CLINICAL PHARMACOLOGY REVIEW

NDA:	22-037 (seq 0007)
Submission Type:	Efficacy Supplement
Brand Name:	INTUNIV™
Generic Name:	Guanfacine (SPD503)
Indication:	Treatment of ADHD as adjunctive treatment with psychostimulants
Route of Administration:	Oral
Formulation and Strength:	Extended release tablets (1, 2, 3, 4 mg)
Sponsor:	Shire
OCP Division:	Division of Clinical Pharmacology 1
OND Division:	Division of Psychiatry Products
Submission Dates:	4/28/2010
Reviewer:	Jee Eun Lee, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

Table of Contents

1 Executive Summary

1.1 Postmarketing commitment

INTUNIV™ (guanfacine HCl, SPD503) is a selective α2A-adrenergic receptor agonist which was approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescent ages 6 to 17 years in 2009. Upon approval, the sponsor was asked to conduct an efficacy and safety study of guanfacine as adjunctive treatment with long-acting oral psychostimulants for the treatment of ADHD in pediatric patients with ages 6 to 17 years. This submission includes three clinical studies: A short-term, placebo-controlled efficacy and safety study (SPD503-313), two drug interaction studies: one with CONCERTA® (SPD503-114), and the other with VYVANSE® (SPD503-115).

1.2 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The two drug interaction studies conclude that there are no drug interactions between guanfacine and methylphenidate following co-administration of 4 mg of INTUNIV™ and 36 mg of CONCERTA®, and between guanfacine and lisdexamfetamine when following co-administration of 4 mg of INTUNIV™ and 50 mg of VYVANSE®.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the relevant regulatory history for the proposed drug product?

This submission includes overviews of nonclinical and clinical data generated to support the safety and efficacy of the administration SPD503 (guanfacine hydrochloride extended-release tablets) in combination with a psychostimulant for the treatment of attention deficit hyperactivity disorder (ADHD). INTUNIV™ is a selective α_{2A}-adrenergic receptor agonist and was approved in September 2009 for the treatment of ADHD in children and adolescents 6-17 years as monotherapy.

When the approval was granted, the sponsor was asked to conduct drug interaction studies with frequently prescribed psychostimulants to the target population. The usual therapy for the treatment of ADHD has been psychostimulatnts, such as methylphenidate and amphetamine. These drugs are controlled substances and have been used in children since 1937 in ADHD and its diagnostic precursors. Despite the effectiveness of psychostimulant medications, some patients have a suboptimal response or have side effects, and possible exacerbation of some common comorbid conditions such as anorexia, tics and insomnia.

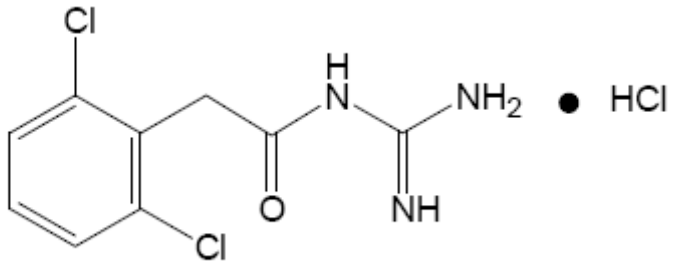
A combination therapy has been introduced as an option to these patients since SPD503 and psychostimulants have different and potentially complementary mechanisms of action. The potential for additive efficacy and the possibility of an offsetting of some common side effects have been reported to occur with either compound alone. Thus combination therapy for psychiatric disorders in children and adolescents has been of interest. However, information based on rigorous, well-controlled data to guide physicians on dosage, drug-drug interactions and potential side effects is limited.

The sponsor completed 24 studies with guanfacine to date. Nineteen of them were included in the original submission and 3 studies are included in this supplementary NDA submission. They are: assessments of pharmacokinetics of guanfacine following administration of INTUNIV in combination with methylphenidate (CONCERTA®) or lisdexamfetamine dimesylate (VYVANSE®) (SPD503-114 and SPD503-115, respectively) and a Phase 3, double-blind, randomized, placebo-controlled, safety and efficacy study examining the combined administration of SPD503 with a long-acting, oral psychostimulant (SPD503-313).

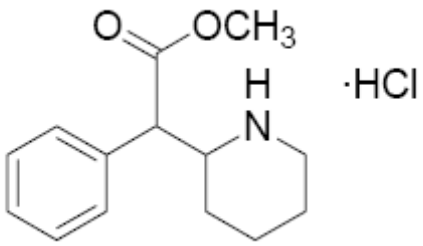
Guanfacine is a substrate of CYP3A4 but either of the two psychostimulants used in the drug interaction studies is not a substrate or inducer of CYP3A4. Therefore, drug-interaction based on CYP metabolism is not expected. The psychostimulants used in the Phase 3 trial were ADDERALL XR® (mixed salts of a single-entity amphetamine product), VYVANSE®, CONCERTA®, FOCALIN XR® (dexmethylphenidate HCl), RITALIN LA® (methylphenidate HCl extended-release), METADATE CD® (methylphenidate HCl), or FDA-approved generic equivalents.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

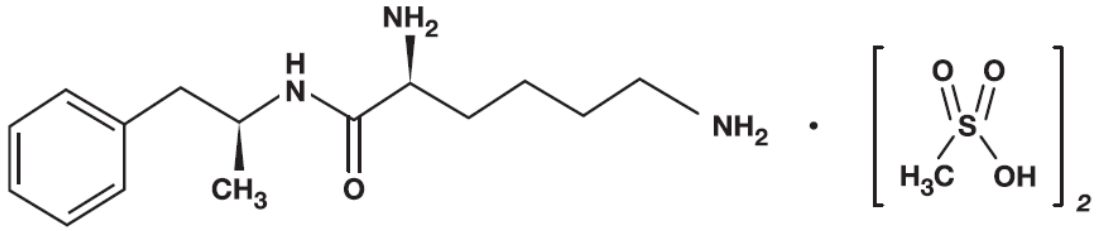
The structure of guanfacine hydrochloride (HCl) is shown in the figure below. Guanafacine HCl is a substituted acetamide whose molecular weight is 282.56.



Four available extended-release tablets of CONCERTA® contain 18, 27, 36, or 54 mg of methylphenidate HCl USP and they are designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is *d,l* (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride and its molecular weight is 269.77. The structure of methylphenidate is shown in the figure below.



The oral capsule of VYVANSE® contains 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg of lisdexamfetamine dimesylate of which molecular weight is 455.60. Lisdexamfetamine is a prodrug of dextroamphetamine and its chemical structure is shown in the figure below.



2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The exact mechanism is unknown. SPD503 is a selective α_2 agonist. Based on preclinical studies, the mechanism of action of guanfacine is hypothesized to be due to an effect on the dorsolateral prefrontal cortex (DLPFC), where guanfacine is thought to mimic the effect of norepinephrine at post-synaptic α2A-adrenoreceptors and increase regional cerebral blood flow to improve the cognition and behavior in patients with ADHD.

2.1.4 What are doses used in drug-drug interaction studies? Are they appropriate?

The recommended starting dose of INTUNIV™ is 1 mg/day and the dose is titrated. The maintenance dose is determined within 1-4 mg/day depending on clinical response and tolerability.

The recommended starting dose of CONCERTA® is 18 mg/day and then titrated by monitoring clinical response and tolerability. The maximum dose is 54 mg/day. The recommended staring dose of VYVANSE® is 30 mg/day and then titrated by monitoring clinical response and tolerability. The maximum recommended dose is 70 mg/day.

The doses used in the drug-drug interaction studies were: 4 mg of INTUNIV™ and 36 mg of CONCERTA® for study SPD503-114; 4 mg of INTUNIV™ and 50 mg of VYVANSE® for study SPD503-115. Since all three drugs have dose proportionality within the dose range, the results from these drug-interaction studies are clinically meaningful.

2.2 General Clinical Pharmacology

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

There are two drug-drug interaction studies for SPD503 and the two psychostimulants, and one Phase 3 clinical trial where SPD503 was evaluated as an adjunctive treatment with various long-acting psychostimulants for ADHD.

Study ID	Phase	Content
SPD503-114	Phase 1	Drug-drug interaction study with CONCERTA® in healthy adults
SPD503-115	Phase 1	Drug-drug interaction study with VYVANSE® in healthy adults
SPD503-313	Phase 3	Dose optimization study evaluating efficacy and safety of SPD503 in combination with psychostimulants in children and adolescents aged 6-17 years with ADHD

The sponsor found that there was no drug-drug interaction between SPD503 and either of the two psychostimulants, *d*-methylphenidate or lisdexamfetamine (*d*-amphetamine) following administration of 4 mg of INTUNIV™ and 36 mg of CONCERTA®, or 4 mg of INTUNIV™ and 50 mg of VYVANSE®.

The equivalence assessment for the data from SPD503-114 indicated that the mean concentrations of guanfacine following co-administration of CONCERTA® along with SPD503 and SPD503 alone are the same. The 90% confidence interval (CI) for the geometric least square mean ratios for both Cmax and $AUC_{0-\infty}$ between the treatments (combination/alone) fell within the range of 0.80-1.25. Another equivalence assessment concluded that the mean concentrations of *d*-methylphenidate following co-administration of CONCERTA® along with SPD503 and CONCERTA® alone are the same. The 90% CI for the geometric least square mean ratios for both Cmax and $AUC_{0-\infty}$ between the treatments fell within the range of 0.80-1.25.

The mean guanfacine Cmax increased by 19% when co-administered with VYVANSE®, which led the 90% CI of the ratio of geometric least square mean of guanfacine Cmax following SPD503 co-administered with VYVANSE® to that of guanfacine Cmax following SPD503 alone fell outside the range of 0.80-1.25. The 90% CI of the ratio of geometric least square mean of guanfacine AUC following SPD503 co-administered with VYVANSE® to that of guanfacine AUC following SPD503 alone fell within the range of 0.80- 1.25. However, the 19% increase in guanfacine Cmax following co-administration of 4 mg of SPD503 and 50 mg of VYVANSE® is not clinically significant.

The 90% CI of the ratio of geometric least square mean of *d*-amphetamine for both Cmax and AUC following VYVANSE® in combination with SPD503 to d-amphetamine following VYVANSE® alone fell within the range of 0.80-1.25.

2.2.2 What are the PK characteristics of the drug?

The general PK characteristics of SPD503 are summarized from the approved label.

Guanfacine is readily absorbed and approximately 70% bound to plasma proteins independent of drug concentration. The extended release form of guanfacine, INTUNIV™ produces peak plasma concentration at approximately 5 hour after oral

administration in children and adolescents with ADHD. Immediate-release guanfacine and INTUNIV™ have different pharmacokinetic characteristics. Since INTUNIV™ was used for this supplement NDA, the pharmacokinetics of the immediate-release guanfacine is not included.

The Cmax (n=52) was 1.0±0.3 ng/mL and Tmax was 6.0 (4.0-8.0) hours post-dose. The $AUC_{0-\infty}$ was 32±9 ng*hr/mL and the half-life was 18±4 hours.

There was a food effect in INTUNIVTM pharmacokinetics. The mean Cmax and AUC increased by 75% and 40 %, respectively, with a high-fat breakfast compared to those under fasting condition.

The Cmax and $AUC_{0-\infty}$ of guanfacine were dose proportional following administration of singles doses of 1 mg, 2 mg, 3 mg, and 4 mg of INTUNIV™ to adults.

Guanfacine is a substrate of CYP3A4/5 thus its exposure may be affected by CYP3A4/5 inducers or inhibitors. Any studies to investigate the impact of renal impairment or hepatic impairment on PK of guanfacine in children have not been conducted.

3 Detailed Labeling Recommendations

7.6 Oral Methylphenidate
In a drug interaction study (N=35), neither INTUNIV™ (4 mg) nor CONCERTA® (methylphenidate HCl) (36 mg) were found to affect the pharmacokinetics of the other drug when co-administered.

7.7 Lisdexamfetamine Dimesylate
In a drug interaction study (N=40), administration of INTUNIV™ (4 mg) in combination with VYVANSE® (lisdexamfetamine dimesylate)(50 mg) increased guanfacine maximum plasma concentration by 19%, whereas exposure (area under the curve; AUC) was increased by 7%. These small changes are not expected to be clinically meaningful. In this study, no effect on d-amphetamine exposure was observed following co-administration of INTUNIV™ and VYVANSE®.

Reviewer's comment: The proposed labeling statements relevant to clinical pharmacology appropriately reflect the results obtained from the two drug-drug interaction studies. They are acceptable.

4 Appendix: Individual Study Summary

SPC503-114

Title: A Phase 1, open-label, randomized, three-period crossover, drug interaction study evaluating the pharmacokinetic profiles of SPD503 and CONCERTA®, administered alone and in combination in healthy adult volunteers

Principal Investigator: Benno G. Roesch, MD

Study duration: 18 May 2009 ~ 06 July 2009

Objectives:

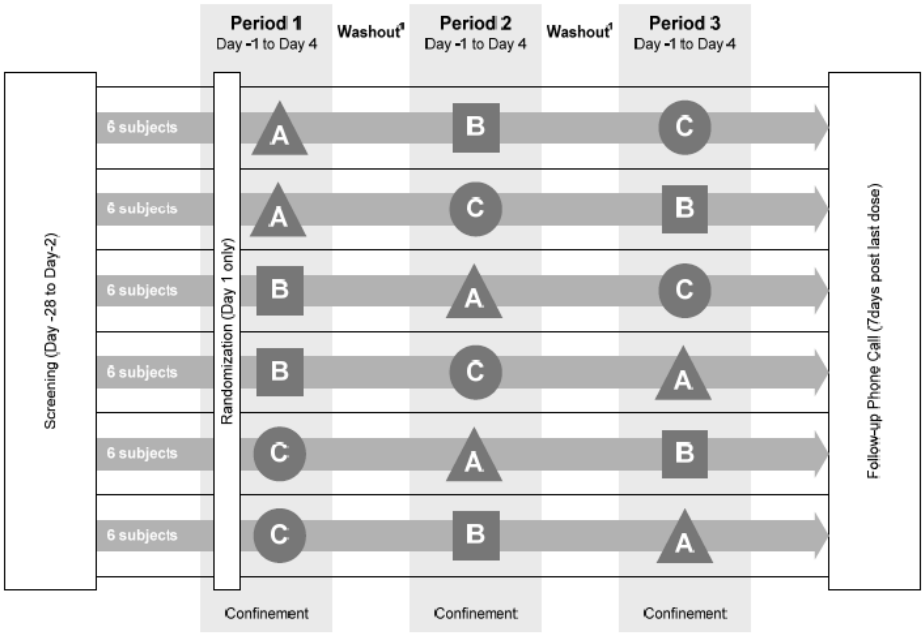
- Primary: to examine the pharmacokinetics of 2 products, SPD503 and methylphenidate hydrochloride (HCl) (CONCERTA®), when administered in single doses alone and in combination.
- Secondary: To provide safety information for SPD503 when administered alone and in combination with CONCERTA®

Population: Forty-two healthy subjects were planned to enroll; 38 (age 18-45 years) were randomized and included in PK analysis and safety assessment. Thirty-five subjects completed the study.

Background: Guanfacine is known to be metabolized by CYP3A4 but methylphenidate is neither a substrate nor an inhibitor/inducer. Therefore no drug-drug interaction caused by CYP3A metabolism is anticipated. This study was conducted because SPD503 is likely to be co-administered with other stimulants such as methylphenidate HCl to treat ADHD.

Methodology: Thirty-eight subjects were randomized after screening. Subjects were confined in the clinic for 4 days during each of the three treatment periods, with a 7-day washout between each treatment.

Arm	Treatment	Dose
Placebo	Placebo	N/A
1	SPD503	4 mg
2	CONCERTA®	36 mg
3	SPD503+ CONCERTA®	4 mg + 36 mg



A Regimen A: SPD503 4mg (extended release)
B Regimen B: Concerta® 36mg
C Regimen C: Co-administered SPD503 4mg (extended release) and Concerta® 36mg

[1]There is to be at least a 7-day Washout between the Day 1 dosing days of the three Periods.

PK Results: Guanfacine concentrations in human plasma from samples from relevant regimens (A and C) were determined using a validated LC/MS/MS method. Likewise, d-methylphenidate and l-methylphenidate concentrations in human plasma from samples from relevant regimens (B and C) were determined using validated LC/MS/MS methods. The LLOQ for guanfacine was 0.05 ng/mL and LLOQ for both d-methylphenidate and l-methylphenidate was 0.25 ng/mL. The assay for each analyte was validated (guanfacine: CV<7% and |Bias|<8% from nominal values; *d*-methylphenidate: CV<7%, |Bias|<7% from nominal values; *l*-methylphenidate: CV<8%, |Bias|<8% from nominal values).

Profiles of guanfacine plasma concentrations following administration of SPD503 alone and in combination with CONCERTA® are shown in Figure 1. As shown in the figure, co-administration of SPD503 with CONCERTA® did not alter the pharmacokinetics of guanfacine. PK parameters following the two treatments are reported in Table 1, and the results from the equivalence assessment for Cmax and AUC are reported in Table 2.

The 90% confidence interval of the ratio of geometric least square mean of Cmax and AUC of guanfacine following SPD503 in combination with CONCERTA® to those of guanfacine following SPD503 alone fell within the range of 0.80-1.25.

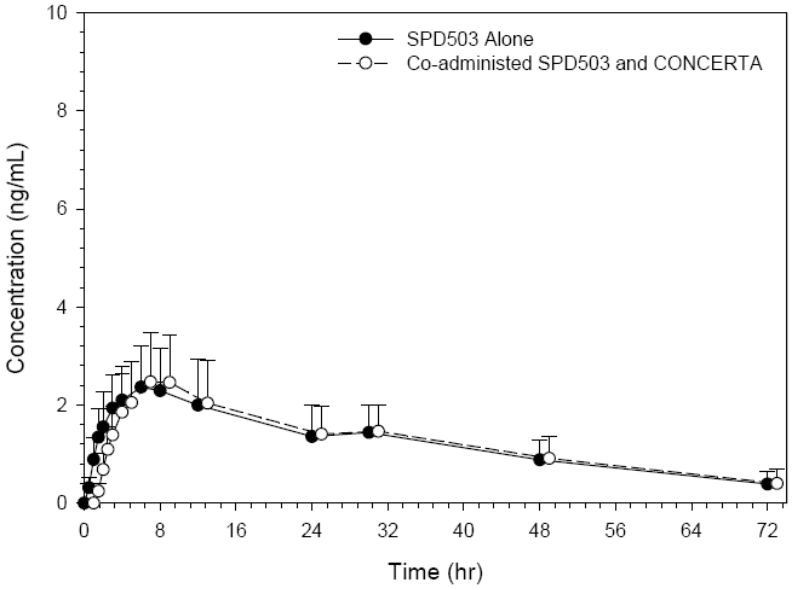


Figure 1. Mean guanfacine concentrations over time following administration of SD503 alone and in combination with CONCERTA®

Table 1. Summary of guanfacine pharmacokinetic parameters

	Cmax (ng/mL)	Tmax (hr)	$AUC_{0-\infty}$ (ng*hr/mL)	$T_{1/2}$ (hr)	CL/F (L/hr/Kg)	Vz/F (L/Kg)
SPC503 alone						
N	37	37	33	33	33	33
Mean (SD)	2.6 (0.9)	8.1 (8.1)	96.5 (7.3)	20.4 (7.9)	0.6 (0.2)	16.9 (5.8)
Median	2.4	6	86.6	17.3	0.6	16.6
Min, Max	1.3, 4.9	2, 48	38.9, 175.2	11, 40.4	0.3, 1.3	6.3, 30.8
SPD503 + CONCERTA®						
N	36	36	34	34	34	34
Mean (SD)	2.7 (0.9)	8.7 (6.3)	106.7 (39.9)	22.7 (10.6)	0.6 (0.2)	16.7 (6.2)
Median	2.6	6	103.7	19.2	0.5	15.1
Min, Max	1.3, 4.9	3, 30	38.5, 218.4	12.7, 55.2	0.25, 1.3	8.9, 34.7

Table 2. Geometric mean ratios of pharmacokinetic parameters for the comparison of guanfacine following administration of SPD503 alone and SPD503+CONCERTA®

Parameter	Geometric LS Means		GLSM Ratio (Test/Reference)	Confidence Interval for GLSM Ratio
	Reference (SPD503 alone)	Test (SPD503+ CONCERTA®)		
$AUC_{0-\infty}$ (ng*hr/ml)	91.67	101.7	1.109	(0.997, 1.235)
Cmax (ng/mL)	2.45	2.61	1.065	(0.945, 1.2)

The mean concentrations of *d*-methylphenidate following administration of CONCERTA® alone and in combination with SPD503 are shown in Figure 2 and they do not show any significant difference. As shown in Table 3, the pharmacokinetic parameters for *d*-methylphenidate following administration of CONCERTA® alone and in combination with SPD503 do not seem to have significant difference. The 90% confidence interval for the geometric least square mean ratios for both Cmax and $AUC_{0-\infty}$ between the treatments fell within 0.8-1.25 as shown in the table below.

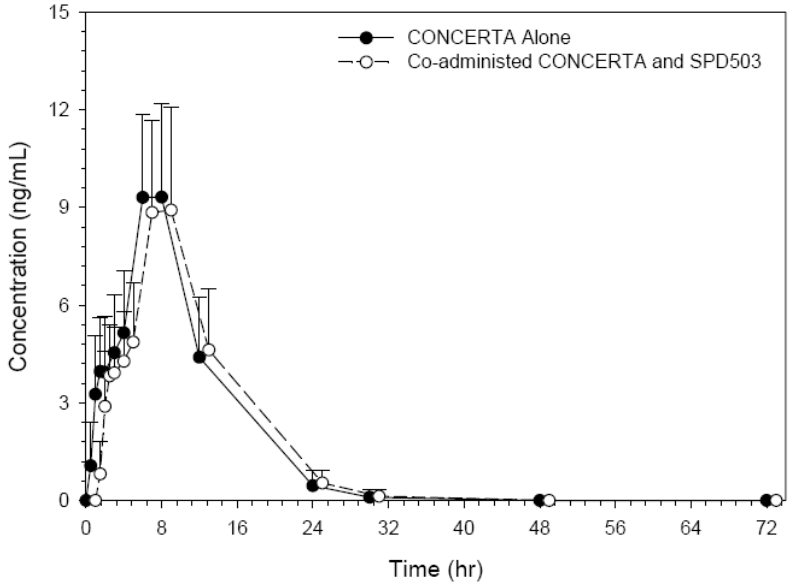


Figure 2. Mean *d*-methylphenidate concentrations over time following administration of CONCERTA® alone and in combination with SPD503

Table 3. A summary of *d*-methylphenidate pharmacokinetic parameters following administration of CONCERTA® alone and in combination with SPD503

	Cmax (ng/mL)	Tmax (hr)	$AUC_{0-\infty}$ (ng*h/mL)	$T_{1/2}$ (hr)	CL/F (L/hr/Kg)	Vz/F (L/Kg)
CONCERTA® alone						
N	38	38	32	32	32	32
Mean (SD)	9.9 (2.8)	6.9 (1)	102.8 (34.6)	3.9 (0.7)	5.1 (1.7)	28.8 (11.6)
Median	10.1	6	100.2	3.8	4.9	24.1
Min, Max	5.1, 16.0	6, 8.1	50.2, 216.3	2.9, 5.7	2.2, 8.7	15.9, 71.3
CONCERTA®+ SPD503						
N	37	37	32	32	32	32
Mean (SD)	9.5 (2.9)	7.4 (1.3)	100.5 (33)	4.1 (0.6)	5.0 (1.4)	28.6 (7.1)
Median	8.8	8	94.9	4	5.2	28.5

Min, Max	5.4, 18.2	6, 12	57.6, 215.7	3.1, 5.3	2.2, 7.2	15.2, 40.2

Table 4. Geometric mean ratios of pharmacokinetic parameters for the comparison of *d*-methylphenidate following administration of CONCERTA® alone and CONCERTA®+SPD503

Parameter	Geometric LS Means		GLSM Ratio (Test/Reference)	90% Confidence Interval for GLSM Ratio
	Reference (CONCERTA® alone)	Test (CONCERTA®+ SPD503)		
$AUC_{0-\infty}$ (ng*hr/ml)	94.73	94.83	1.001	0.958, 1.046
Cmax (ng/mL)	9.60	9.19	0.957	0.907, 1.01

Furthermore, as shown in Figure 3, there is no difference in the mean *l*-methylphenidate plasma concentrations following administration of CONCERTA® alone and in combination with SPD503.

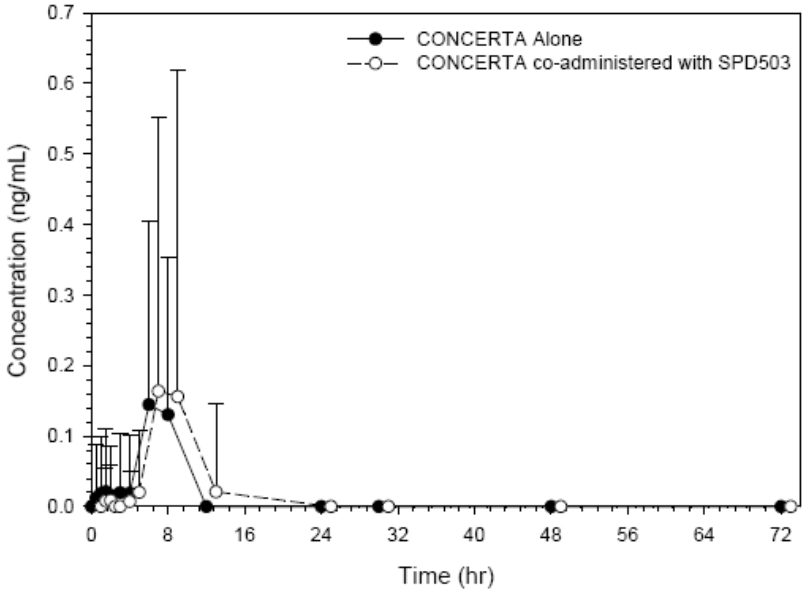


Figure 3. Mean *l*-methylphenidate concentrations over time following administration of CONCERTA® alone and in combination with SPD503

Safety Results: Forty-two percent of subjects reported at least one treatment-emergent AE (TEAE). None of the TEAEs were unexpected. The most frequently reported TEAE was headache, which occurred most frequently following administration of CONCERTA®. There were no differences in type, incidence, or severity of TEAE between treatments.

Reviewer's comments: The dose of SPD503 was 4 mg, which is the maximum recommended dose and the dose of CONCERTA® was 36 mg (the maximum

recommended dose is 54 mg), thus the negative drug-interaction results obtained from this study are clinically useful and acceptable. There is no drug-drug interaction between SPD503 and methylphenidate.

SPD503-115

Title: A phase 1, open-label, randomized, three-period crossover drug interaction study evaluating the pharmacokinetic profiles of SPD503 and VYVANSE®, administered alone and in combination in healthy adult volunteers

Objectives:

- Primary: To examine the pharmacokinetics of the two products, SPD503 and dextroamphetamine (*d*-amphetamine) resulting from lisdexamfetamine dimesylate (VYVANSE®), when administered in single doses alone and in combination.
- Secondary: To provide safety information for SPD503 when administered alone and in combination with VYVANSE®

Rationale: SPD503 is likely to be co-administered with other stimulants such as lisdexamfetamine dimesylate to treat ADHD. Pharmacokinetic drug-drug interactions can occur when two drugs are co-administered, resulting in a change in ADME. Guanfacine is known to be metabolized by CYP3A4. However, lisdexamfetamine is not metabolized by CYP3A4 and is neither an inducer nor inhibitor of CYP3A4.

Methodology: Open-label, randomized, single-center, 3-period crossover, drug-drug interaction study.

Population: Forty two healthy adults (mean 30.5 years, range 18-45 years, 78.6% male) were randomized and included in pharmacokinetics analysis and safety. Forty subjects completed the study.

Treatments: Single-oral doses of 4 mg SPD503 and 50 mg VYVANSE® (lisdexamfetamine dimesylate) alone and in combination.

Regimen A	SPD503 4 mg
Regimen B	VYVANSE® 50 mg
Regimen C	SPD503 4 mg + VYVANSE® 50 mg

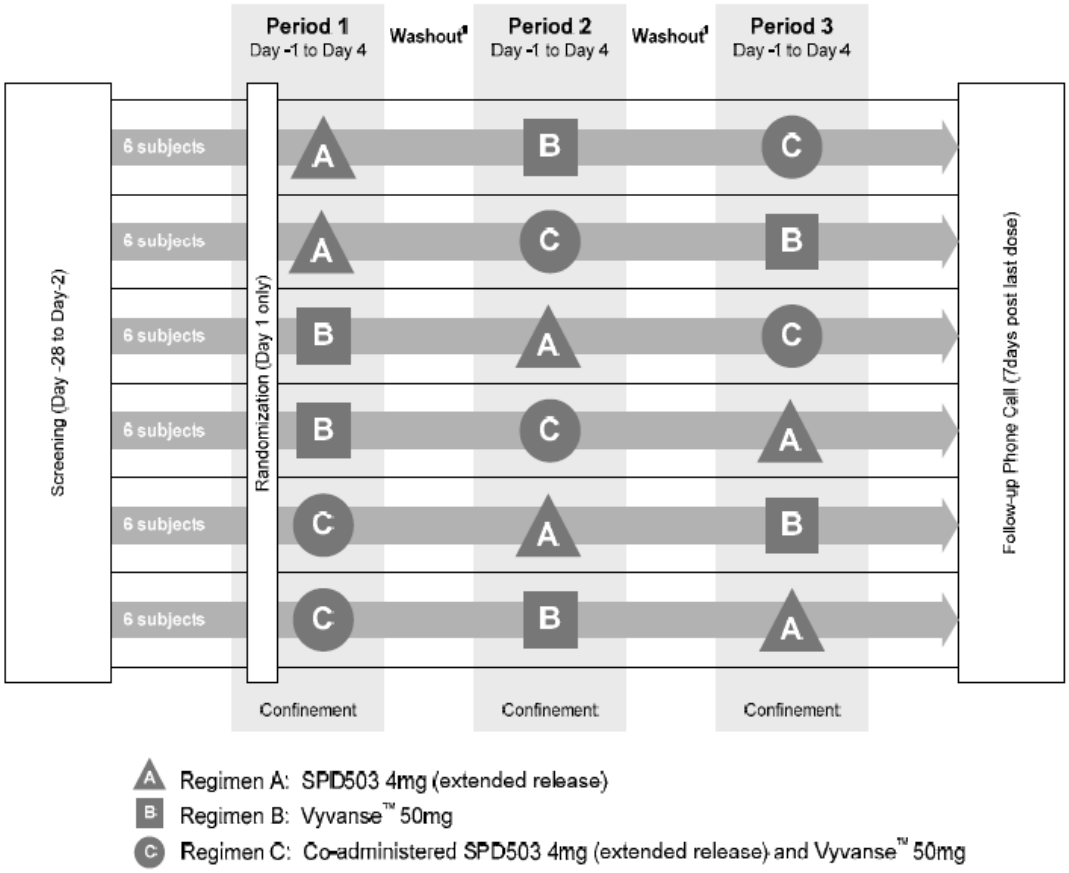


Figure 4. Study design flow chart (There was a 7-day washout between treatments)

Duration of treatment: Subjects were confined to the unit for 4 days during each of the three treatment periods, with a 7-day washout between each treatment. The total confinement for this study was 12 days.

Pharmacokinetic results:

Blood samples were to be collected at Pre-dose (within 30 minutes of administration) and at 0.5, 1.0, 1.5., 2.0, 3.0, 4.0, 6.0, 8.0, 12, 24, 30, 48, and 72 hours after receiving the investigational medicinal product on Day 1 of Treatment Periods 1, 2, and 3. They were analyzed to measure plasma concentrations of guanfacine, lisdexamfetamine, and *d*-amphetamine using a validated LC/MS/MS. The LLOQ of guanfacine, *d*-amphetamine, and lisdexamfetamine were 0.05 ng/mL, 2 ng/mL, and 1 ng/mL, respectively. The assay for each analyte was validated (guanfacine: CV<7%, |Bias|<12% from nominal values; lisdexamfetamine: CV<7%, |Bias|<5% from nominal values; *d*-amphetamine: CV<5%, |Bias|<6% from nominal values)

The mean guanfacine plasma concentrations following administration of SPD503 alone and in combination with VYVANSE® are shown in Figure 5. As shown in the figure, the mean guanfacine plasma concentration following administration of SPD503 alone were slightly lower than the mean guanfacine plasma concentration following co-administration with VYVANSE®. As reported in Table 5, the Cmax of guanfacine

following co-administration of SPD503 with VYVANSE® is higher than that following administration of SPD503 alone. The guanfacine Cmax was increased by 19% when co-administered with VYVANSE® and the equivalence assessment (Table 6) shows that 90% CI for the ratio of geometric least square mean for Cmax of guanfacine fell outside the range of 0.80-1.25. The 90% confidence interval for the geometric ratio of guanfacine $AUC_{0-\infty}$ following SPD503 in combination with VYVANSE® to guanfacine following SPD503 alone fell within the range of 0.8 to 1.25.

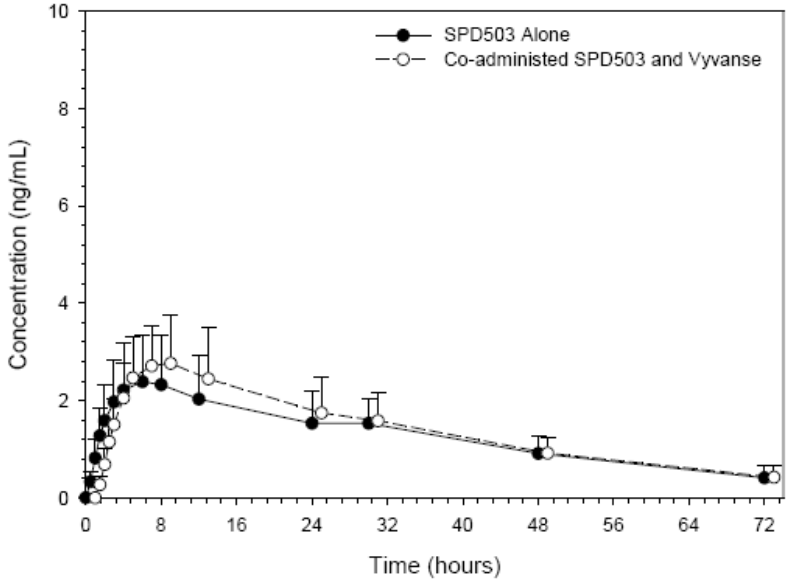


Figure 5. Mean guanfacine concentrations over time following administration of SPD503 alone and in combination with VYVANSE®

Table 5. Summary of guanfacine pharmacokinetic parameters

	Cmax (ng/mL)	Tmax (hr)	$AUC_{0-\infty}$ (ng*h/mL)	$T_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)
SPD503 Alone						
N	40	40	37	37	37	37
Mean (SD)	2.55 (1.03)	8.6 (7.7)	104.9 (34.7)	23.5 (10.2)	0.54 (0.17)	17.36 (7.54)
Median	2.30	6	102.4	20.5	0.51	15.34
Min, Max	0.98, 5.79	1.5, 30	54, 218.2	11.4, 50	0.27, 1.04	7.02, 38.05
SPD503 + VYVANSE®						
N	41	41	39	39	39	39
Mean (SD)	2.97 (0.98)	7.9 (5)	112.8 (35.7)	21.4 (8.2)	0.5 (0.15)	15.33 (7.35)
Median	2.87	6	109.4	18.8	0.46	13.61
Min, Max	1.52, 5.60	3, 30	61.5, 213.6	11.9, 48.2	0.3, 0.89	6.36, 44.79

Table 6. Equivalence assessment for drug interaction for guanfacine following administration of SPD503 alone and in combination with VYVANSE®

Parameter	Geometric LS Means		GLSM Ratio (Test/Reference)	90% Confidence Interval for GLSM Ratio
	Reference (SPD503 Alone)	Test (SPD503+ VYVANSE®)		
$AUC_{0-\infty}$ (ng*hr/mL)	101.2	108.0	1.068	0.981, 1.162
Cmax (ng/mL)	2.38	2.83	1.187	1.066, 1.321

The mean *d*-amphetamine plasma concentrations following administration of VYVANSE® alone and in combination with SPD503 are shown in Figure 6. As shown in the figure and Table 7, there is no significant effect of co-administration with SPD503 on the *d*-amphetamine pharmacokinetics. The 90% CI of the geometric mean ratio of *d*-amphetamine following VYVANSE® in combination with SPD503 to *d*-amphetamine following VYVANSE® alone fell within the interval (0.80, 1.25) for Cmax and $AUC_{0-\infty}$.

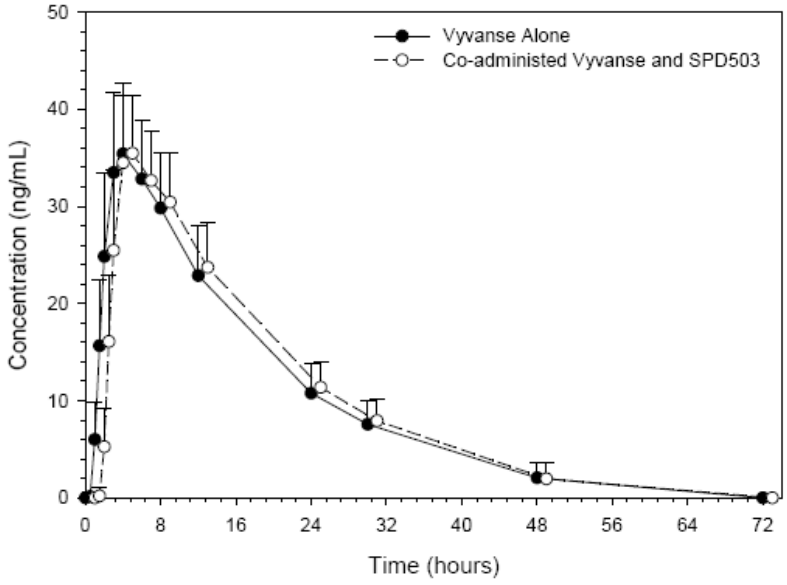


Figure 6. Mean *d*-amphetamine concentrations over time following administration of VYVANSE® alone and in combination with SPD503.

Table 7. Summary of *d*-amphetamine pharmacokinetic parameters

	Cmax (ng/mL)	Tmax (hr)	$AUC_{0-\infty}$ (ng*hr/mL)	$T_{1/2}$ (hr)	CL/F (L/hr/kg)	Vz/F (L/kg)
VYVANSE® Alone						
N	41	41	41	41	41	41

Mean (SD)	36.48 (7.13)	4.2 (1.1)	686.9 (159.8)	11.2 (1.6)	0.99 (0.23)	15.58 (2.52)
Median	36.95	4	687.7	11.3	0.93	15.33
Min, Max	20.51, 57.15	3.6	324.6, 1070	8.3, 14.6	0.66, 1.8	11.16, 21.77
VYVANSE® + SPD503						
N	41	41	41	41	41	41
Mean (SD)	36.50 (6.00)	3.9 (1.1)	708.4 (137.8)	11.2 (1.5)	0.95 (0.17)	15.11 (2.37)
Median	35.71	4	713.6	11	0.95	14.43
Min, Max	23.05, 53.06	3, 8	456.1, 954.1	8, 15.1	0.67, 1.34	11.45, 23.8

Table 8. Equivalence assessment for drug interaction for *d*-amphetamine following administration of SPD503 alone and in combination with VYVANSE®

Parameter	Geometric LS Means		GLSM Ratio (Test/Reference)	90% Confidence Interval for GLSM Ratio
	Reference (VYVANSE® Alone)	Test (VYVANSE®+ SPD503)		
$AUC_{0-\infty}$ (ng*hr/ml)	672.1	685.9	1.02	0.983, 1.06
Cmax (ng/mL)	36.03	35.78	0.993	0.967, 1.019

The prodrug, lisdexamfetamine's mean concentration did not change significantly either following co-administration of SPD503 and VYVANSE® compared to VYVANSE® alone (Figure 7). No pharmacokinetics parameters and equivalence assessment were reported.

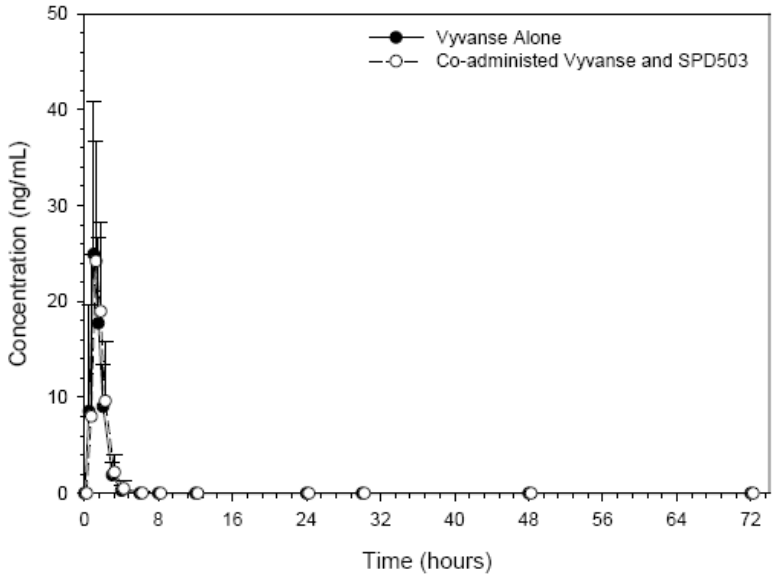


Figure 7. Mean lisdexamfetamine concentrations over time following administration of VYVANSE® alone and in combination with SPD503.

Conclusions: The 90% CI of the ratio of geometric least square mean of guanfacine AUC following SPD503 co-administered with VYVANSE® to that of guanfacine AUC following SPD503 alone fell within the range of 0.80-1.25. However the 90% CI of the ratio of geometric least mean ratio of guanfacine Cmax following SPD503 co-administered with VYVANSE® to that of guanfacine Cmax following SPD503 alone did not fall within the range of 0.80- 1.25.

The 90% CI of the ratio of geometric least square mean of *d*-amphetamine for Cmax and AUC following VYVANSE® in combination with SPD503 to *d*-amphetamine following VYVANSE® alone fell within the range of 0.80-1.25.

Although 19% increase in guanfacine Cmax following co-administration of SDP503 and VYVANSE® was observed, it is not clinically meaningful to be interpreted as drug-drug interaction.

Reviewer's Comments: The recommended initial dose for guanfacine is 1 mg and the recommended maintenance doses are 1–4 mg. According to the approved labeling, the pharmacokinetics of guanfacine is dose-proportional within the range of 1–4 mg. Thus the conclusion for the drug interaction could be applied to all doses. In clinical practice, the two drugs will be given at different times, with amphetamine administered in the morning and guanfacine at bedtime. The DDI study has both administered together at the same time, which shows for an increase in Cmax of guanfacine. Clinically there will be a considerable time elapsed between their respective administrations, such that by the time guanfacine is given at bedtime, a considerable amount of amphetamine will have been eliminated. Therefore, the 19% increase in Cmax and the 7% increase in AUC of guanfacine following co-administration of 4 mg of guanfacine and 50 mg of VYVANSE® represent the most rigorous situation.

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/s/

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11/02/2010

RAMAN K BAWEJA
11/02/2010