linear model. The model included terms for period and subject. Point estimates and 90% confidence intervals (CI) for the ratios of the treatment means (SPD503 with rifampin/SPD503 alone) were provided.

Results

Assay:

Plasma samples were analyzed for guanfacine using a validated liquid chromatograph-tandem mass spectrometry (LC/MS/MS) method.

Parameter	Measure	Reviewer Comment
Linearity	0.05 ng/mL to 25ng/mL	Satisfactory
Precision (CV %)	≤ 8.5%	Satisfactory
Accuracy Between day	between 3.3% and 2.4%	Satisfactory
LLOQ	0.02ng/mL	Satisfactory
Specificity		Satisfactory

The characteristics of rifampine assay were not present, LLOQ was 50 ng/mL for both rifampine and its metabolite.

Demographics

The demographic characteristics are shown below.

Characteristic		All Subjects Treated (N=20)	
Age (yr)	Mean (SD)	34	(11.2)
	Median (Min, Max)	33	(18, 53)
Race, n(%)	Black	1	(5.0%)
	Caucasian	6	(30.0%)
	Hispanic	13	(65.0%)
Sex, n(%)	Female	8	(40.0%)
	Male	12	(60.0%)
Weight (lb)	Mean (SD)	168	(30.7)
	Median (Min, Max)	166	(117, 244)
Height (in)	Mean (SD)	67	(4.0)
	Median (Min, Max)	66	(61, 75)

Pharmacokinetics

The administration of guanfacine after treatment with rifampin 600mg once daily (QD) for 7 days resulted in a substantial decrease in its exposure, (Rifampin is an inducer of CYP3A4/5, of which guanfacine is a substrate). The mean Cmax of guanfacine decreased from 3.46 to 1.64ng/mL, while mean AUC0-t and AUC0-8 decreased from 111 to 36.5h•ng/mL and from 116 to 39.9h•ng/mL.

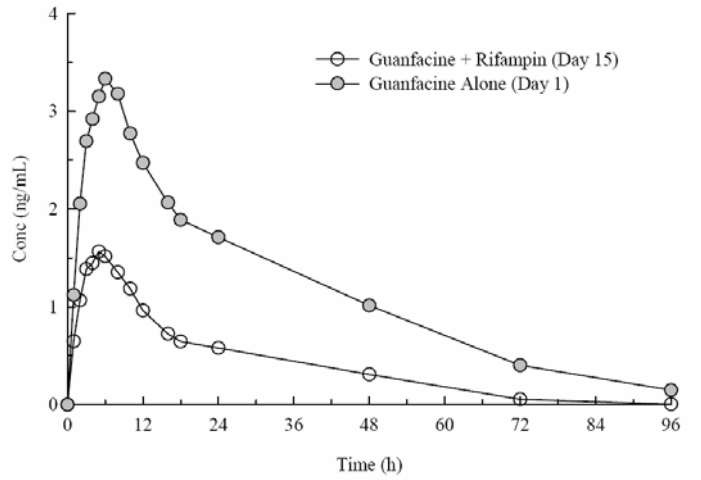


Figure 19. Mean Plasma Concentrations of Guanfacine After Oral Administration of Single 4mg Doses on Day 1 (Alone) and Day 15 (After Rifampin 600mg Once Daily for 7 Days) to Healthy Subjects

The mean guanfacine CL/F increased more than 3-fold.The actual increase in CL may be greater, however, as the induction of CYP3A4/5 may have also decreased the fraction absorbed (F) by increasing first-pass metabolism. Vz/F increased more than 2-fold. The elimination t½, decreased by approximately 20% from a mean of 16.2h for guanfacine alone to 12.7h after treatment with rifampin.

Table 23. Summary of Pharmacokinetic Parameters for Guanfacine after Oral Administration of Single 4mg Doses on Day 1 (Alone) and Day 15

Parameter[1]	Guanfacine Alone (N=19)	Guanfacine + Rifampin (N=19)
C_{max} (ng/mL)	3.46 ± 0.91	1.64 ± 0.59
t_{max}	6.00	5.00
AUC_{0-t} (h•ng/ml)	112 ± 34.6	36.5 ± 14.5
$AUC_{0-\infty}$ (h•ng/mL)	119 ± 39.5	39.9 ± 16.0
λz (h^{-1})	0.0449 ± 0.0099	0.0649 ± 0.0287
$t_{1/2}$ (h)	16.5 ± 5.23	12.7 ± 5.80
CL/F (mL/min)	644 ± 201	2,356 ± 1,733
Vz/F (L)	881 ± 250	2,304 ± 1,285

The geometric mean ratios, guanfacine+rifampin to guanfacine alone, for Cmax, AUC0-t and AUC0-8 were 45.6%, 31.1% and 37.2%, respectively).

Table 24. Statistical Comparison of Pharmacokinetic Parameters for Guanfacine After Oral Administration of Single 4mg Doses on Day 1 (alone) and Day 15 (after Rifampin 600mg Once Daily for 7 Days) to Healthy Subjects

Parameter	Ratio (%)[1]	
	Estimate	90% Confidence Interval
C_{max}	45.64	38.75 → 53.75
AUC_{0-t}	30.92	25.22 → 37.92
$AUC_{0-\infty}$	37.19	23.84 → 58.03

REVIEWER COMMENTS

1. Coadministration with rifampin significantly decreases exposure to guanfacine with a decrease in Cmax of more than 50%, AUC0-t by 60% and AUC0-∞ by 70%.
2. Concomitant intake of guanfacine with drugs that induce CYP3A4/5 activity (rifampin) is likely to result in lower than normal plasma levels of guanfacine, potentially leading to a decrease in pharmacodynamic effects.
3. Although the ECG measurements were performed, the sponsor did not analyzed the results and therefore, did not attempt to correlate the effect with plasma concentrations.
4. The sponsor proposed in the label to increase the dose of (b) (4) within the recommended dose range when patients are taking (b) (4) concomitantly with a CYP3A4 inducer. Since the dose of guanfacine is always titrated in the clinic to the desirable effect (the dose range covers 4-fold), the reviewer considers that the up titration of guanfacine dose is reasonable up to highest dose of 4 mg QD.

4.1.6 A Phase I, Pharmacokinetic Study in Healthy Volunteers to Assess the Bioequivalence of SPD503 2mg and 4mg Tablets Manufactured at (b)(4) and SUMI Following a Single Dose Each of 2mg and 4mg (103)

Study number: SPD503-103 Study drug: SPD503, guanfacine hydrochloride
Investigators: Principal Investigator: Magdy Shenouda, MD
Study centre(s): MDS Pharma Services 1930 Heck Avenue Building 2 Neptune, NJ 07753
Study period: 04 January 2004 to 24 February 2004
Phase of development: I

Objectives	Primary: evaluate the bioavailability and to assesss the bioequivalence of SPD503 tablets manufactured at the current manufacturing site and a potential new site following single doses of 2mg and 4mg.
Study Design	An open-label, single-dose, 4-treatment (two dosing sequence groups), 2-treatment period, randomized, crossover study. Screening: within 2 weeks prior to randomization. Baseline: at Day 0. Treatment Periods 1 and 2: Subjects were randomly assigned to one of two dosing sequence groups. Each of the subjects received their assigned treatment after an overnight fast during the first treatment period and then was crossed over to the alternate treatment for the second treatment period.

Dosing Sequence	Treatment Period 1 Day 1	Treatment Period 2 Day 1
1 (N=10)	(b)(4) 2mg PO once	SUMI 2mg PO once
2 (N=10)	SUMI 2mg PO once	(b)(4) 2mg PO once
3 (N=10)	(b)(4) 4mg PO once	SUMI 4mg PO once
4 (N=10)	SUMI 4mg PO once	(b)(4) 4mg PO once

Study Population	Healthy adult males and females aged 18-55 years (yrs) inclusive, Planned: 40 subjects, 40 subjects completed the study.
Diagnosis and main criteria for admission	Screening blood pressure within normal range (<130mmHg systolic/<85mmHg diastolic) and a screening ECG within normal range. Subjects with any cardiac conditions or family history were excluded.
Investigational Drug	SPD503 (Guanfacine Hydrochloride), an extended-release tablet formulation **Treatment A:** SPD503 2mg tablets Manufactured by (b)(4) on 10/15/ 2002 **Treatment B:** SPD503 2mg tablets Manufactured by SUMI 9/5/2003 **Treatment C:** SPD503 4mg tablets Manufactured by (b)(4) 10/18/ 2002 **Treatment D:** SPD503 4mg tablets Manufactured by SUMI 9/6/ 2003
Test Treatment	The test products were SPD503 2mg SUMI (Treatment B), Lot number B03052; and SPD503 4mg SUMI (Treatment D), Lot number B03053, administered orally.
Reference therapy	SPD503 2mg (b)(4) (Treatment A), Lot No. B03050 and SPD503 4mg (b)(4) (Treatment C), Lot number B03051.
Sampling: Blood	Predose) and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 18, 24, 48, 72 and 96hrs postdose.
Assay	HPLC with LS/MS/MS detection. Chromatograms were shown.
PK Assessment	AUC0-t, AUC0-∞, Cmax, Cmin, t1/2, Tmax, FI CL/F, Vz/F,

	non-compartmental analysis
Statistical methods	A parametric general linear model. Analysis of variance (ANOVA) for a 2-way crossover design. The model included: sequence, subject-within-sequence, period and manufacturer. The sequence effect was tested using the subject-within-sequence effect, and all other effects were tested using the residual error of the model. A null hypothesis of zero difference in a parameter under consideration between the two manufacturers was assessed at the 0.05 level, with the alternative hypothesis of non-zero differences.
Bioequivalence statistics:	The log-transformed AUC0-t, AUC0-8 and Cmax data were analyzed using a general linear model.

Table 25 Lot Information

Drug	Bulk lot #	Manufacturer	Batch Size
Guanfacine 2mg 40 ct	2027.003F	[redacted]	[redacted]
Guanfacine 4mg 40 ct	2030.001F		
Guanfacine 2mg 100 ct	ODV030108	SUMI	
Guanfacine 4mg 100 ct	ODV030113	SUMI	

Results

Demographic characteristics

Baseline assessments were within normal range for the male and female subjects in this study.

Table 26. Summary of Subject Demographic Characteristics

Characteristic		All Subjects Treated (N=40)
Age (yr)	N	40
	Mean (SD)	33 (10.1)
	Median (Min, Max)	35 (18, 53)
Race, n(%)	Black	21 (52.5%)
	Caucasian	11 (27.5%)
	European/Middle Eastern	1 (2.5%)
	Hispanic	6 (15.0%)
	Mixed	1 (2.5%)
Sex, n(%)	Female	9 (22.5%)
	Male	31 (77.5%)
Weight (lb)	N	40
	Mean (SD)	178 (34.6)
	Median (Min, Max)	178 (101.6, 287.
Height (in)	N	40
	Mean (SD)	68 (3.1)
	Median (Min, Max)	68 (59, 75)

Bioanalytical results: Assay validation for guanfacine is shown in the Table below. Chromatograms were shown.

Table 27: Assay Characteristics for Guanfacine

Parameter	Measure	Reviewer Comment
Linearity	0.02ng/mL to 25mcg/mL	Satisfactory
Precision (CV %)	$\leq$ 6.9%	Satisfactory
Accuracy Between day	between -4.6% and 1.3%	Satisfactory
LLOQ	0.02 ng/mL	Satisfactory
Specificity		Satisfactory

Pharmacokinetics

Guanfacine 2mg single dose

Table 28. Summary Guanfacine PK Parameters Following 2mg

Treatment	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	t_{max} (h)	C_{max} (ng/mL)	λ_z (h^{-1})	$t_{1/2}$ (h)
[redacted]						
Mean	51.1	52.7	6.0†	1.574	0.0434	16.4
SD (N)	19.9(18)	20.9(17)	3-24‡(18)	0.657(18)	0.0071(17)	2.7(17)
SUMI						
Mean	57.7	59.7	6.0†	1.666	0.0411	17.5
SD (N)	20.6(19)	22.0(18)	3-24‡ (19)	0.519(19)	0.0079(18)	3.7(18)

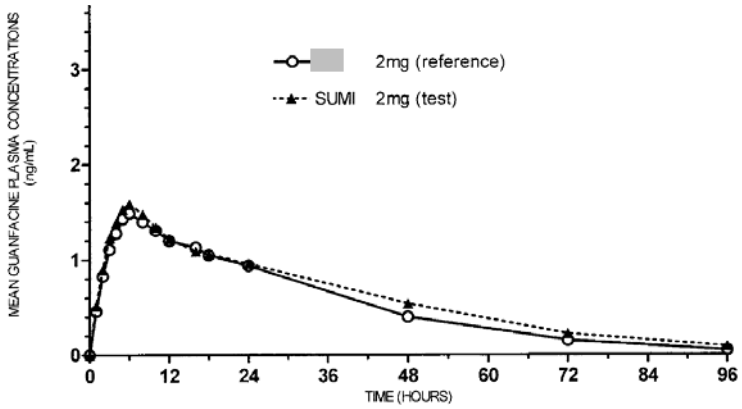


Figure 20. Mean plasma concentration time profiles after the dose of 2 mg SPD503

Table 29. Summary of Average Bioequivalence Analysis

PK parameter	Ratio Estimate (SUMI to [redacted] (b) (4))	90% Confidence interval around ratio of LS means	
		Lower CI	Upper CI
AUC_{0-t} (ng.h/mL)	1.12	0.95	1.33
$AUC_{0-\infty}$ (ng.h/mL)	1.12	0.94	1.33
C_{max} (ng/mL)	1.09	0.99 †	1.20†

For the 2mg tablet the SUMI peak exposure (Cmax) upper confidence interval was high, but just within the upper bioequivalence limit. The total exposure (AUC parameters) upper confidence intervals were higher than the limit. Systemic exposure was higher for the 2mg t ablets made at SUMI compared to the 2mg [redacted] (b) (4) reference tablets; the formulations were therefore not bioequivalent.

Guanfacine 4mg single dose

Table 30. Summary Guanfacine PK Parameters Following 4mg

Treatment	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	t_{max} (h)	C_{max} (ng/mL)	λ_z (h^{-1})	$t_{1/2}$ (h)
[redacted]						
Mean	119.7	127.8	6.0†	3.659	0.0442	16.3
SD (N)	38.2(20)	38.7(19)	4-48‡ (20)	1.57(20)	0.0083(19)	3.6(19)
SUMI						
Mean	105.9	110.6	6.0†	2.898	0.0444	16.2
SD (N)	32.3(20)	35.6(20)	4-48‡ (20)	1.047(20)	0.0080(20)	3.6(20)

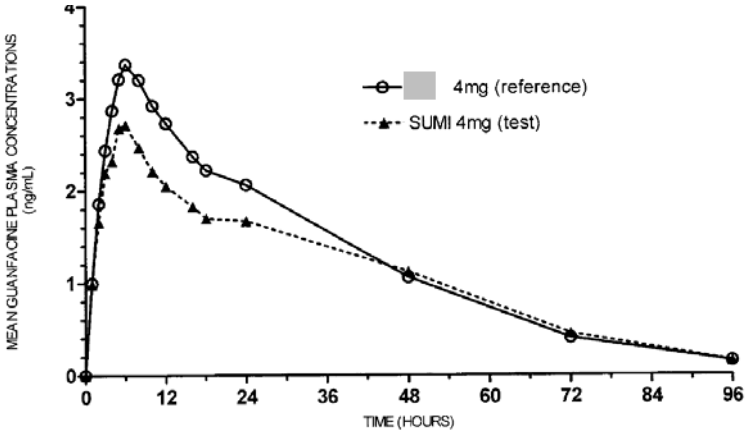


Figure 21. Mean plasma concentration time profiles after the dose of 4 mg SPD503

Table 31. Summary of Average Bioequivalence Analysis

PK parameter	Ratio Estimate (SUMI to [redacted]	90% Confidence interval around ratio of LS means	
		Lower CI	Upper CI
AUC_{0-t} (ng.h/mL)	0.88	0.78	1.00
$AUC_{0-\infty}$ (ng.h/mL)	0.87	0.77	0.98
C_{max} (ng/mL)	0.81	0.70	0.93

For the 4mg tablet, the lower confidence limit for both the peak exposure and total exposure was below the lower limit for bioequivalence. Systemic exposure for the tablets made at SUMI was lower than that for the (b) (4) reference tablets.
The clearance and volume of distribution values for each treatment and dose are compared in the Figure below.

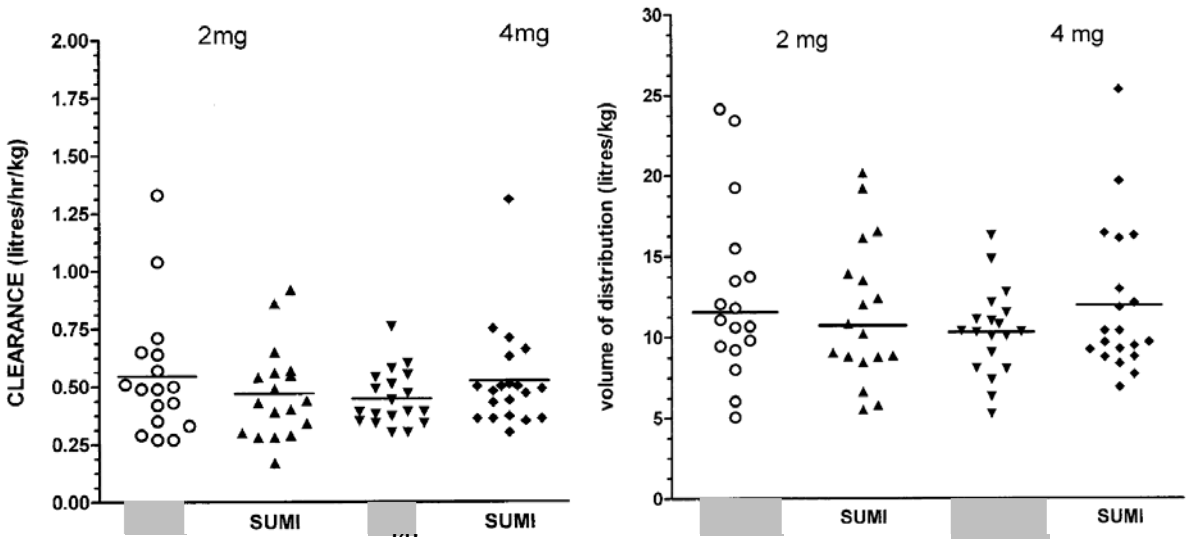


Figure 22. Weight-normalized CL values (left panel) and Vd values (right panel) for individual subjects. Horizontal lines are the mean values for the treatment.

REVIEWER COMMENTS

1. The exposure measured as both AUC and Cmax was higher for the 2mg tablet made at SUMI. The bioequivalence criteria were met for Cmax and were not met for AUC. On the contrary, for the 4mg tablet the exposure measured as both AUC and Cmax was lower for the tablet made at SUMI. The bioequivalence critereia were not met for both AUC and Cmax.

2. The inter-individual variability in pharmacokinetics of guanfacine was very high. Coefficients of variation for the plasma concentration were up to 156% for the 2 mg dose and up to 106% for the 4 mg dose of guanfacine. It is possible that the number of subjects in this study was not sufficient to properly power the study.

3. The 2mg and 4mg SPD503 manufactured at the proposed new site (SUMI) were not bioequivalent to the corresponding 2 and 4mg reference tablets made at the (b) (4) site.

4.1.7 A Phase I, Pharmacokinetic Study in Healthy Volunteers to Assess the Bioequivalence of SPD503 2mg and 4mg Tablets Manufactured at (b) (4) and SUMI Following a Single Dose Each of 2mg and 4mg (109)

Study number: SPD503-109 Study drug: SPD503, guanfacine hydrochloride
Investigators: Principal Investigator: (b) (4)
Study center: (b) (4)
Study period: 30 June 2004 to 02 August 2004
Phase of development: I

Objectives	Primary: evaluate the bioavailability and to assesss the bioequivalence of SPD503 tablets manufactured at the current manufacturing site and a potential new site following single doses of 2mg and 4mg. Secondary: to assess the dose proportionality of 1mg, 2mg and 4mg SPD503 tablet formulations.
Study Design	A randomized, open-label, single-dose, five-period, four-treatment crossover design with a separate lead-in period. Fifty-two subjects were enrolled in the study. In Period 1 (lead-in), subjects were administered a single 1mg SPD503 tablet. Prior to Period 2, subjects were randomly assigned to one of four treatment sequences. During Periods 2-5, subjects received their assigned treatment (a single oral dose SPD503 2mg or 4mg manufactured at (b) (4) or SUMI after an overnight fast. Subjects were randomized to the 2mg SPD503 doses for Periods 2 and 3. Subjects were randomized to the 4mg SPD503 doses for Period 3 and 4. The four treatment sequences (each with 13 subject):

Sequence Number	Period 1 (Lead-In)	Sequence Groups			
		Period 2	Period 3	Period 4	Period 5
1	(b) 1mg once (Treatment A)	(b) 2mg (Treatment B)	SUMI 2mg (Treatment C)	[redacted] 4mg (Treatment D)	SUMI 4mg (Treatment E)
2	(b) 1mg once (Treatment A)	SUMI 2mg (Treatment C)	[redacted] 2mg (Treatment B)	[redacted] 4mg (Treatment D)	SUMI 4mg (Treatment E)
3	(b) 1mg once (Treatment A)	(b) 2mg (Treatment B)	SUMI 2mg (Treatment C)	SUMI 4mg (Treatment E)	[redacted] 4mg (Treatment D)
4	(b) 1mg once (Treatment A)	SUMI 2mg (Treatment C)	[redacted] 2mg (Treatment B)	SUMI 4mg (Treatment E)	[redacted] 4mg (Treatment D)

Study Population	Healthy adult males and females aged 18-55 years (yrs) inclusive, Planned: 52 subjects, 49 subjects completed the study.
Diagnosis and main criteria for admission	Screening blood pressure within normal range (<140mmHg systolic/<90mmHg diastolic) and a screening ECG within normal range. Subjects with any cardiac conditions or family history were excluded.
Investigational Drug	SPD503 (Guanfacine Hydrochloride), an extended-release tablet formulation

Treatment	Manufacturing Site	Lot Number	Shape/Color	Manufacturing Date
A (1mg)	(b) (4)	2026-001E	Round/White	09 October 2002
B (2mg)		2027-002E	Oval/White	10 October 2002
C (2mg)	SUMI	ODV030108	Oval/White	05 September 2003
D (4mg)	(b) (4)	2030-001	Oval/Green	18 October 2002
E (4mg)	SUMI	ODV030114	Oval/Green	06 September 2003

Blood Sampling	Predose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 18, 24, 48, 72 and 96hrs postdose.
Assay	HPLC with LS/MS/MS detection. Chromatograms were shown.
PK Assessment	AUC0-t, AUC0-∞, Cmax, Cmin, t1/2, Tmax, FI CL/F, Vz/F, non-compartmental analysis
Statistical methods	Comparison of Cmax, AUC0-t, and AUC0-∞: ANOVA with subject within sequence, period, treatment, and sequence as the classification variables using the natural logarithms of the data. Confidence intervals (90%) were constructed for the ratios (SUMI-to [redacted] (b) (4) of the parameters using the two one-sided t tests procedure. The point estimates and confidence limits were exponentiated back to the original scale. BE based on the 90% CI within 80 and 125%. Cmax, AUC0-t, and AUC0-∞ compared among doses and sites: ANOVA (subject within sequence, manufacturer, dose, and sequence, after normalizing to the 1mg dose. Dose proportionality: geometric mean ratios and 90% CIs from the same analysis.

Table 32. Tablet Lot Information

Drug	Bulk lot #	Manufacturer	Batch Size
Guanfacine 1mg 9ct.	2026.001E	[redacted]	[redacted]
Guanfacine 2mg 40ct.	2027.002E		
Guanfacine 4mg 40ct.	2030.001		
Guanfacine 2mg 100ct.	ODV030108	SUMI	
Guanfacine 4mg 100ct.	ODV030114	SUMI	

Results

Demographics: The demographic information is summarized in the table below.

Table 33. Subject Demographic Characteristics

Characteristic		All Subjects Treated (N=52)
Race, n(%)	Black	5 (9.6%)
	Caucasian	7 (13.5%)
	Hispanic	40 (76.9%)
Sex, n(%)	Female	24 (46.2%)
	Male	28 (53.8%)
Age (yr)	Mean (SD)	32.9 (10.3)
	Median (Min, Max)	29.0 (18, 54)
Weight (lb)	Mean (SD)	161.5 (34.6)
	Median (Min, Max)	152 (109, 264)
Height (in)	Mean (SD)	66.1 (4.4)
	Median (Min, Max)	65.8 (59, 74)

Baseline assessments were within normal range for the male and female subjects in this study.

Bioanalytical results: Assay validation for guanfacine is shown in the Table below.

Table 34: Assay Characteristics for Guanfacine

Parameter	Measure	Reviewer Comment
Linearity	0.02ng/mL to 25mcg/mL	Satisfactory
Precision (CV %)	≤ 5.6%	Satisfactory
Accuracy Between day	between 0.5% and 7.6%	Satisfactory

LLOQ	0.02 ng/mL	Satisfactory
Specificity		Satisfactory

Pharmacokinetics

Bioequivalence of the 2mg (b) (4) and SUMI tablets

The mean plasma concentrations after administration of the 2mg SUMI tablet and the 2mg (b) (4) tablet were very similar (Figure below).

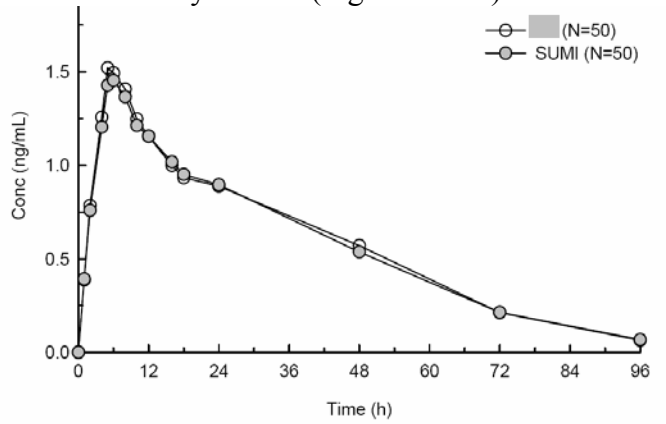


Figure 23 Mean Plasma Concentrations of Guanfacine After Oral Administration of 2mg as (b) (4) and SUMI Tablets to Healthy Volunteers

The arithmetic mean values for Cmax, AUC0-t and AUC0-8 are compared in the Table below.

Table 35. Summary of PK for Guanfacine After Oral Administration of 2mg as (b) (4) and SUMI Tablets to Healthy Subjects

Parameter*†	(b) (4) (N=50)	SUMI (N=50)
C_{max} (ng/mL)	1.59 ± 0.49	1.54 ± 0.53
t_{max} (h)	6.00	6.00
AUC_{0-t} (h•ng/ml)	55.0 ± 18.0	54.0 ± 17.6
$AUC_{0-\infty}$ (h•ng/mL)	58.1 ± 18.8	57.8 ± 19.1
λz (h^{-1})	0.0439 ± 0.0075	0.0434 ± 0.0086
$t_{1/2}$ (h)	16.4 ± 3.46	16.7 ± 4.12
CL/F (mL/min)	647 ± 253	638 ± 206
Vz/F (L)	894 ± 328	889 ± 241

Table 36. Statistical Comparison of Pharmacokinetic Parameters for Guanfacine After Oral Administration of 2mg as (b) (4) and SUMI Tablets to Healthy Subjects

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
C_{max}	97.18	90.79 → 104.01
AUC_{0-t}	98.78	92.85 → 105.09
$AUC_{0-\infty}$	98.23	92.19 → 104.66

The 90% CIs for the geometric mean ratios, SUMI-to- (b) (4) are contained within 80% : 125%.

Bioequivalence of the 4mg (b) (4) and SUMI tablets
The mean plasma concentrations after administration of the 4mg SUMI tablet and of the 4mg (b) (4) tablet were very similar.

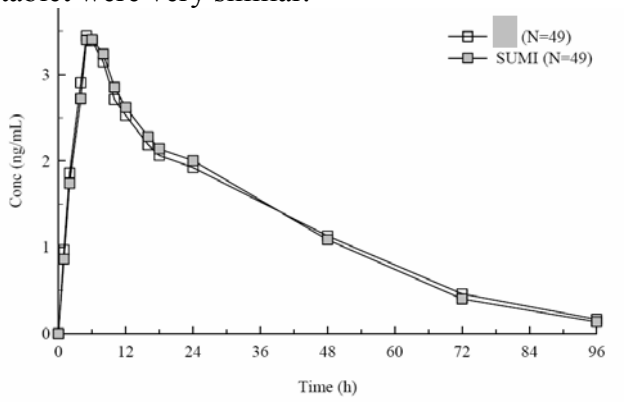


Figure 24. Mean Plasma Concentrations of Guanfacine After Oral Administration of 4mg as (b) (4) and SUMI Tablets to Healthy Volunteers

The arithmetic mean values for Cmax, AUC0-t and AUC0-8 are compared in the Table below:

Table 37. Summary of Pharmacokinetic Parameters for Guanfacine After Oral Administration of 4mg as (b) (4) and SUMI Tablets to Healthy Subjects

Parameter*		SUMI
C_{max} (ng/mL)	3.58 ± 1.39	3.59 ± 1.40
t_{max}(h)	5.01	6.00
AUC_{0-t} (h•ng/ml)	120 ± 41.5	119 ± 43.4
$AUC_{0-\infty}$ (h•ng/mL)	125 ± 46.0	123 ± 44.6
λz (h^{-1})	0.0434 ± 0.0098	0.0448 ± 0.0089
$t_{1/2}$ (h)	17.1 ± 5.51	16.2 ± 4.15
CL/F (mL/min)	599 ± 213	638 ± 331
Vz/F (L)	854 ± 294	866 ± 393

The 90% CIs for the geometric mean ratios, SUMI-to- (b) (4) were contained within 80 and 125%.

Table 38. Statistical Comparison of Pharmacokinetic Parameters for Guanfacine After Oral Administration of 4mg as (b) (4) and SUMI Tablets to Healthy Subjects

Parameter	Geometric Mean Ratio (%)*			
	Estimate	90% Confidence Interval		
C_{max}	99.50	90.85	→	108.97
AUC_{0-t}	97.39	88.82	→	106.78
$AUC_{0-\infty}$	96.88	88.17	→	106.45

Dose proportionality

Mean plasma concentrations for guanfacine increased in a dose-proportional manner after the administration of 1, 2, and 4mg and there was a reasonably dose-proportional increase in Cmax, AUC0-t and AUC0-8.

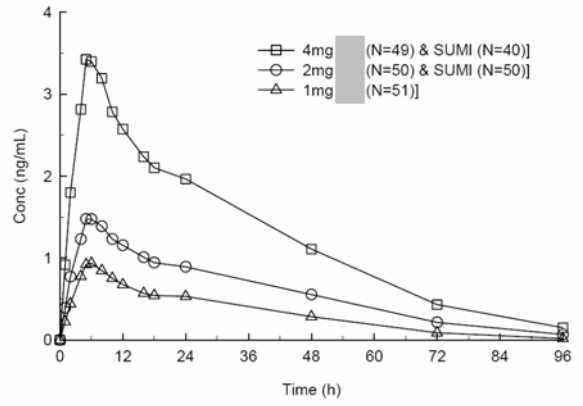


Figure 25. Mean Plasma Concentrations of Guanfacine After Oral Administration of 1mg as a (b) (4) Tablet and 2mg and 4mg as (b) (4) and SUMI Tablets to Healthy Subjects

Table 39. PK Parameters for Guanfacine After Oral Administration of 1mg as a (b) (4) Tablet and 2mg and 4mg as (b) (4) and SUMI Tablets to Healthy Subjects

Parameter*†	1mg (N=52)	2mg (N=50)	2mg SUMI (N=50)	4mg (N=49)	4mg SUMI (N=49)
C_{max} (ng/mL)	0.98 ± 0.26	1.59 ± 0.49	1.54 ± 0.53	3.58 ± 13.9	3.59 ± 1.40
t_{max}	6.00	6.00	6.00	5.01	6.00
AUC_{0-t} (h•ng/ml)	29.3 ± 8.84	55.0 ± 18.0	54.0 ± 17.6	120 ± 41.5	119 ± 43.4
$AUC_{0-\infty}$ (h•ng/mL)	32.4 ± 8.78	58.1 ± 18.8	57.8 ± 19.1	125 ± 46.0	123 ± 44.6
λz (h^{-1})	0.0416 ± 0.0088	0.0439 ± 0.0075	0.0434 ± 0.0086	0.0434 ± 0.0098	0.0448 ± 0.0089
$t_{1/2}$ (h)	17.5 ± 3.83	16.4 ± 3.46	16.7 ± 4.12	17.1 ± 5.51	16.2 ± 4.15
CL/F (mL/min)	560 ± 194	647 ± 253	638 ± 206	599 ± 213	638 ± 331
Vz/F (L)	823 ± 249	894 ± 328	889 ± 241	854 ± 294	866 ± 393

The 90% confidence intervals for the geometric mean ratios of the three dose-normalized parameters between the 1 and 4mg doses, and 2 and 4mg doses bracketed 1.0, with the exception of Cmax between the 1 and 2mg doses. The geometric mean ratio for Cmax between the 1 and 2mg doses was 1.26 and the lower limit of the associated 90% CI was >1.0, indicating a slight lack of proportionality at the lowest dose.

PK Parameter	Ratio Estimate (1mg/2mg)	90% CI Of Ratio (1mg/2mg)	Ratio Estimate (1mg/4mg)	90% CI Of Ratio (1mg/4mg)	Ratio Estimate (2mg/4mg)	90% CI Of Ratio (2mg/4mg)
AUC (0-inf)	1.0849	(1.0094 - 1.1660)	1.0211	(0.9502 - 1.0973)	0.9412	(0.8938 - 0.9912)
AUC (0-t)	1.0782	(1.0081 - 1.1533)	0.9988	(0.9335 - 1.0686)	0.9263	(0.8800 - 0.9750)
Cmax	1.2581	(1.1692 - 1.3538)	1.1115	(1.0326 - 1.1965)	0.8835	(0.8355 - 0.9342)

REVIEWER COMMENTS:

1. The inter-subject variability in this study was as high as in the study 503-103, however, the increased number of subjects in the study 503-109 allowed enough

power to declare the bioequivalence between the 2mg and 4mg guanfacine tablets produced at SUMI and at (b) (4)

2. The PK of guanfacine are reasonably linear over the dose range of 1 to 4mg although mean values for Cmax and AUC0-t and AUC0-∞ increased somewhat less than 2-fold between the 1 and 2mg doses.

4.1.8 A Phase I, Pharmacokinetic Study to Investigate the Bioequivalence of SPD503 2.5 mg Tablets (110)

Study number: SPD503-110 Study drug: SPD503, guanfacine hydrochloride
Investigators: Principal Investigator: (b) (4)
Study center: (b) (4)
Study period: 12 November 2004 to 19 December 2004
Phase of development: I

Objectives	Primary: to assess the dose-adjusted bioequivalence of SPD503 2.5 mg tablets versus SPD503 2mg g.
Study Design	A randomized, open-label, single-dose, three-treatment crossover design. Each subject received a single dose of his/her treatment for the period (either a 2 or a 2.5mg SPD503 tablet manufactured at (b) (4) or a 2.5mg SPD503 tablet manufactured at SUMI. The study consisted of the screening, baseline and treatment phases. Dosing schedule is shown below:

Treatment Group Total N	Sequence Groups		
	Period 1	Period 2	Period 3
N=8 (Sequence Number 1)	2.5mg- (Treatment B)	2.5mg-SUMI (Treatment A)	2mg- (Treatment C)
N=8 (Sequence Number 2)	2.5mg-SUMI (Treatment A)	2mg- (Treatment C)	2.5mg- (Treatment B)
N=8 (Sequence Number 3)	2mg- (Treatment C)	2.5mg- (Treatment B)	2.5mg-SUMI (Treatment A)
N=8 (Sequence Number 4)	2.5mg- (Treatment B)	2mg- (Treatment C)	2.5mg-SUMI (Treatment A)
N=8 (Sequence Number 5)	2.5mg-SUMI (Treatment A)	2.5mg- (Treatment B)	2mg- (Treatment C)
N=8 (Sequence Number 6)	2mg (b) (Treatment C)	2.5mg-SUMI (Treatment A)	2.5mg- (Treatment B)

Study Population	Healthy adult males and females aged 18-55 years (yrs) inclusive, Planned: 48 subjects, 48 subjects completed the study.
Diagnosis and main criteria for admission	Screening blood pressure within normal range (<140mmHg systolic/<90mmHg diastolic) and a screening ECG within normal range. Subjects with any cardiac conditions or family history were excluded.
Investigational Drug	SPD503 (Guanfacine Hydrochloride), an extended-release tablet formulation

Drug	Bulk lot #	Manufacturer	Batch Size
Guanfacine 2mg (b) (4) 100ct.	2027.005		)
Guanfacine 2.5mg (b) 100ct.	2034.003		
Guanfacine 2.5mg (SUMI) 100ct.	ODV040142	SUMI	

Blood Sampling	Predose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 18, 24, 48, 72 and 96hrs postdose.
Assay	HPLC with LC/MS/MS detection. Chromatograms were shown.
PK Assessment	AUC0-t, AUC0-∞, Cmax, Cmin, t1/2, Tmax, FI CL/F, Vz/F, non-compartmental analysis
Statistical methods	Summary statistics for SPD503 plasma concentration data and the derived PK parameters for each tablet. The $\log_e$-transformed dose-normalized AUC0-t, AUC0-8 and Cmax data were analyzed using a general linear model with terms for sequence, subject within sequence, period, and treatment fitted using fixed effects. Point estimates and 90% confidence intervals (CI) for the ratios of the 2mg- (b) (4) tablet and

	2.5mg-SUMI tablet means (2mg-(b)(4)2.5mg-SUMI) were provided. BE based on the 90% CI for the ratios of the dose-adjusted means for AUC and Cmax within the range of 80% to 125%.

Results

Demographics: The demographic information is summarized in the table below.

Table 40. Subject Demographic Characteristics

Characteristic		All Subjects Treated (N=48)	
Age (yr)	Mean (SD)	33.1	(8.4)
	Median (Min, Max)	32.0	(20, 55)
Race, N(%)	Asian	1	(2.1%)
	Black	1	(2.1%)
	Caucasian	10	(20.8%)
	Hispanic	36	(75.0%)
Frame, N(%)	Small	20	(41.75%)
	Medium	24	(50.0%)
	Large	4	(8.3%)
Sex, N(%)	Female	34	(70.8%)
	Male	14	(29.2%)
Weight (lb)	Mean (SD)	149.5	(27.9)
	Median (Min, Max)	145.0	(95, 227)
Height (in)	Mean (SD)	64.9	(3.8)
	Median (Min, Max)	64.2	(59, 74)

Pharmacokinetics

Bioequivalence of the 2.5mg SUMI and 2mg (b)(4) tablets

The mean plasma concentrations after administration of the 2.5mg SUMI tablet were ~40% greater than after administration of the 2mg (b)(4) tablet.

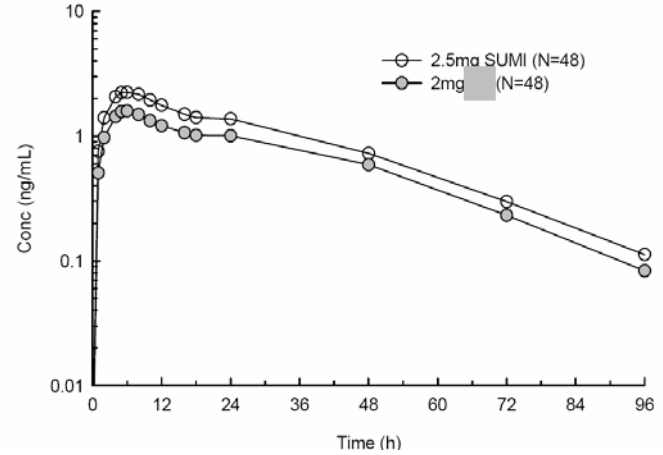


Figure 26. Mean Plasma Concentrations of Guanfacine After Oral Administration of 2.5mg as SUMI and 2mg as (b)(4) Tablets to Healthy Subjects

Table 41. PK Parameters of Guanfacine

Parameter*	2.5mg SUMI (N = 48)	2mg (b)(4) (N = 48)
C_{max}		
(ng/mL)	2.49 ± 0.93	1.71 ± 0.56
(ng/mL)/mg	0.99 ± 0.37	0.86 ± 0.28
T_{max} (h)	6.00 (4.00 - 48.0)	6.00 (3.99 - 24.1)
AUC_{0-t}		
(h•ng/mL)	81.3 ± 35.4	59.8 ± 20.9
(h•ng/mL)/mg	32.5 ± 14.2	29.9 ± 10.4
$AUC_{0-\infty}$†		
(h•ng/mL)	85.0 ± 37.4	64.2 ± 22.6
(h•ng/mL)/mg	34.0 ± 14.9	32.1 ± 11.3
λ_z (h^{-1})†	0.0458 ± 0.0114	0.0427 ± 0.0116
$t_{½}$ (h)†	16.7 ± 7.36	17.7 ± 5.80
CL/F†		
(mL/min)	591 ± 283	612 ± 303
(mL/min/kg)	8.82 ± 4.18	8.96 ± 3.80
V_z/F†		
(L)	809 ± 406	884 ± 382
(L/kg)	12.0 ± 5.78	12.9 ± 4.58

The 90% CI for the dose-normalized geometric mean ratios, 2.5mg SUMI-to-2mg (b)(4) were contained within 80% . 125%

Table 42. Statistical Comparison of PK Parameters for Guanfacine After Oral Administration of 2.5mg as SUMI and 2mg as (b)(4) Tablets to Healthy Subjects

Parameter	Geometric Mean Ratio (%)*			
	Estimate	90% Confidence Interval		
C_{max}	114.50	106.20	→	123.45
AUC_{0-t}	106.79	98.33	→	115.97
$AUC_{0-\infty}$	105.53	97.14	→	114.64

*Ratio of SUMI to PII. Based on analysis of natural log-transformed data.

<u>Bioequivalence of the 2.5mg and 2mg (b)(4) tablets</u>

The mean plasma concentrations after administration of the 2.5mg (b)(4) tablet were ~30% greater than after administration of the 2mg (b)(4) tablet.

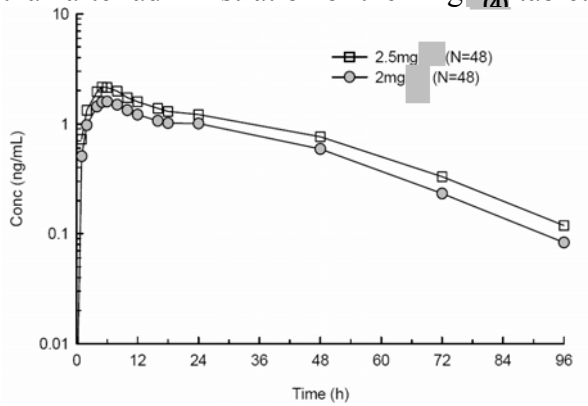


Figure 27. Man Plasma Concentrations of Guanfacine After Oral Administration of 2.5mg and 2mg as (b)(4) Tablets to Healthy Subjects — Semi-Logarithmic

Table 43. PK Parameters for Guanfacine After Oral Administration of 2.5mg and 2mg as (b) (4) Tablets to Healthy Subjects

Parameter*	2.5mg (N = 48)	2mg (N = 48)
C_{max}		
(ng/mL)	2.26 ± 0.67	1.71 ± 0.56
(ng/mL)/mg	0.90 ± 0.27	0.86 ± 0.28
T_{max} (h)	5.01 (4.00 - 16.0)	6.00 (3.99 - 24.1)
AUC_{0-t}		
(h•ng/mL)	77.8 ± 30.4	59.8 ± 20.9
(h•ng/mL)/mg	31.1 ± 12.1	29.9 ± 10.4
$AUC_{0-\infty}$†		
(h•ng/mL)	84.5 ± 34.2	64.2 ± 22.6
(h•ng/mL)/mg	33.8 ± 13.7	32.1 ± 11.3
λ_z (h^{-1})†	0.0401 ± 0.0119	0.0427 ± 0.0116
$t_{½}$ (h)†	19.0 ± 6.64	17.7 ± 5.80
CL/F†		
(mL/min)	598 ± 299	612 ± 303
(mL/min/kg)	8.62 ± 3.86	8.96 ± 3.80
Vz/F†		
(L)	915 ± 390	884 ± 382
(L/kg)	13.2 ± 4.53	12.9 ± 4.58

The 90% CI for the dose-normalized geometric mean ratios, 2.5mg (b) (4) to-2mg (b) (4) were contained within 80% . 125%.

Table 44 Statistical Comparison of PK Parameters for Guanfacine After Oral Administration of 2.5mg and 2mg as (b) (4) Tablets to Healthy Subjects.

Parameter	Geometric Mean Ratio (%)*			
	Estimate	90% Confidence Interval		
C_{max}	106.17	98.47	→	114.47
AUC_{0-t}	102.85	94.71	→	111.70
$AUC_{0-\infty}$	103.08	94.74	→	112.14

REVIEWER COMMENTS:

1. The 2.5mg guanfacine tablets produced at (b) (4) and SUMI are each bioequivalent to the 2mg guanfacine tablets produced at (b) (4) when normalized by dose.

4.1.9 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) 203

Study No. 503-203
Investigator(s) (b) (4)
Study period: May-20-2002 - August-18-2002
Clinical Phase II

Objectives	Primary: to assess, under controlled conditions, the safety and tolerability of SPD503 1.0, 2.0, 3.0 and 4.0 milligrams/day, administered to children with Attention Deficit Hyperactivity Disorder (ADHD). Secondary: to examine the pharmacokinetic profile of SPD503 after a 1mg single dose and multiple doses of 1mg and 4mg/day.
Study Design	An open-label, dose escalation, safety and tolerability study of SPD503 in children with ADHD. **Phase I,** Screening & Washout Period: 1-week period prior to washout. **Phase II,** Open-Label Treatment: Eligible subjects received SPD503 for 7 weeks of total treatment. The design was a forced dose escalation and downward titration (Table below). The doses began at 1mg/day during week 1 and were escalated in 1mg/week up to 4mg/day. PK: Day 1 of week 1 (single dose); Day 7, week 1 and Day 7, week 4 (multiple doses) Week 5: Doses reduced in 1mg /week. **Phase III,** Follow-up: additional two visits during week 8.
Study Population	Subjects, N=20, aged 6 to 12 years who satisfied DSM-IV criteria diagnosis of ADHD, combined or hyperactive subtypes with BW ≥25 kg.
Investigational Drug	The SPD503 MR formulated (b) (4) the active pharmaceutical ingredient along with other functional excipients (b) (4) round-shaped, white to off-white tablet
D and A	Oral doses of 1, 2, 3, and 4 mg QD
Blood Sampling	Visit 1, 3 and 11: pre-dose and 1, 2, 3, 4, 5, 6, 8 and 10 hours post dose
Assay	HPLC with MS detection (Table), chromatograms were shown.
PK Assessment	Cmax(ng/mL), Cmax/dose, Tmax (hr), AUC0-24(ng·hr/mL), AUC0-24/dose (ng·hr/mL/mg), Cmin (ng/mL), Cmin/dose (ng/mL/mg), Cavg (ng/mL), Cavg/dose (ng/mL/mg), FL, MRT0-24 (hr)
PD Assessment	NA
Safety Assessment	Visits 1, 3 and 11, a full-day evaluation of safety: pulse, blood pressure monitoring and ECG collection at pre-dose and 3, 4, 6, 7, 8 and 10 hours post dose. Vital Signs, Laboratory Parameters: (hematology, chemistry, and urinalysis, at Visit -1, 0 and 17), Electrocardiograms: At Visit 0, and at pre-determined intervals (each visit).

Table 45. Study Schedule

Week	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Week 0 No dose	Phone contact from site to initiate washout	Washout	Washout	Washout	Washout	Washout	Visit 0 Baseline & practice Visit 7:30am – 3:30pm
Week 1 1mg q AM	Visit 1 Full day safety & PK 7:00am – 6:15pm	Visit 2 24 hr PK Draw 7:30am – 8:30am					Visit 3 Full day safety & PK 7:00am – 6:15pm
Week 2 2mg q AM	Visit 4 Half day of safety 7:30am – 3:30pm						Visit 5 Full day of safety 7:30am – 5:30pm
Week 3 3mg q AM	Visit 6 Half day of safety 7:30am – 3:30pm			Visit 7 Full day of safety 7:30am – 5:30pm			Visit 8 Full day of safety 7:30am – 5:30pm
Week 4 4mg q AM	Visit 9 Half day of safety 7:30am – 3:30pm			Visit 10 Full day of safety 7:30am – 5:30pm			Visit 11 Full day safety & PK 7:00am – 6:15pm
Week 5 3mg q AM	Visit 12 Half day of safety 7:30am – 3:30pm			Visit 13 Full day of safety 7:30am – 5:30pm			Phone Reminder from site to begin new dosage
Week 6 2mg q AM				Visit 14 Full day of safety 7:30am – 5:30pm			Phone Reminder from site to begin new dosage
Week 7 1mg q AM				Visit 15 Full day of safety 7:30am – 5:30pm			
Week 8 Off Drug				Visit 16 Full day of safety 7:30am – 5:30pm			Visit 17 Close-out Half day of safety 7:30am – 3:30pm

Results: This study was completed as scheduled.

Table 46. Demographics

Characteristic		All Subjects Treated (N=20)	
Age (yr)	N	20	
	Mean (SD)	10	(1.7)
	Median (Min, Max)	11	(6,12)
Age Group, n(%)	6-8 Years	3	(15.0%)
	9-12 Years	17	(85.0%)
Race, n(%)	Caucasian	13	(65.0%)
	Black	6	(30.0%)
	Other	1	(5.0%)
Sex, n(%)	Male	16	(80.0%)
Characteristic		All Subjects Treated (N=20)	
	Female	4	(20.0%)
Weight (lb)	N	20	
	Mean (SD)	88	(26.6)
	Median (Min, Max)	84	(55 – 129)
Height (in)	N	20	
	Mean (SD)	57	(4.2)
	Median (Min, Max)	57	(49 – 65)

The assay characteristics are shown below.

Table 47. Assay Characteristics

Parameter	Measure	Reviewer Comment
Linearity	0.05 to 2.5 ng/mL	Satisfactory
Precision (CV %)	$\leq$ 8.1%	Satisfactory
Accuracy Between day	between 0% and 4.6%	Satisfactory
LLOQ	0.02ng/mL	Satisfactory
Specificity		Satisfactory

The mean time to peak exposure Tmax for all three treatments was ~5 hours and consistent with an extended-release formulation. When dose-normalized, the exposure (AUC0-24), peak exposure (Cmax), minimum concentration (Cmin) and average concentration values (Cavg) following multiple dosing with 4mg were similar to those found following multiple dosing with 1mg. Comparison of the fluctuation index of the 4mg and 1mg multiple dose treatments suggested that the extent of fluctuation was not dependent on dose. A comparison of the mean plasma concentration time profiles, mean (Tmax) and mean residence time (MRT0-24), indicated the time course of drug absorption and elimination did not appear to be influenced by the dose. Interindividual variabilities were moderate (did not exceed 40%) and were similar between the 1 and 4 mg doses.

Table 48. PK parameters of Guanfacine

	1mg single dose(N=20)			1mg multiple dose(N=20)			4mg multiple dose(N=19)		
guanfacine									
	Mean	Stdev	%CV	Mean	Stdev	%CV	Mean	Stdev	%CV
Parameter									
C_{max}(ng/mL)	1.951	0.547	28.1	3.130	1.006	32.1	13.393	3.690	27.5
C_{max}/dose				3.130	1.006	32.1	3.348	0.922	27.5
T_{max} (hr)	5.2	1.6	30.4	4.9	1.6	33.0	4.8	1.4	28.6
AUC_{0-24}(ng·hr/mL)	29.7	7.8	26.4	50.3	15.9	31.6	213.5	69.2	32.4
AUC_{0-24}/dose (ng·hr/mL/mg)	n/a	n/a	n/a	50.3	15.9	31.6	53.4	17.3	32.4
C_{min} (ng/mL)	n/a	n/a	n/a	1.187	0.455	38.3	4.670	1.860	39.8
C_{min}/dose (ng/mL/mg)	n/a	n/a	n/a	1.187	0.455	38.3	1.168	0.465	39.8
C_{avg} (ng/mL)	n/a	n/a	n/a	2.096	0.663	31.6	8.897	2.884	32.4
C_{avg}/dose (ng/mL/mg)	n/a	n/a	n/a	2.096	0.663	31.6	2.224	0.721	32.4
FI	n/a	n/a	n/a	0.92	0.17	18.8	1.03	0.25	23.8
MRT_{0-24} (hr)	11.0	0.8	7.0	10.2	0.6	5.8	10.1	0.6	5.5

The mean plasma concentration time values are shown in the Figure below.

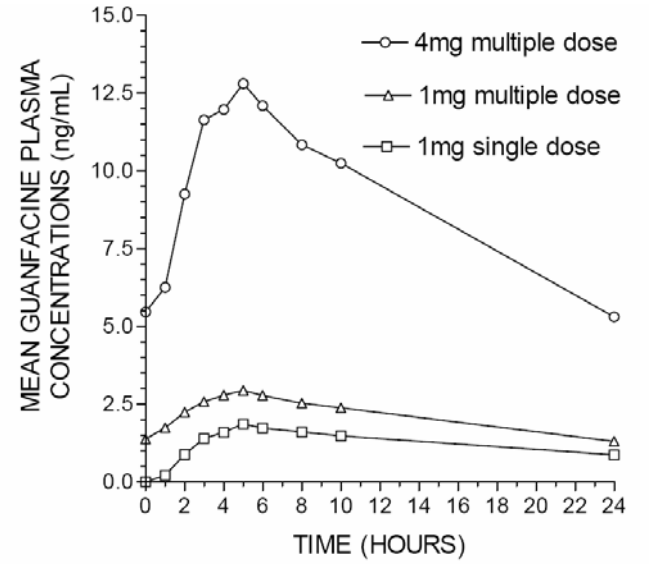


Figure 28. Mean Plasma Concentration vs. time values

The pharmacokinetics of the 1mg single dose and 1mg, 4mg multiple dose treatments with SPD503 showed the extended-release characteristics of the formulation in ADHD patients. The comparison of the normalized AUC0-24, Cmax, Cmin, and Cavg (Table 6) for 1 and 4 mg doses of SPD503 indicate that its pharmacokinetics is linear at these doses. The dose normalized parameters are shown in Figure 29 and Figure 30.

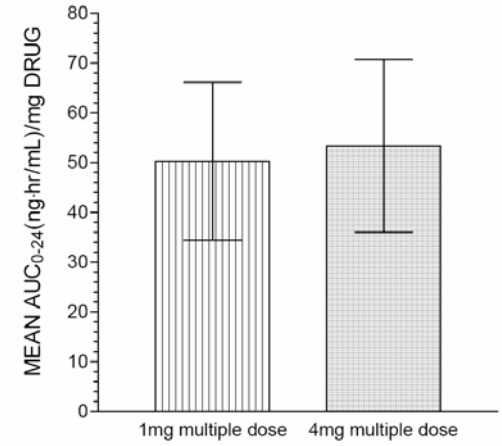


Figure 29. Normalized Exposure AUC0-24

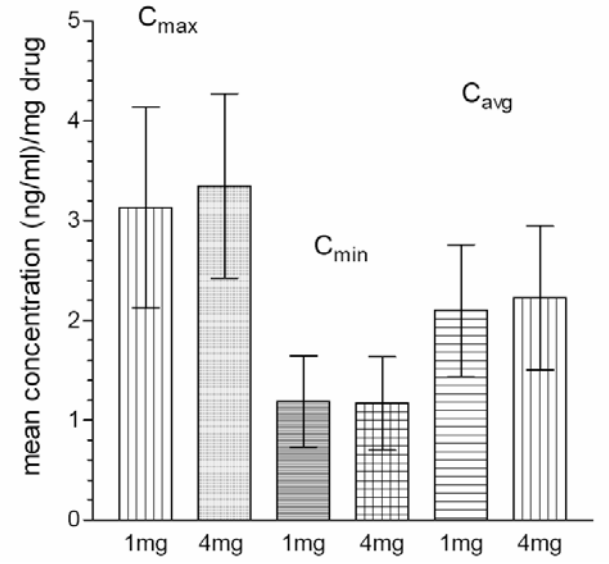


Figure 30. Normalized Plasma Concentration Parameters

COMMENTS:

1. The half-life was not estimated properly in this study due to fact that plasma sampling w ere collected up to24 hours only.
2. The dose normalized pharmacokinetics parameters were similar between 1mg and 4mg treatments; therefore, the SPD503 pharmacokinetics was dose proportional in the dose range of 1 mg and 4 mg per day at steady state.

4.1.10 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) 206

Study No. 503-206
Investigators: Coordinating Principal Investigator: Scott Kollins PhD, Assistant Professor Duke University Medical Center 718 Rutherford Street Durham, NC 27705.
Study centre(s): Multi-center study.
Total number of sites: 10 initiated, 9 enrolled subjects (US)
Study period: 12 May 2005 to 05 Oct 2005 Clinical phase: II

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 ADHD, (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, (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)
Study Design	A phase II, randomized, double-blind, multi-center, placebo-controlled, dose-optimization study. Approximately 11 visits (~1 visit/week) over the 15-week study (Screening/Washout – 4wks, Visit -1/Baseline – 0.5wks, Treatment – 6.5wks, Follow-up – 4wks). Treatment Period: All subjects began with 1mg dose of SPD503/ matching placebo with the following increase (1mg/week) to a maximum of 3mg/day based on the subject's reduction in ADHD symptoms. Visits 1, 2, 3, 5, and 7: a full-day assessment (the cognitive battery at 2, 5, and 8 hours post-dose, and on the

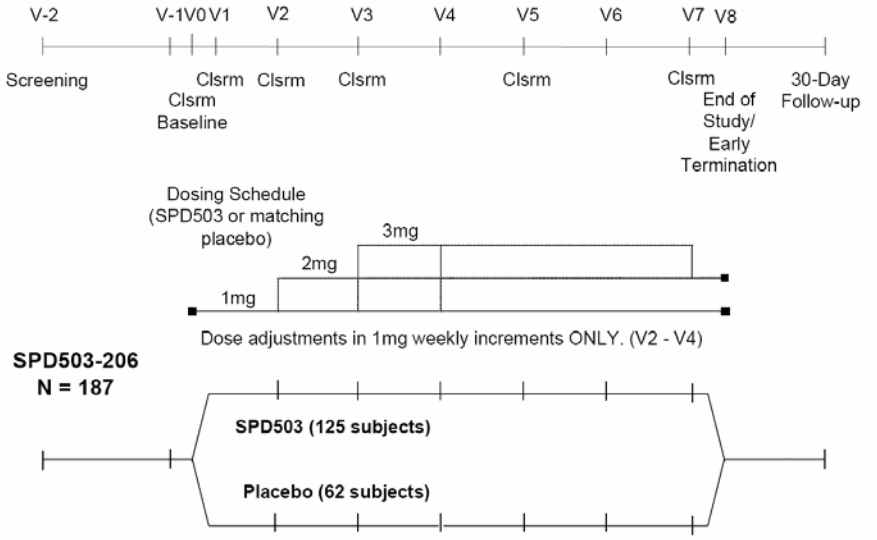
	first day of dosing during weeks 1, 2, and 3). Any CNS side effects assessed pre-dose, 2, 5, 8, 10 and 12 hours post-dose and at corresponding time points on the fourth day of each week via the PSS. 
Study Population	Male and female subjects aged 6-17 years with a primary diagnosis of ADHD (ADHD-RS-IV score of 24 and CGI-S score = 4). A screening blood pressure and ECGs within normal range. Subjects with any specific cardiac conditions, family history of cardiac conditions, or sleep disorders, were excluded. A total of 182 subjects were enrolled.
Investigational Drug	SPD503, guanfacine hydrochloride in 1, 2, and 3mg strength tablets from batch numbers ODV040125, ODV030109, ODV030111.
Dosage and Administration	Oral doses of 1, 2, and 3 mg QD in the morning within one-half hour after breakfast.
Reference drug product	Matching placebo in 1, 2, and 3mg strength tablets from batch numbers 2020.001, 2021.001, and 2023.001.
Blood Sampling	Visit 5: pre-dose and 1, 2, 3, 4, 5, 6, and 8 hours post dose
Assay	HPLC with MS detection, chromatograms were shown.
PK Assessment	Cssmax(ng/mL), Tmax (hr), AUCss(0-t)(ng·hr/mL), Cssmin (ng/mL), Cssavg (ng/mL/mg), Tmin (hr)
PD Assessment	Guanfacine plasma concentration versus time data and PK parameters were summarized statistically. Dose proportionality of AUCss(0-t) and Cssmax: a power model. PERMP and CRT endpoints (RT, MT, and TT) for Visit 5 and the relationships between PD parameters and guanfacine plasma concentrations and PK parameters were graphically explored. Relationships between Visit 5 ECG data (HR, QT, QTcB, QTcF and population-based QT correction [QTcP]) and guanfacine plasma concentrations were explored graphically.

Table 49. Study Schedule

	Screening	Day -1 or -2	Baseline	Treatment Period							EOS/ET	Follow-up*
Visit Number	-2	-1	0	1	2	3	4	5	6	7	8	9
Study Day	-28	-2 or -1	0	1	7	14	21 (±2)	28	35 (±2)	42	45 (+2)	75 (±2)
Informed Consent	X											
Inclusion/Exclusion	X		X†									
Medical/MED History‡	X											
Psychiatric Evaluation	X											
KBIT	X											
Physical Examination§	X		X§								X	
Vital Signs#	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG	X		X**					X			X	
Clinical Lab Tests††	X										X	
Urine Drug Screen	X		X								X	
Pregnancy Test	X		X								X	
PK Blood Draws								X				
Call IVRS	X		X		X	X	X	X	X	X		
SPD503 Dose				X	X	X		X		X		
ADHD-RS-IV	X		X		X	X	X	X	X	X		
PERMP		X	X	X	X	X		X		X		
CGI-S	X		X									
CGI-I					X	X	X	X	X	X		
Cognitive Battery		X	X	X	X	X		X		X		
PSS			X	X	X	X	X	X	X	X		
PDSS	X		X		X	X	X	X	X	X		
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X

Results: This study was completed as scheduled. The assay characteristics are shown below.

Table 50. Assay Characteristics

Parameter	Measure	Reviewer Comment
Linearity	0.05 to 2.5 ng/mL	Satisfactory
Precision (CV %)	≤ 8.0%	Satisfactory
Accuracy Between day	between -8.3% and 5.9%	Satisfactory
LLOQ	0.02ng/mL	Satisfactory
Specificity		Satisfactory

Pharmacokinetics

The time to reach maximum steady state concentration (Cssmax) was approximately 5 hours, beyond which concentrations appeared to plateau. Peak concentrations were maintained through about 8 hours post-dose.

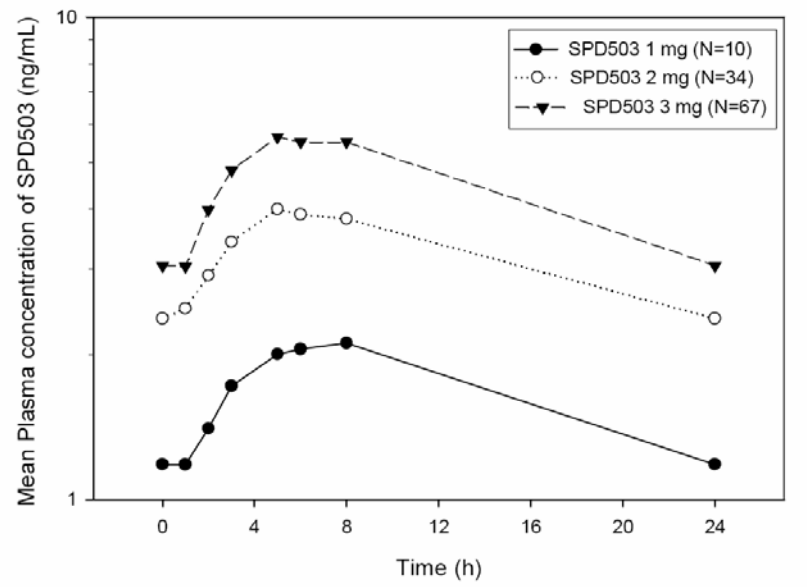
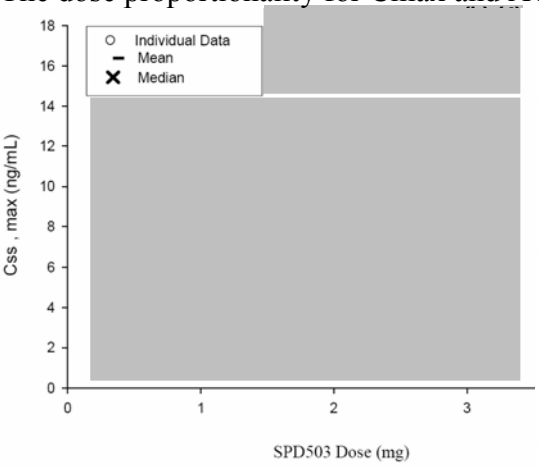


Figure 31. SPD503 Mean plasma concentration versus time by dose.

Table 51. Mean PK parameters of Guanfacine

Parameter (Units)	SPD503 1mg (N=10)	SPD503 2mg (N=33)	SPD503 3mg (N=66)
Css_{max} (ng/mL)	2.272 (43.3)	4.225 (43.9)	6.164 (48.0)
T_{max}* (h)	5.75 (0.00-8.00)	4.93 (1.82-7.97)	4.86 (1.88-8.00)
$AUCss_{(0-\tau)}$ (ng×h/mL)	39.24 (49.2)	76.39 (54.2)	111.6† (55.9)
$Css_{avg(0-\tau)}$ (ng/mL)	1.636 (49.2)	3.186 (54.4)	4.654† (56.0)
Css_{min} (ng/mL)	1.073 (62.8)	2.344 (75.0)	2.779 (85.4)

The dose proportionality for Cmax and AUC is assessed in Figures below.



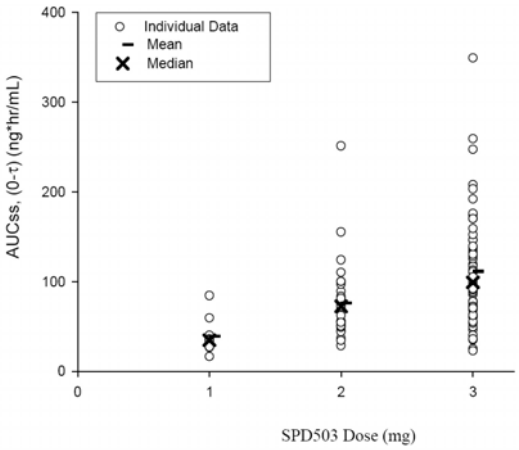


Figure 32. Cmax vs SPD503 dose **Figure 33. AUC vs SPD503 dose**

The sponsor concluded the guanfacine dose proportionality based on the calculated 95%CI for the estimate of the slope.

Pharmacodynamic Analysis

The effect was assessed by the evaluation of cognitive function and efficacy (several variables). The differences in primary (reaction time) and secondary cognitive functions were not statistically significant between the placebo and treatment arms except for the PERMP.

Table 52. Change from Baseline in PERMP Score by Visit and by Treatment Group

Time point Statistic	Placebo (N=35)	SPD503 (N=80)
Baseline		
n	35	80
Mean actual value (SD)	170.9 (68.27)	158.3 (62.13)
Visit 1 (Day 1)		
n	35	80
Mean change (SD)	29.2 (42.53)	36.0 (38.14)
P-value for treatment*		0.266
Visit 2 (Day 7)		
n	34	79
Mean change (SD)	23.8 (56.07)	44.7 (45.72)
P-value for treatment*		0.030
Visit 3 (Day 14)		
n	35	80
Mean change (SD)	16.1 (67.75)	51.5 (54.15)
P-value for treatment*		0.003
Visit 5 (Day 28)		
n	34	80
Mean change (SD)	7.2 (80.59)	31.0 (57.50)
P-value for treatment*		0.072
Visit 7 (Day 42)		
n	35	79
Mean change (SD)	17.2 (83.60)	39.2 (75.10)
P-value for treatment*		0.144
Endpoint†		
n	35	80
Mean change (SD)	17.2 (83.60)	38.7 (74.80)
P-value for treatment*		0.151

An analysis of PERMP scores actual values and the change from baseline showed that the treatment group difference was greater in the 6-12 years category compared with the 13-17 years category. The treatment effect was significant at Visits 2 and 3, with trends (p=0.09) observed at Visits 5, 7, and endpoint in the 6-12 years category but not in the 13-17 years category. Therefore, SPD503 at doses of 1, 2, and 3mg once daily does not impair performance on measures of attention and psychomotor functioning in children and adolescents with ADHD. For the spatial working memory (SWM) a trend for greater improvement was observed in the SPD503 group compared with the placebo group that reached statistical significance at Visit 5. Analysis of PERMP scores showed a greater improvement in the SPD503 group compared with the placebo group, confirming that there was no evidence of impairment with SPD503 treatment. The sponsor evaluated the possible relationship between guanfacine plasma concentrations and various PD measurements.

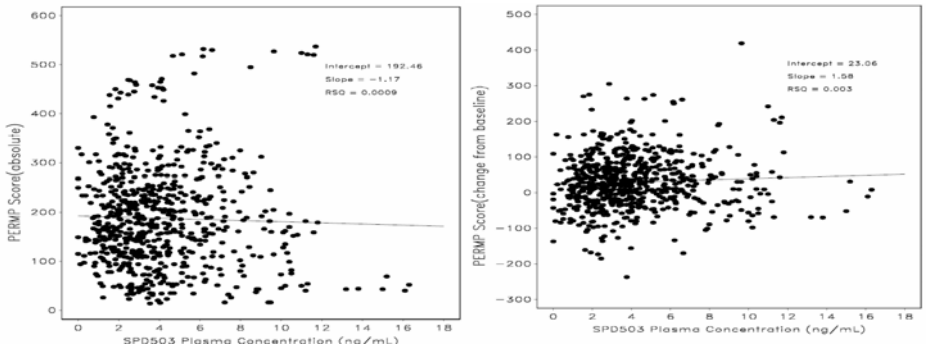


Figure 34. PERMP score (absolute and change from baseline) vs SPD503 plasma concentrations

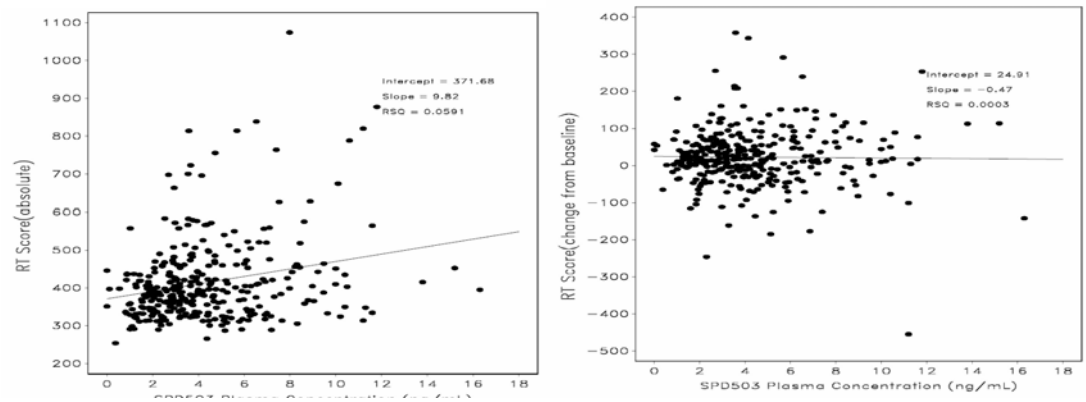


Figure 35 Reaction time (RT) score (absolute and change from baseline) versus SPD503 plasma concentrations

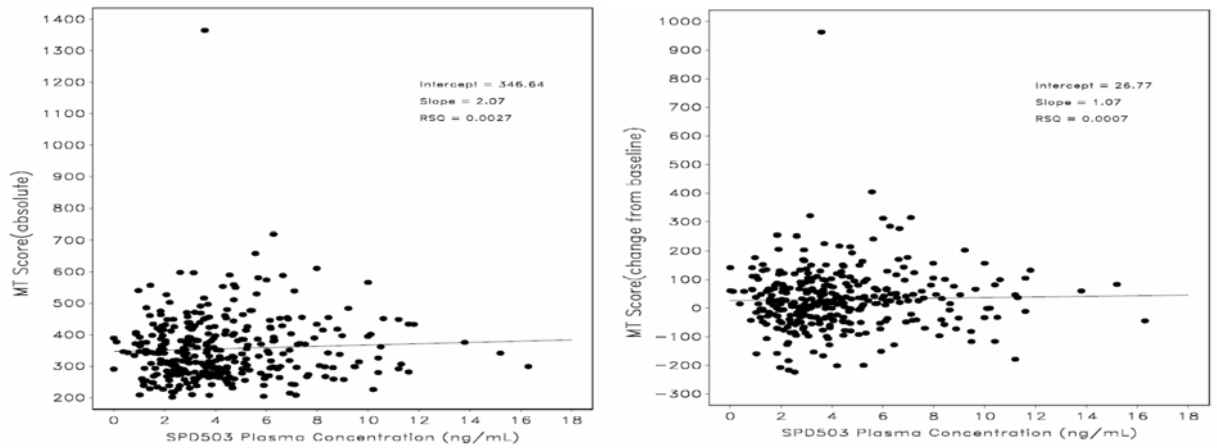


Figure 36 Movement time (MT) score (absolute and change from baseline) versus SPD503 plasma concentrations

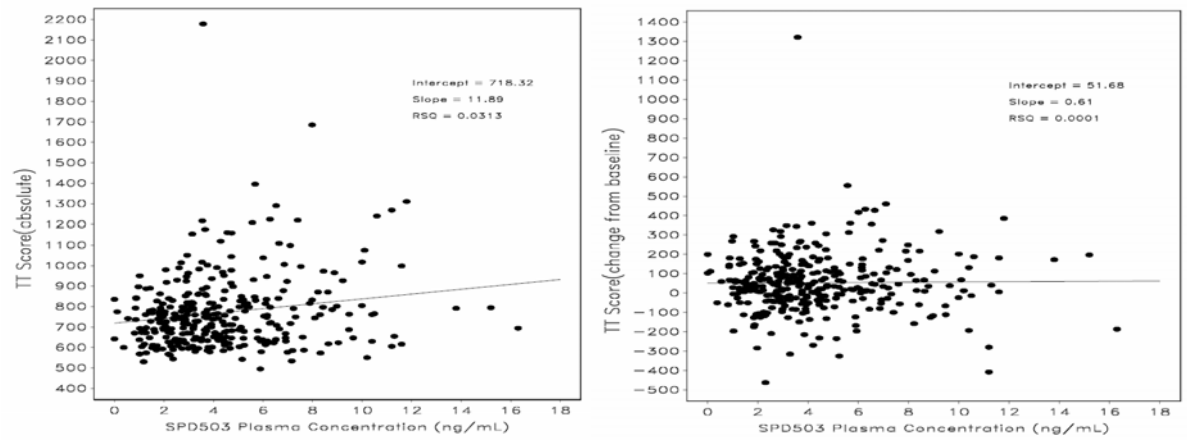


Figure 37 Total time (TT) score (absolute and change from baseline) versus SPD503 plasma concentrations

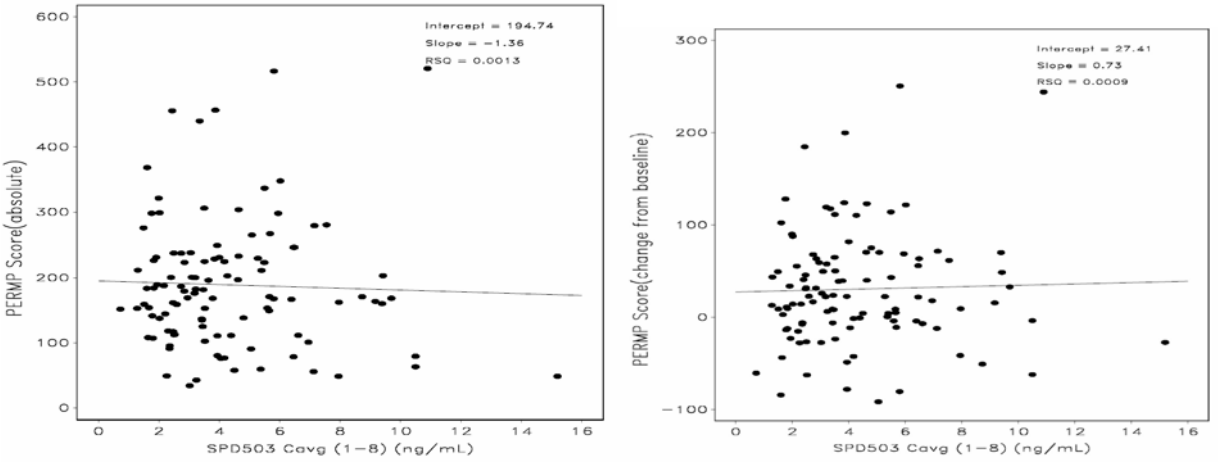


Figure 38 Scatter plot of individual time – averaged PERMP score (absolute and change from baseline) versus Cavg (1 – 8) SPD503

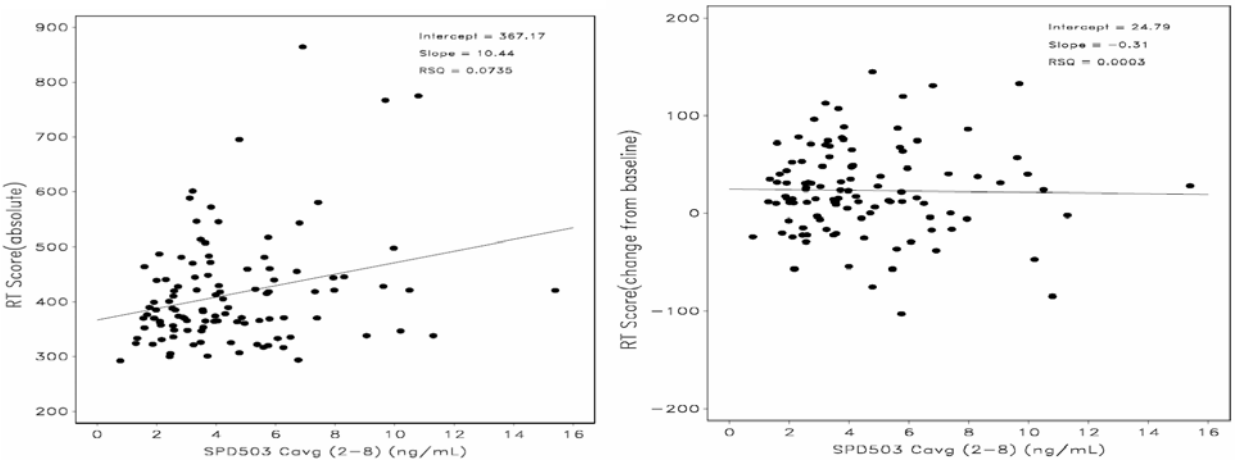


Figure 39 Scatter plot of individual time – averaged PERMP score (absolute and change from baseline) versus Cavg (2 – 8) SPD503

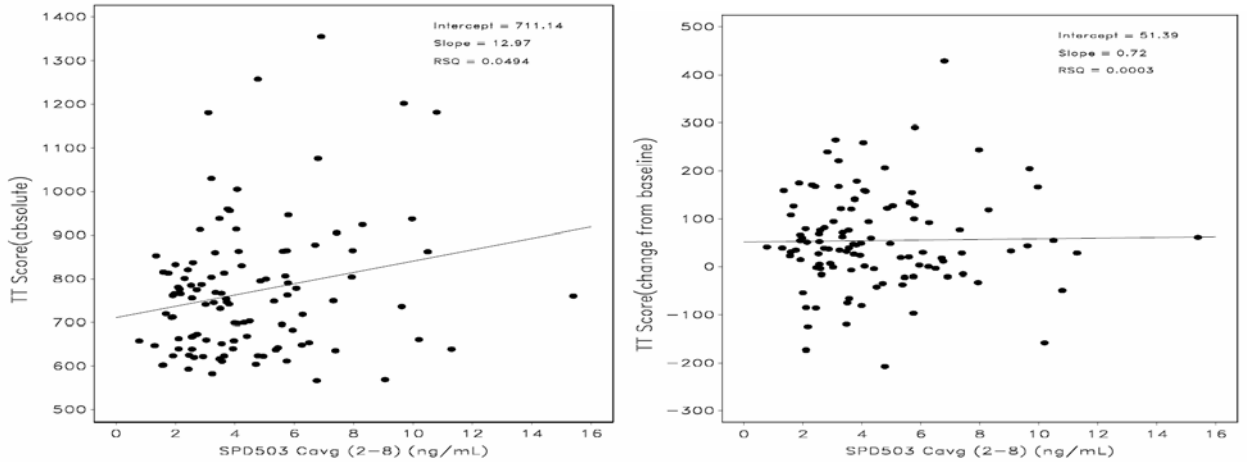


Figure 40 Scatter plot of individual time – averaged total time (TT) score (absolute and change from baseline) versus Cavg (2 – 8) SPD503

These plots evaluated the relationship between the changes of the various responses from the baseline values vs plasma concentration. These relationships were very shallow, indicating that the responses did not depend on the guanfacine plasma concentrations.
The safety response parameters were also examined graphically.

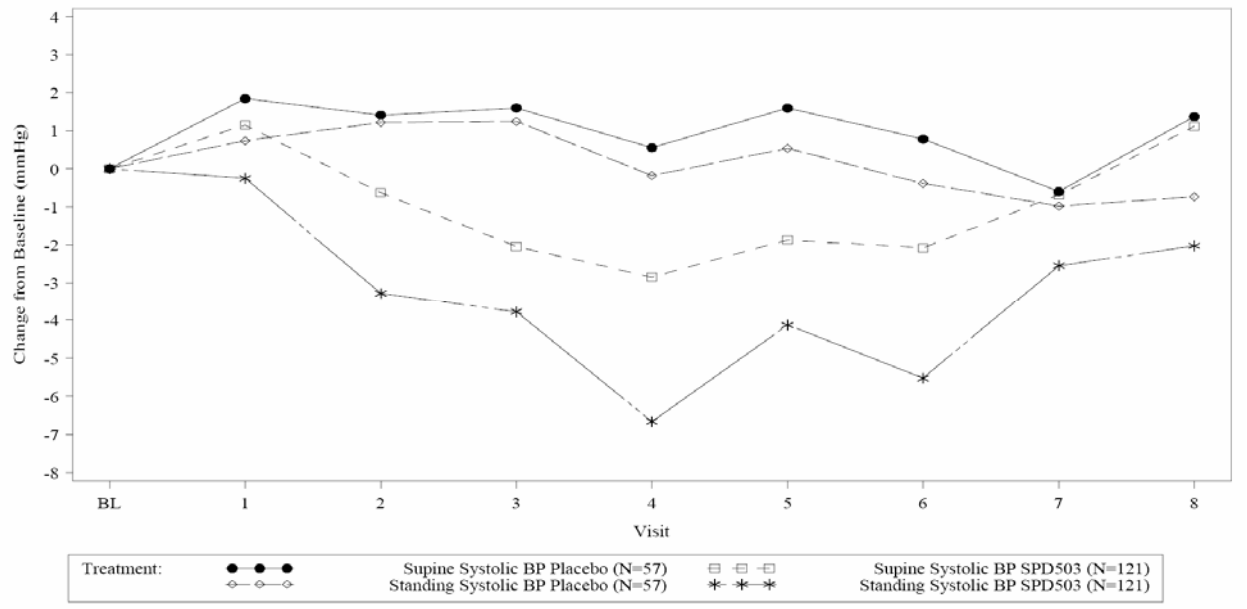


Figure 41 Systolic Blood Pressure Change from Baseline by Treatment and Visit

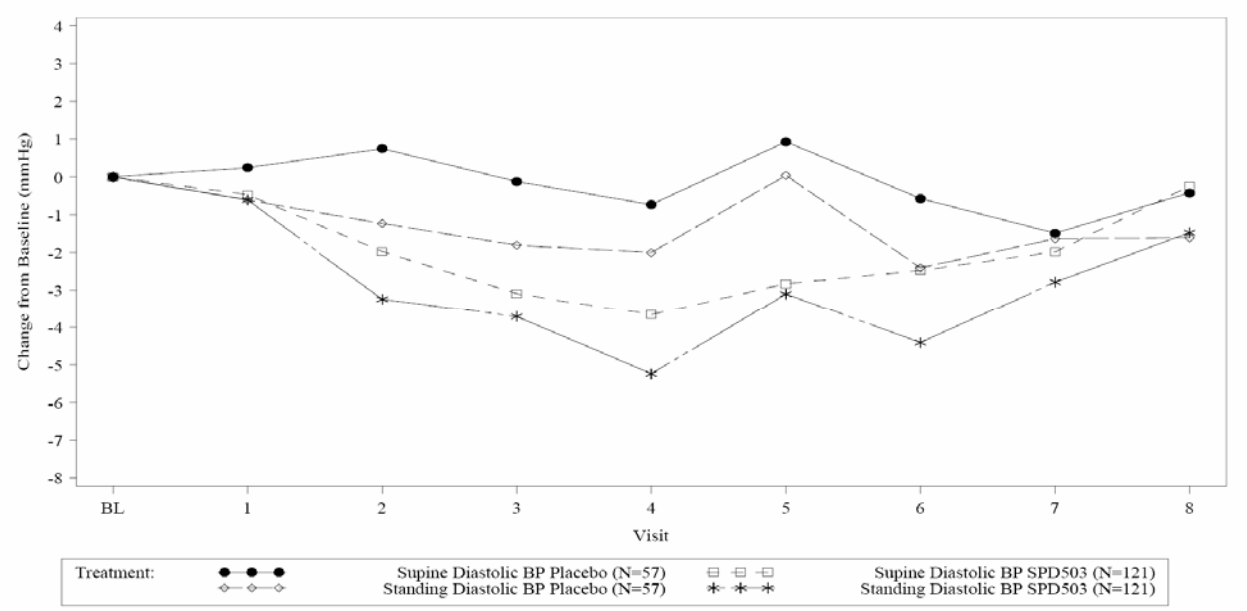


Figure 42 Diastolic Blood Pressure Change from Baseline by Treatment and Visit

Guanfacine was approved for the treatment of mild hypertension. In children with normal blood pressure it causes a mean decrease of the supine SBP by about 3 mmHg, and standing SBP by 5.5 mmHg at visit 4. The supine DBP decreased by 3.5 mmHg, and standing DPB decreased by 5.5 mmHg at visit 4. There were cases of fatigue in this study.

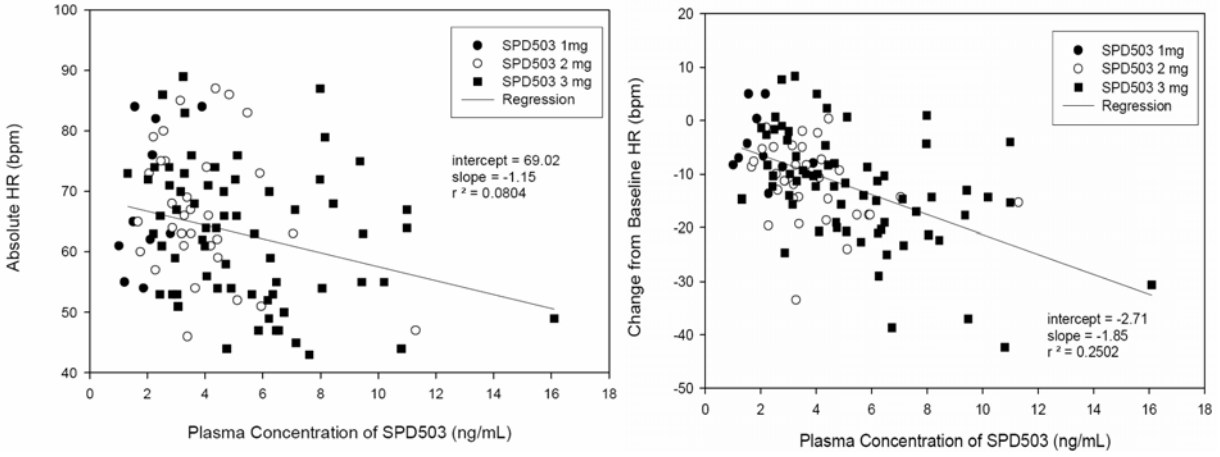


Figure 43. Heart Rate vs SPD503 plasma concentrations

At the steady state Cmax after a dose of 1 mg/day is 3 ng/mL, which causes a decrease in heart rate of about 10 bpm. If the dose is 4 mg/day (Cmax 10 ng/mL in children of 6 to 12 years of age), the heart rate dropped by 23 bpm on average.

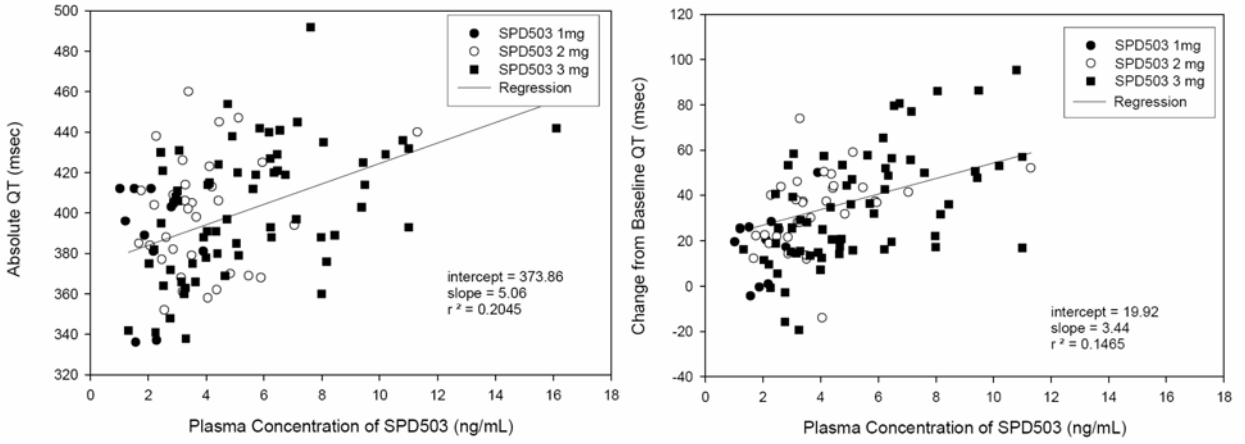


Figure 44. QT interval change vs SPD503 plasma concentrations

This plot shows that at 3 ng/mL (Cmax of 1mg/day dose) QT increased by 30 msec on average. At the worst case scenario, in pediatric patients (6-12 years of age) after doses of 4 mg/day Cmax was 10±7 ng/mL (study 107). At this plasma concentration thea 55 msec on average prolongation of QT interval may be expected.

Although when the Bazett correction ($QT_CB=QT/RR^{1/2}$) was applied to the QT interval data in the study, there was no prolongation observed. Since guanfacine causes a marked concentration dependent decrease of heart rate, the corrections of QT interval using Bazett formula should be interpreted with caution.

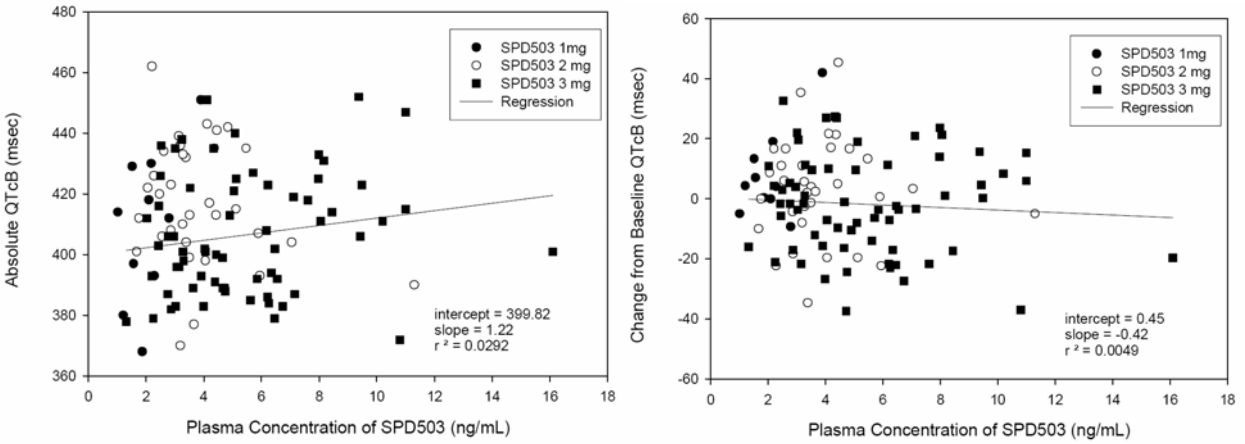


Figure 45. QTcB interval change vs SPD503 plasma concentrations

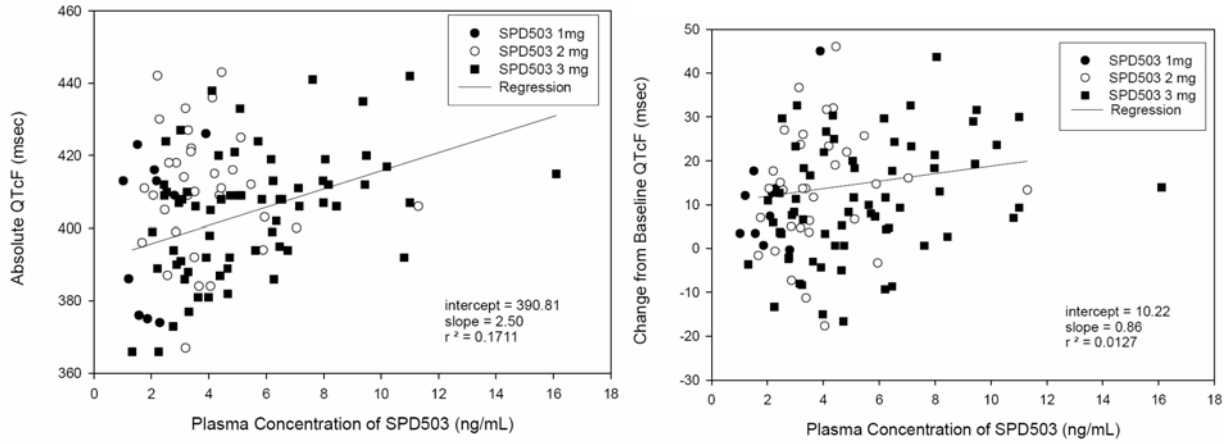


Figure 46 QTcF interval change vs SPD503 plasma concentrations

The correction of QT interval using Fredericia formula ($QT_CF=QT/RR^{1/3}$) indicated prolongation by about 20 msec at Cmax of 10 ng/mL.
The QTc interval at Cmax of 10 ng/mL was prolonged by about the same 20 msec as QTcF.

CONCLUSIONS:
Guanfacine at doses of 1, 2, and 3mg once daily did not impair performance on measures of attention and psychomotor functioning (PERMP scores) in children and adolescents with ADHD. There was no difference between doses, and no correlation between the guanfacine plasma concentration and any of the PD measurements.

COMMENTS:

1. Guanfacine is approved for the mild hypertension. In children with normal blood pressure it causes a mean decrease of the supine SBP by about 3 mmHg, and standing SBP by 5.5 mmHg at visit 4. The supine DBP decreased by 3.5 mmHg, and standing DPB decreased by 5.5 mmHg at visit 4. The case of fatigue was reported as an adverse event leading to discontinuation in this study; however, the sponsor did not assess the correlation between this effect and drug plasma concentration.
2. The sponsor performed only graphic correlation of the effect of guanfacine on the heart rate. Guanfacine causes bradicardic effect: At the steady state Cmax after a dose of 1 mg/day is 3 ng/mL, and decrease in heart rate is about 10 bpm. At 4 mg/day dosing (Cmax 10±7 ng/mL in children of 6 to 12 years of age), the heart rate dropped by 23 bpm on average. The sponsor did not evaluate the relationship between guanfacine plasma concentrations and effect on heart rate
3. The sponsor did not performed a thorough QT study for guanfacine. However, from the graphic exploration (changes in QT interval vs. guanfacine plasma concentrations) there were several alarming findings: At Cmax of 3 ng/mL (1mg/day dose) QT increased by 30 msec on average. At the worst case scenario, in pediatric patients (6-12 years of age) after doses of 4 mg/day Cmax was 10±7 ng/mL (study 107). At this plasma concentration the 55 msec on average prolongation of QT interval may be expected.
4. When the Bazett correction ($QT_CB=QT/RR^{1/2}$) was applied to the QT interval data in the study, there was no prolongation observed. Since guanfacine causes a marked concentration dependent decrease of heart rate, the corrections of QT interval using

Bazett formula should be interpreted with caution. When the Fredericia formula was applied ($QT_CF=QT/RR^{1/3}$) QTcF was prolonged by about 20 msec at Cmax of 10 ng/mL. The QTc interval at Cmax of 10 ng/mL was prolonged by about the same 20 msec as QTcF

5. The reviewer consulted the QT-specialist to evaluate the safety findings in the submission. The detailed data analyses of safety can be found in the PM review.

4.1.11 Identification of Human Cytochrome P450 Isoenzymes Involved in the In Vitro Metabolism of Guanfacine

Authors: (b) (4)
Study performed: (b) (4)

Study # V00652-SPD503-IIIG
Report Date: 14 November 2003

OBJECTIVE
To determine the involvement of specific cytochrome P450 isoenzymes in the metabolism of guanfacine using human hepatic microsomes and expressed human cytochromes P450.

DESIGN AND PROCEDURES
Pooled human hepatic microsomes (8 male and 7 female donors).
Recombinant (cDNA-expressed) human cytochromes P450:
CYP1A2 + P450 reductase (CYP1A2), CYP2A6 + P450 reductase + cytochrome b5 (CYP2A6), CYP2B6 + P450 reductase + cytochrome b5 (CYP2B6), CYP2C8 + P450 reductase + cytochrome b5 (CYP2C8), CYP2C9*1 (Arg144) + P450 reductase + cytochrome b5 (CYP2C9), CYP2C19 + P450 reductase + cytochrome b5 (CYP2C19), CYP2D6*1 + P450 reductase (CYP2D6), CYP2E1 + P450 reductase + cytochrome b5 (CYP2E1), CYP3A4 + P450 reductase + cytochrome b5 (CYP3A4), insect cell control (vector control), and P450 reductase + cytochrome b5 insect cell (vector control + cytochrome b5).
Incubation for 60 min in 1.0 mL with and without of NADPH solution in 100 mM potassium phosphate buffer, pH 7.4, containing 1 mM EDTA). The in vitro incubation conditions of guanfacine using pooled human hepatic microsomes were optimized using various conditions.
Assay: LC/MS/MS.

Selective Inhibitors of CYP450
α-Naphthoflavone (10 μM), sulfaphenazole (5 μM), omeprazole (25 μM), quinidine (10 μM), diethyldithiocarbamate (DETC, 100 μM), and ketoconazole (1 μM) were selected as isoenzyme-selective inhibitors to assess the involvement of CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4, respectively, in guanfacine metabolism.

RESULTS
Metabolism of guanfacine was very slow and did not depend on glutathione presence.

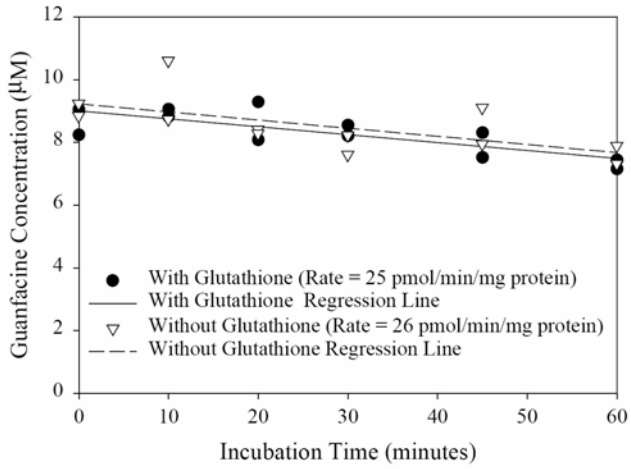


Figure 47. Metabolism of guanfacine over time in incubations with human hepatic microsomes

Kinetic Analysis Using Pooled Human Hepatic Microsomes

Optimal conditions: 1.0 mg microsomal protein/mL, 60-minute incubation time, guanfacine concentration range of 2.5 to 100 μM.

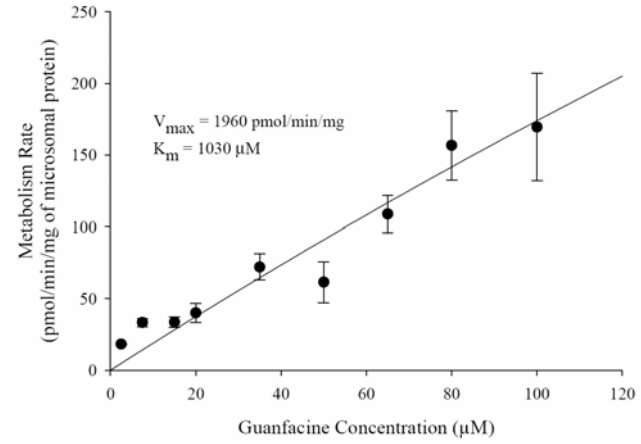


Figure 48. Michaelis-Menten plot of the in vitro metabolism of guanfacine by human hepatic microsomes

The Km value for guanfacine metabolism by human hepatic microsomes was estimated to be large (1030 μM). A guanfacine concentration of 10 μM, well below the Km value and exceeding the therapeutic plasma levels was used in later experiments.

The effect of CYP-isoenzyme-selective inhibitors on the metabolism of guanfacine in human hepatic microsomes is presented in the Figure below.

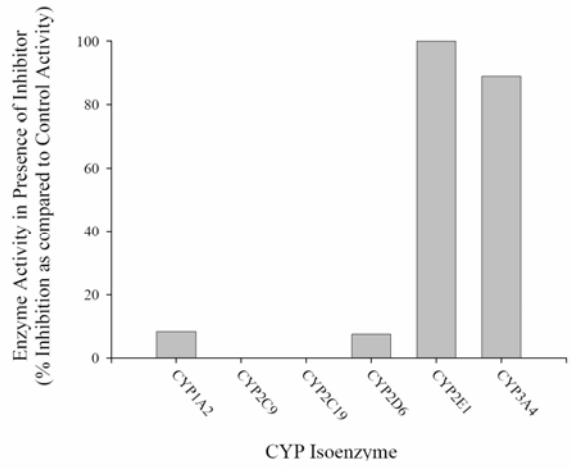


Figure 49. Enzyme activity in pooled human hepatic microsomes (1.0 mg microsomal protein/mL) incubated for 60 minutes in the presence of CYP-selective inhibitors

The only inhibitors that produced a significant inhibition of guanfacine metabolism were diethyldithiocarbamate (selective for CYP2E1) and ketoconazole (selective for CYP3A4). Thus, the involvement of CYP2E1 and/or CYP3A4 in the metabolism of guanfacine is implicated.

The ability of selected cDNA-expressed human hepatic CYPs to metabolize guanfacine in vitro was examined in microsomes prepared from baculovirus-infected BTI-TN-5B1-4 or Sf9 insect cells.

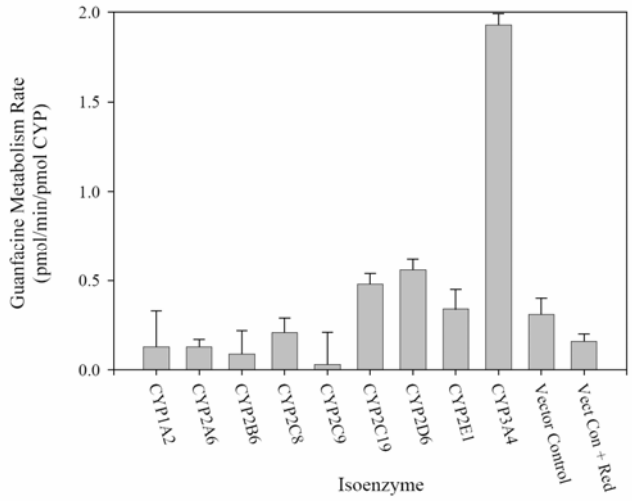


Figure 50. Guanfacine (10 µM) metabolism rates by cDNA-expressed human hepatic CYPs prepared from baculovirus infected BTI-TN-5B1-4 or Sf9 insect cells and vector-treated control microsomes with and without P450 reductase.

The results confirm the involvement of CYP3A4 in the in vitro metabolism of guanfacine. However, the involvement of CYP2E1 in the in vitro metabolism of guanfacine is not supported by these data.

CONCLUSIONS:

1. The apparent Km value for guanfacine metabolism by human hepatic microsomes is 1030 μM.
2. The guanfacine metabolism was inhibited when incubated with diethyldithiocarbamate (selective for CYP2E1) or ketoconazole (selective for CYP3A4).
3. In the experiment with microsomes expressing recombinant human CYPs, the in vitro metabolism of guanfacine by CYP3A4 was confirmed and but was not the case for CYP2E1.
4. Guanfacine at a concentration much less than the Km value (10 μM) is metabolized by CYP3A4.

4.1.12 Inhibitory Potential of Guanfacine Towards Human Hepatic Microsomal Cytochrome P450 Isoenzymes

Investigator: (b) (4)
Study Center: (b) (4)
Study # V00651-SPD503-IIIG
Report Date 10 April 2003.

OBJECTIVE
To characterize the in vitro inhibitory potential of guanfacine towards specific isoenzymes of human hepatic cytochromes P450.

TEST SYSTEM
Characterized, pooled, human hepatic microsomes from fourteen individuals (Lot No. HHM-0291A) were obtained from (b) (4)

STUDY DESIGN
Assays selective for five human hepatic microsomal cytochrome P450 isoenzymes were performed to assess the reversible inhibitory potential of guanfacine. Human hepatic microsomes were incubated with isoenzyme-selective substrates at concentrations approximating the average Km value in each assay. Assays were performed in the absence and presence of guanfacine (0.035 to 3.5 µM), and the activities determined for each isoenzyme-selective substrate. The low concentrations were chosen based on CmaxSS values for guanfacine after a once daily 4 mg dose. The experiment conditions are shown in table below.

Table 53. Method Procedures

CYP	Substrate	Concentration, mcM	Incubation Time, min
1A2	Phenacetin O-Deethylase	100	15
2C9	Diclofenac 4'-Hydroxylase	10	10
2C19	S-Mephenytoin 4'-Hydroxylase	50	60
2D6	Bufuralol 1'-Hydroxylase	10	30
3A4/5	Testosterone 6ß-Hydroxylase	50	3
3A4	Midazolam 1'-Hydroxylase	5	1

Assays were also performed to assess the potential for guanfacine-mediated biotransformation-dependent inhibition of cytochromes P450, which may include reversible inhibition, irreversible inhibition due to test article bioactivation, and product (metabolite) inhibition. The type of inhibition, if present, however, could not be elucidated with the current study design. Briefly, human hepatic microsomes were incubated with NADPH in the absence and presence of guanfacine (3.5 µM) prior to the addition of isoenzyme-selective substrate. Substrate selective for each cytochrome P450 assay was added and the activity determined.

RESULTS
Isoenzyme-selective P450 activities were not substantially affected by guanfacine compared with control incubations. Percent activity remaining was high for all cytochrome P450 assays with

>93% of the activity remaining at the highest guanfacine concentration (3.5 μM). These data indicate that guanfacine is not a reversible-type inhibitor of human cytochromes P450 in vitro under the conditions of this study and suggest that guanfacine may have little inhibitory potential in vivo.
Incubation of human hepatic microsomes with guanfacine (3.5 μM) prior to the addition of substrate had no substantive effect on subsequent cytochrome P450 activities. Percent activity remaining was >83% for all cytochromes P450 assayed compared with control incubations, suggesting that guanfacine may not be an irreversible-type inhibitor and that guanfacine metabolites formed under the conditions of this study may have little substantive inhibitory potential of CYP450. The extent of biotransformation of guanfacine, however, was not assessed in this study and, therefore, no definitive conclusions can be drawn regarding the inhibitory potential of any guanfacine metabolites.

SPONSOR'S CONCLUSIONS
The data presented indicate that guanfacine is not a reversible- or irreversible-type inhibitor of cytochromes P450 CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 in vitro under the conditions of this study.

REVIEWER COMMENT:
In this study, guanfacine did not seem to inhibit the following human CYP450 in vitro: CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.

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4.3 Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	22-037	Brand Name	(b) (4)
OCPB Division (I, II, III)	DIV-1	Generic Name	Guanfacine hydrochloride
Medical Division	PHYCHIATRY	Drug Class	selective postsynaptic agonist of α_2-adrenergic receptors
OCPB Reviewer	ELENA MISHINA	Indication(s)	ADHD
OCPB Team Leader	P. Marroum	Dosage Form	(b) (ER) Tablets
INDs	63,551, (b) (4)	Dosing Regimen	1,2 (b) 3, 4 mg QD
Date of Submission	August 24, 2006	Route of Administration	oral
Estimated Due Date of OCPB Review	May 24, 2007	Sponsor	Shire Development Inc
PDUFA Due Date	June 24, 2007	Priority Classification	S

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	7		
multiple dose:	X	1		
Patients-				
single dose:	X	1		
multiple dose:	X	1		
Dose proportionality -				
fasting /non-fasting single dose:	X	1		
fasting /non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X	1		
gender:	X	1		
pediatrics:	X			
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	3		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	3		
Phase 3 clinical trial:	X	4		
Population Analyses -				

Data rich:				
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X	1		
solution as reference:				
alternate formulation as reference:	X	1		Reference IR tablets
Bioequivalence studies -				
traditional design; single /multi dose:	X	2		
replicate design; single /multi dose:	X	1		
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVIVC):	X			
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Electrophysiololgy Study				
Pharmacodynamic studies				
Total Number of Studies	20+references			
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm?		none		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 22-037, HFD-850(Lee), HFD-860 (Marroum, Mehta, Mishina), Biopharm (CDER)

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Elena Mishina
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Patrick Marroum
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