CLINICAL REVIEW

Application Type:	NDA
Submission Number:	22,037
Submission Code:	
Letter Date:	August 24, 2006
Stamp Date:	August 27, 2006
PDUFA Goal Date:	June 24, 2007
Reviewer Name:	Robert L. Levin, M.D.
Review Completion Date:	June 12, 2007
Established Name:	Guanfacine hydrochloride
Proposed Trade Name:	Intuniv
Therapeutic Class:	Central ά-2adrenergic-receptor agonist
Applicant:	Shire
Priority Designation:	S
Formulation:	Oral, extended-release tablet
Dosing Regimen:	Once daily
Indication:	Attention-Deficit/Hyperactivity D/O
Intended Population:	Pediatrics (ages 6-17)

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1 EXECUTIVE SUMMARY

1.1 Recommendations on Regulatory Action

I recommend that the Division of Psychiatry Products take an Approvable action for NDA 22-037. In my opinion, the sponsor has demonstrated the efficacy and safety of Intuniv (guanfacine extended-release) in the treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in children and adolescents (ages 6-17 years-old). Studies 301 and 304 were adequate and well-controlled trials that demonstrated the efficacy of Intuniv, as measured by the change in mean Attention Deficit-Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) scores. There was a statistically and clinically significant difference in the treatment effect of Intuniv compared to placebo in both placebo-controlled trials. Furthermore, the treatment effect was dose-related and exposure-related.

In my opinion, treatment with Intuniv was reasonably safe and well tolerated in the trials. While there were clinically significant adverse events in the trials, many of the potential safety concerns can be managed largely through rational dosing on an mg/kg basis. For, a considerable portion of the common and significant adverse events appear to be dose-related and exposure-related. Guanfacine exposures were highly correlated (inversely) with subjects' body weights. Furthermore, the sponsor used fixed doses, instead of dosing per body weight in the trials.

1.2 Recommendations on Postmarketing Actions

1.2.1 Required Postmarketing Commitments

- The sponsor should conduct a dedicated, thorough QT study of guanfacine in healthy adult subjects. (Preliminary details will be discussed below in the Cardiorenal QT Interdisciplinary Review Team consult).
- The sponsor should conduct a controlled trial in adolescent subjects with ADHD, in order to confirm that treatment with Intuniv is safe and effective in this population.
- The sponsor should conduct a controlled trial of adjunctive treatment with guanfacine stimulant medications in children and adolescents with ADHD.
- The sponsor should continue to collect ECG data in ongoing pediatric trials.
- The sponsor should conduct a placebo-controlled maintenance trial to assess the long-term efficacy and safety of guanfacine in children and adolescents with ADHD. This should probably be a placebo-controlled randomized withdrawal study.
- The sponsor should conduct a separate long-term safety study, focusing on the following safety concerns: growth, weight gain, metabolic effects, QT interval prolongation, syncope and other cardiovascular safety parameters, seizures, sedative adverse events, cognitive performance, and effects on growth hormone and bilirubin concentrations.

1.2.2 Risk Management Activity

The sponsor should submit a detailed Risk Management Plan that focuses on managing the potential cardiovascular risks of QT prolongation, syncope, hypotension, and bradycardia. Risk management should also focus on the common sedative adverse events. The plan should include a detailed discussion of the exposure-related and dose-related risks and a dosing and titration plan based on body weight.

In addition, it would be useful for the sponsor to develop a Med Guide or similar form of communication for educating patients, parents, and caregivers about the potential safety concerns listed above. In developing a Risk Management Plan, the sponsor should probably consult with pediatric cardiologists.

Finally, the sponsor should incorporate should incorporate the data from the American Association of Poison Control Centers publication on pediatric guanfacine overdosages in the labeling for Intuniv™.

1.2.1 Other Phase 4 Requests

We will consider recommending that the sponsor conduct specific drug interaction studies, including guanfacine interactions with: valproic acid and moderate inhibitors of the CYP3A4/5 system.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of the Clinical Program

The clinical development program for Intuniv included ten (10) studies in children and adolescents with a diagnosis of ADHD and eight (8) studies in healthy adult volunteers. The studies in ADHD subjects were: 107, 201, 202, 203, 205, 206, 301, 303, 304, and 305. Studies 301 and 304 were the two (2) pivotal controlled efficacy and safety trials. Studies 303 and 305 were long-term, open-label extension studies of 301 and 205/304, respectively. The eight healthy volunteer studies included studies 101, 102, 103, 104, 106, 108, 109, and 110. Intuniv was used in all of the clinical studies with the exception of studies 101, 201, 202, and 203, which used formulations that are no longer being developed and/or Tenex. In the clinical program, a total of 843 pediatric ADHD subjects were exposed to guanfacine, and 270 adult healthy subjects were exposed to guanfacine.

The pivotal controlled trials (Studies 301 and 304) included 662 subjects. A total of 513 subjects were treated with Intuniv, and 149 subjects were treated with placebo. Subjects were treated with daily Intuniv doses of 1, 2, 3, or 4 mg. (Only Study 304 included an arm with subjects randomized to 1 mg/day).

Study 301 was a multicenter, randomized, double blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of Intuniv compared with placebo in pediatric subjects (ages 6-17) with a diagnosis of ADHD. The study used a

forced dose titration design. Subjects were randomized to target doses of 2, 3, or 4mg/day of Intuniv or placebo. Double-blind assessment proceeded for 8 weeks, with weekly clinic visits scheduled for evaluation and medication dispensing. (There were 48 principal investigators in 48 U.S. study centers. The study period was January 29, 2003 to August 23, 2003).

Study 304 was a multicenter, randomized, double blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of Intuniv compared with placebo in pediatric subjects (aged 6-17) with a diagnosis of ADHD. The study used a forced dose titration design. Subjects were randomized to target doses of 1, 2, 3, or 4mg/day of Intuniv or placebo. Double-blind assessment proceeded for 9 weeks, with weekly clinic visits scheduled for evaluation and medication dispensing. (There were 45 principal investigators at 45 U.S. study sites. The study period was March 30, 2004 to October 7, 2004).

The Phase 1 studies evaluated various early development formulations and the pharmacokinetics, pharmacodynamics, bioavailability, drug metabolism, and drug interactions of Intuniv. The Phase 2 studies continued to evaluate Tenex, early development formulations of Intuniv, and Intuniv in children and adolescents with ADHD.

1.3.2 Efficacy Findings

Two adequate and well controlled trials demonstrated the efficacy of Intuniv in ADHD. Each was positive separately for the primary efficacy endpoint: change in mean ADHD-RS scores for the randomized (intended fixed dose). In addition to being statistically significant, the reductions in mean ADHD-RS in the Intuniv groups, compared to the placebo groups, were clinically significant. The placebo-adjusted changes in mean ADHD-RS scores ranged from − 6.5 to − 10.1 points for the primary efficacy analysis. The results were also positive for the non-pre-specified efficacy analyses: change in mean ADHD-RS in both the actual-dose analysis and the weight-adjusted actual-dose analyses. Furthermore, the efficacy of Intuniv was dose-related and exposure-related. For the actual-dose and weight adjusted actual-dose analyses, the Intuniv treatment effects were larger than those in the randomized dose analysis. The greatest placebo-adjusted treatment effects in these analyses ranged from − 8.9 to − 19 points on the ADHD-RS scale, all of which are clinically significant. In addition, the efficacy analyses were positive separately for the Inattention as well as the Hyperactivity-Impulsivity Subscales.

1.3.3 Safety Findings

Treatment with Intuniv was reasonably safe and well tolerated. There were no deaths in the clinical program. There were few serious adverse events in the placebo-controlled trials. None of them were drug-related: Only four (4) SAE were reported in the controlled trials. None of the SAE appears to have been related to treatment with guanfacine. In Study 301, two (2) subjects treated with guanfacine had serious adverse events. One

subject had an exacerbation of asthma, and another subject with a history of asthma had a pneumothorax. In Study 301, none of the subjects in the placebo group had a serious adverse event. In Study 304, one subject treated with guanfacine had a head injury, concussion, and seizure. One subject in the placebo group had a fracture of the tibia and fibula.

There were a number of discontinuations due to adverse events, most of which were probably drug-related. In the controlled trials, a higher proportion of subjects in the guanfacine group discontinued due to adverse events compared to the placebo group (12% and 4%, respectively). Several of the adverse events in the guanfacine group were likely related to treatment with guanfacine. These included: hypotension (6), QT interval prolongation (3), bradycardia (1), somnolence (19), sedation (11), fatigue (8), asthenia (1), lethargy (1), dizziness (3), nightmare (1), insomnia (1), and headache (5). Adverse events leading to discontinuation that were possibly related to treatment with guanfacine included: affective lability (2), hostility (1), and depression (2).

Adverse events were most commonly reported for the following categories: nervous system, psychiatric, and gastrointestinal. The most commonly reported specific adverse events in the Intuniv group were: somnolence (30%), headache (23%), fatigue (14%), sedation (10%), abdominal pain (10%), hypotension (6%), dizziness (6%), lethargy (6%), irritability (6%), nausea (6%), and insomnia (5%). It is likely that all of these types of adverse events were related to treatment with Intuniv, based on the pattern of AE reports (compared to placebo) and the previous clinical experience with guanfacine. The following adverse events were dose-related or exposure-related in the clinical trials: hypotension, somnolence, sedation, abdominal pain, dizziness, dry mouth, and constipation.

Sedative adverse events were quite commonly reported in the controlled trials. Sedative adverse events included somnolence, sedation, hypersomnia, fatigue, lethargy, and asthenia. In the Intuniv group in the controlled trials, 53% of subjects reported sedative adverse events, compared to 17% of the placebo group. Sedative events were dose-related overall (combining all sedative type events).

Less commonly reported adverse events that were probably drug-related included bradycardia, asthenia, dyspepsia, blood pressure decreased, orthostatic hypotension, QT interval prolongation, weight gain, and postural dizziness. It is possible that the following adverse events were related to treatment with guanfacine: atrioventricular block-first degree, sinus arrhythmia (unspecified), enuresis, and Pollakiuria.

Psychiatric adverse events were reported for a higher proportion in the Intuniv group than in the placebo group. These included: irritability (5%), affective lability (4%); aggression (1.4% vs. 0.7%), agitation (1.4%), depressed mood (0.8%), and anxiety (0.4%). There were single cases of paranoia, psychomotor retardation, bradyphrenia, constricted affect, cognitive slowing, and mental status change. In controlled trials, there were no reports of suicidal ideation or suicidal behavior. There were no reports of mania or hypomania.

Other important findings that were dose-related included decreased blood pressure and decreased heart rate. There were also transient rebound increases in blood pressure and heart rate upon abrupt discontinuation of treatment with Intuniv. In addition, QT interval prolongation occurred in an exposure-related manner.

Syncope was reported for ten (10) pediatric subjects in the Intuniv clinical program. One subject had two episodes. These subjects represented approximately 1.2% of the entire pediatric population exposed to guanfacine. All of these cases of syncope occurred during the long-term, open-label phases of the studies, relatively long after subjects were first exposed to guanfacine. The rate of syncope in the clinical program was higher than the estimated background rate of syncope in the general pediatric population. Several of these patients sought medical attention for the syncopal events. The rate of those seeking medical attention due to syncope in the guanfacine clinical program exceeds the relevant estimated background rate of pediatric patients seeking or reaching medical attention for syncope. It seems likely that exposure to guanfacine was a factor contributing to syncope in at least some of these cases, given the drug's effect on blood pressure and heart rate. In many of the syncope cases, another factor appeared to at least contribute to the syncopal event. These specific factors included: dehydration, heat, exercise, pain, injury, sight of blood, acute psychosocial stressors, gastrointestinal illness, and previous history of presyncopal episodes.

1.3.4 Dosing Regimen and Administration

Intuniv™ is an extended-release tablet and should be dosed once daily. The dosage strengths include 1, 2,(b) (4) 3, and 4 mg tablets. Tablets should not be crushed, chewed, or broken before swallowing, because this will increase the rate of guanfacine release. Patients should begin treatment with a dose of 1 mg per day. The dose should be increased in increments of no more than 1 mg per week. The dose should be maintained within the range of 1mg to 4 mg per day, depending on clinical response and the emergence of adverse events. The clinician should consider dosing on an mg per kg basis, in order to balance the exposure-related potential benefits and risks of treatment. There was a strong inverse correlation between body weight and serum guanfacine concentration in clinical trials. Clinical improvements were observed beginning at doses in the range 0.05-0.08 mg/kg/day. Generally, efficacy increased with increasing weight-adjusted dose (mg/kg). If well tolerated, doses up to 0.12 mg/kg/day were demonstrated to provide additional benefit. Doses above 4 mg have not been studied.

There is a significant food effect on the absorption of Intuniv. When administered with a large high-fat meal, the mean exposures increased significantly. The AUC increased by approximately 40%, and the Cmax increased by approximately 77%, compared to dosing in a fasted state. The food effect could be clinically significant, because many of the important adverse effects of Intuniv occurred in a dose-related or exposure-related manner. Thus, to minimize the potential risks, patients should take Intuniv without food or with a light meal, and they should avoid taking Intuniv with a large or high-fat meal.

Treatment with Intuniv should not be discontinued abruptly, since patients may develop transient increases in blood pressure and heart rate. To minimize the risk of developing these effects, the dose should be tapered in decrements of no greater than 1 mg every 3 to 7 days.

1.3.5 Drug-Drug Interactions

CYP3A4/5 Inhibitors

Guanfacine is metabolized in vitro by cytochrome P4503A4/5. There was a substantial increase in the rate and extent of guanfacine exposure when guanfacine was co-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. These results indicate that concomitant administration of Intuniv and drugs that inhibit CYP3A4 activity could result in increased plasma concentrations of guanfacine, potentially leading to adverse pharmacodynamic effects. When patients are treated concomitantly with Intuniv and a CYP3A4/5 inhibitor, the dose of Intuniv should be reduced appropriately.

CYP3A4 Inducers

There was a significant decrease in the rate and extent of guanfacine exposure when guanfacine was co-administered with rifampin, an inducer of the CYP3A4 system. The Cmax for guanfacine decreased by more than 50% in the presence of rifampin, while AUC0-t and AUC0-inf both decreased by 60% to 70%. Concomitant administration of Intuniv and drugs that induce CYP3A4 activity could result in decreased plasma concentrations of guanfacine, potentially leading to a loss of pharmacodynamic effect and loss of effectiveness. When patients are treated concomitantly with Intuniv and a CYP3A4 inducer, an increase in the dose of Intuniv (within the recommended dose range) should be considered.

Valproic Acid

Published literature indicates that co-administration of guanfacine and valproic acid can result in elevated concentrations of valproic acid. Plasma valproate levels rapidly increased when guanfacine was co-administered. Furthermore, plasma valproate concentration decreased by 41% after guanfacine was tapered and discontinued. Guanfacine may increase plasma valproate concentrations via competition for the glucuronidation pathway, as both drugs are eliminated by this pathway. However, the mechanism of this interaction has not been definitively documented. When Intuniv is co-administered with valproic acid, dosing adjustments may be required.

1.3.6 Special Populations

Renal Impairment

The pharmacokinetics of guanfacine immediate-release was studied in patients with impaired renal function. After intravenous administration to subjects with normal, moderately impaired, or severely impaired renal function. In patients with impaired renal function, there was a substantial reduction in the cumulative urinary excretion of guanfacine and in renal clearance of guanfacine. The degree of the reduction in renal clearance increased as the degree of renal impairment increased. The clinician should consider adjusting the dose of Intuniv in patients with impairment of renal function.

Hepatic Impairment

The pharmacokinetics of guanfacine have not been studied in patients with hepatic impairment. Cytochrome P450 3A4 is the predominant enzyme involved in the oxidative metabolism of guanfacine. Since all subsequent metabolic steps require this initial process, it is likely that abolition of CYP3A4 activity (as might be expected in severe hepatic impairment) will result in a similar increase in guanfacine exposure. Ketoconazole is a potent inhibitor of CYP3A4 activity. Thus, its effect on guanfacine exposure guanfacine following co-administration might be expected to approximate those in hepatic impairment. Guanfacine Cmax was essentially doubled, while AUC0-t and AUC0-inf both increased by about three-fold in the presence of ketoconazole. This suggests that there would be an approximately 2-3 fold increase in Cmax of Intuniv in patients with hepatic impairment. The clinician should consider adjusting the dose of Intuniv in patients with impairment of hepatic function.

Effect of Body Weight on Pharmacokinetics

There were inverse relationships between dose-normalized Cmax and AUC and body weight which were statistically significant. As expected from the decrease in dose-normalized AUC, there was an increase in clearance (CL/F), which was also statistically significant. The volume of distribution (Vz/F) also increased with increasing body weight. Consistent with the increases in clearance and volume of distribution, there was no change in half-life ($t_{1/2}$) with changes in body weight.

Effect of Age and Gender

Increasing age had a significant inverse relationship with dose-normalized Cmax and had a significant direct relationship with half-life ($t_{1/2}$). There were no significant relationships between age and dose-normalized AUC, clearance, or volume of distribution.

Exposure to guanfacine was higher in children (ages 6-12) compared to adolescents (ages 13-17) and adults. After oral administration of multiple doses of Intuniv 4mg, the Cmax in children (ages 6-12) and adolescents (ages 13-17) was 10ng/mL and 7ng/mL

respectively, and the AUC was 162ng.h/mL and 116ng.h/mL respectively. These differences are attributed to the lower body weight of children compared to adolescents and adults. Likewise, minor gender effects on guanfacine pharmacokinetics were considered related to bodyweight rather than gender per *se*, as male subjects tended to have higher body weight than female subjects in the studies.

The pharmacokinetics and dose-proportionality of guanfacine after single- and multiple dose administration of SPD503 have been examined in children (6-12 years) and adolescents (13-17 years) with ADHD. The pharmacokinetics of guanfacine has been studied in subjects with impaired renal function, the elderly, and patients with hypertension. In vivo drug interaction studies with ketoconazole and rifampin were conducted to examine the impact of inhibition and induction of cytochrome P4503A4/5 on the pharmacokinetics of guanfacine administered as SPD503.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.1.1 Product Name and Description

The established name of the subject product of this application is guanfacine hydrochloride (USP). The dosage form is an extended-release tablet that is available in the following (b) (4) dose strengths: 1, 2, (b) (4) 3, (b) (4) and 4 mg. The product is intended for once daily dosing. The proposed trade name of the product is Intuniv™. Thus, Intuniv™ is an oral, extended-release tablet formulation of guanfacine hydrochloride.

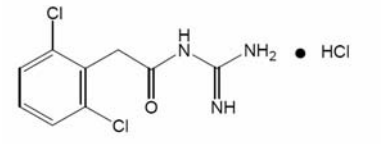
Guanfacine is a weakly basic drug that has pH-dependent solubility, exhibiting higher solubility at acidic pH conditions than at basic pH conditions. Intuniv™ has been formulated as a matrix tablet containing functional excipients to control the rate of drug release over the physiologic pH range of the gastrointestinal tract. Four functional excipients (b) (4) 1) Hydroxypropyl methyl cellulose (b) (4) 2) (b) (4) (methacrylic acid copolymer (b) (4) 3) fumaric acid (b) (4) and 4) (b) (4) (glyceryl dibehenate), (b) (4)

The Intuniv™ tablets also contain excipients (b) (4). These include: microcrystalline cellulose, fumaric acid, lactose (b) (4) crospovidone, povidone, and a coloring agent. The specific colorant included depends on the tablet strength: green pigment (PB-1763) for the 3 and 4mg tablets; (b) (4) for the (b) (4) tablet; and (b) (4) for the (b) (4) mg tablet.

2.1.2 Chemical Class

Guanfacine HCl is a substituted acetamide. Its empirical formula is $C_9H_9Cl_2N_3O \cdot HCl$. The compound has a molecular weight of 282.56 (g/mol). The structure of guanfacine hydrochloride is illustrated in the figure below.

Figure 1: The Structural Formula of Guanfacine HCl



2.1.3 Pharmacological Class

Guanfacine is a centrally acting, selective α_2-adrenergic receptor agonist, which was approved in 1986 for the treatment of hypertension (as monotherapy or in combination with other antihypertensive drugs) in patients $\geq$ 12 years old. Guanfacine has greater selectivity for α_2-adrenergic receptors than for α_1-adrenergic receptors, and it has greater selectivity than clonidine for α_2-adrenergic receptor. Furthermore, guanfacine has a 15- to 20-fold lower affinity for the α_{2B} and α_{2C} adrenergic receptor subtypes compared to the α_{2A} subtype. Like clonidine, guanfacine acts centrally to lower blood pressure and heart rate. By activating brainstem receptors, guanfacine suppresses sympathetic nerve activity from the vasomotor center to the heart and blood vessels. As a result, there are decreases in heart rate, peripheral vascular resistance, renal vascular resistance, and blood pressure. Cardiac output is generally unchanged. Guanfacine also lowers catecholamine levels and renin activity in the plasma.

2.1.4 Possible Therapeutic Mechanism in ADHD

Guanfacine's mechanism of action in ADHD has been attributed to modulation of prefrontal cortical cognitive functions. For, guanfacine has been demonstrated to enhance executive function, working memory, attention, and behavioral inhibition in rats, monkeys and humans. Cortical imaging in monkeys demonstrated that systemically administered guanfacine increased cerebral blood flow to the regions of the prefrontal cortex thought to be responsible for spatial working memory.1 Evidence suggests that α2A-adrenergic receptor agonists act directly in the prefrontal cortex to enhance executive function. Arisen (1985) demonstrated that stimulation of post-synaptic α2A-adrenergic receptors in the prefrontal cortex of monkeys led to improved performance on cognitive tasks2.

2.2 Available Treatments For Attention Deficit-Hyperactivity Disorder

For many years, the mainstays of approved treatment for ADHD have been the stimulants, methylphenidate and amphetamines. Included in this category are dexmethylphenidate, dextroamphetamine, methamphetamine, and amphetamine single and mixed salts. As listed below, there are numerous immediate-release and extended-release formulations of stimulants available for the treatment of ADHD. Atomoxetine (Strattera) is a non-stimulant drug approved for the treatment of ADHD. It is a selective norepinephrine reuptake inhibitor.

Listing 2.2: Available Treatments for ADHD

- Adderall (mixed salts of a single entity amphetamine product) Tablets
- Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules
- Concerta (methylphenidate hydrochloride) Extended-Release Tablets
- Daytrana (methylphenidate) Transdermal System
- Desoxyn (methamphetamine HCl) Tablets
- Dexedrine (dextroamphetamine sulfate) Spansule Capsules and Tablets

- Focalin (dexmethylphenidate hydrochloride) Tablets
- Focalin XR (dexmethylphenidate hydrochloride) Extended-Release Capsules
- Metadate CD (methylphenidate hydrochloride) Extended-Release Capsules
- Methylin (methylphenidate hydrochloride) Oral Solution
- Methylin (methylphenidate hydrochloride) Chewable Tablets
- Ritalin (methylphenidate hydrochloride) Tablets
- Ritalin SR (methylphenidate hydrochloride) Sustained-Release Tablets
- Ritalin LA (methylphenidate hydrochloride) Extended-Release Capsules
- Strattera (atomoxetine HCl) Capsules
- Vyvanase (lisdexamfetamine: a pro-drug of amphetamine)

Although not approved for the indication, several other drugs that are thought to be effective in treating some patients with ADHD. These include bupropion (Wellbutrin), tricyclic antidepressants (e.g., imipramine and desipramine), and clonidine.
Like guanfacine, clonidine is an $\acute{\alpha}_{2A}$-adrenergic receptor agonist that is indicated for the treatment of hypertension.

2.3 Availability of the Proposed Active Ingredient in The U.S.

The active ingredient would be readily available in the United States

2.4 Important Issues with Pharmacologically Related Products: Clonidine

2.4.1 Introduction and Description of Clonidine

Clonidine is the prototypic α_2 adrenergic receptor agonist. Clonidine reduces blood pressure and heart rate by activating α_2 receptors in the autonomic control centers in the CNS. This action suppresses the outflow of sympathetic nervous system activity from the brain. Clonidine decreases discharges in sympathetic preganglionic fibers in the splanchnic nerve and in postganglionic fibers of cardiac nerves. Clonidine also stimulates parasympathetic outflow, which may contribute to the slowing of heart rate as a consequence of increased vagal tone and diminished sympathetic drive.

2.4.2 Adverse Events Associated with Clonidine

The most common adverse events reported with clonidine treatment are dry mouth and sedation. Many adverse events associated with clonidine use are dose-dependent. Other common adverse events include orthostasis, hypotension, bradycardia, dizziness, fatigue, weakness, nausea, vomiting, constipation, sexual dysfunction, headache, withdrawal syndrome, nervousness, agitation, and weight gain.

2.4.3 Clonidine Toxicity and Overdosage

In overdose, patients may have a decreased level of consciousness, miosis, bradycardia, hypotension, respiratory depression, and hypotonia. CNS depression may range from drowsiness to coma. Respiratory depression, intermittent apnea, and bradycardia are

relatively common in children. Toxic effects typically occur within 30 to 90 minutes of ingestion, and they may persist for 1 to 3 days. A retrospective study by Nichols et al [77] reviewed the cases of 80 children admitted for clonidine ingestion between 1987 and 1992. Average time to onset of symptoms was 35 minutes. The most common presenting sign or symptom was reduced level of consciousness (96%). Six children required intubation, but no deaths occurred. In this study, most of the clonidine (54%) belonged to the patients' grandmothers.

The package insert for clonidine includes the following language regarding overdosage with clonidine:

Hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis. The frequency of CNS depression may be higher in children than in adults. Large overdoses may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma and seizures. Signs and symptoms of overdose generally occur within 30 minutes to two hours after exposure.

2.5 Presubmission Regulatory History For The Development Of Intuniv

2.5.1 IND (Investigational New Drug Applications)

Shire opened two INDs to support the development of SPD503 (guanfacine HCl extended-release tablets)

1. **(b) (4)**
2. IND 63,551: guanfacine HCl extended-release

2.5.1 NDA (New Drug Application- 22-037)

On August 24, 2006, Shire submitted a 505(b) (2) type NDA for SPD503 (22-037) and included all data and study reports generated under the two INDs. Shire also made reference to the 1986 NDA 19-032 approval documents for Tenex® guanfacine immediate-release (Dr. Reddy Labs; previously held by AH Robbins). The following tables outline highlights of regulatory interactions between Shire and FDA (DNPDP and DPP)

Table 2.5 Synopsis of Regulatory History

(b) (4)	
03/13/2000	**Original (b) (4) submission** of Shire's guanfacine extended release sent to the FDA's DNDP with protocol 201 (Proposed a randomized, double-blind, placebo cross-over evaluation of guanfacine immediate-release formulation in children 6-12 years with ADHD at up to 1.25 mg BID (2.5mg/day).
05/01/2001	**Final Study 201 CSR Submitted** (Serial No. 012) "An Open Label Safety and Tolerability Dose Escalation Study of Guanfacine" Hydrochloride (TENEX ®) Administered to Children with ADHD

02/26/2003 **Final Study 202 CSR Submitted** (Ser. No. 025) "A Randomized, Double-Blind. Placebo controlled. Parallel Group Study of Guanfacine Hydrochloride (SDP503 IR) Administered to Children with ADHD"

IND 63,551 – (SPD503) guanfacine HCl extended-release

10/26/2001 **Original IND 63,551 submission** of Shire's guanfacine extended release sent to FDA's DNDP, with protocol 101 (Evaluated three guanfacine extended-release formulations vs. Tenex® immediate-release)

10/08/2002 **End-of-Phase 2 (EOP2) Meeting and Minutes – Clinical Topics**

- The proposed pediatric ADHD pivotal trials are generally acceptable
- DNDP requested that Shire collect specific endocrine data
- The statistical analysis plan should protect the overall alpha of $p<0.05$; and should include adjustment for multiplicity of analyses
- Key secondary outcomes for regulatory claims would have to be agreed upon a priori with DNDP
- Exposure request: 450 subjects to any dose; 230 exposed to 4 mg/day; 200 exposed for 6 months at various doses
- 4-Month Safety Update: 150 subjects exposed for a year; 295 for 6 mo.; and 600 for any duration. Open label safety data will include height, weight, ECG monitoring, vital signs, and 30-days follow-up post treatment.
- Rebound hypertension: DNDP requested continuous in-patient monitoring for the first two days after discontinuing drug treatment

01/28/2004 **Type C Meeting to discuss pivotal studies in ADHD clinical program**

- Discussed pivotal study 301 preliminary results and 304 study plans. FDA considered the program acceptable for NDA support, expressing interest in dosing by weight (mg/kg).
- Noted that the abrupt cessation study could be run in healthy adult volunteers study as long as sufficient data and expert medical justification linking to applicability to pediatrics is provided in the NDA
- Duration of Action claim using Conners' Parent and Teacher assessments may be possible assuming that the statistical plan is appropriate.
- Recommended that drug-drug interactions with potent inducers (rifampin) and inhibitors (ketoconazole) be performed
- FDA recommended a safety study to assess SPD503/stimulant combination use
- FDA expressed a willingness to write a PWR to include children and adolescents; required inclusion of 25% adolescents and 25% females.
- Effects of somnolence and sedation, and their impact on patient functioning, as well as effects on BP/orthostasis and ECG are to be characterized in the NDA

10/18/2004 **Pivotal Study 304 (Discussions)**

through

02/04/2005

- Assessment of duration of effect should include the 12 waking hours during which a patient would manifest the symptoms of ADHD. Proper statistical tests are needed to adjust for multiplicity and/or missing data.
- ECGs near Cmax, orthostatic BP and rebound hypertension should be captured in the development program if not collected in the 304 study.
- Daytime sleepiness assessments should rely not only on the child's report, but also on adult observations (i.e. parents and teachers) or perhaps a sleep lab Daytime Sleep Latency Test. In addition, cognitive impairment for this drug should be assessed.

02/23/2005 **Type C Clinical Issues Teleconference (CNS Effects)**

- Shire needs to characterize CNS effects (somnolence, sedation)
- Daytime dosing: same day evaluations of sedation/somnolence, cognitive function, psychomotor skills, possibly driving (simulation)
- Suggested study of CNS function: assess cognitive function (such as sustained attention) and

sedation with the entire dose range

05/18/2005 **End of Phase 3, Type B Meeting**

- Efficacy has been established in dose range 1-4mg for the entire population studied (6-17 years); although, adolescent data might be inconclusive because of under-dosing heavier patients. Labeling may be achieved to give guidance for higher dosing in these patients, based on weight-based analyses to be provided in the NDA. The review will determine any age and weight dosing recommendations, and related descriptions in the Clinical Trials section of the product labeling.
- The available data should be sufficient to assess heart rate and QT effects; detailed descriptions of each syncopal event be provided in the NDA.
- Functional impairment does not appear to be coincident with sedative effects. Dosing on a mg/kg basis may allow a more favorable benefit/risk profile than the forced-dose mg dosing used in the clinical trials
- Although there is a food effect, the overall exposure of guanfacine is limited (3mg fed is roughly equivalent to 4mg fasted at steady state).
- FDA requested that data describing CYP2C8 inhibition, induction of CYP450 and interaction with P-glycoprotein be provided in the NDA... A specific hepatic impairment study may not be needed if sufficient justification is provided.
- All adverse reactions and dosing recommendations will need to be reflected appropriately in the labeling.

8/03/2005 **Pediatric Development Discussions Prior to PWR**

- Shire's Information package (Serial No 152; 07/15/2005)
- FDA Minutes and Shire Minutes (Serial No 156; 08/11/2005)

Based on FDA's preliminary view of the pivotal data prior to the August 2005 teleconference, we noted that the PWR might include one or more of the following studies:

1. Adolescent ADHD study, since the pivotal data in this group is difficult to interpret.
2. Combined use of SPD503 with stimulants, since alpha-2 agonists are often used with stimulants in ADHD treatment, and such a study would supplement the body of safety data available (Study 205). A single add-on study, if positive, could be enough to get an adjunctive use claim.
3. Placebo-controlled evening vs. morning dosing study (mono- or adjunct-therapy), since guanfacine IR is used mostly in the evening in combination with stimulants during the day. Possible stratification based on the presence or absence of insomnia. Several once-a-day SPD503 doses might be needed to address diurnal exposure.
4. A randomized withdrawal study to evaluate long-term efficacy

3 SIGNIFICANT FINDINGS FROM OTHER DISCIPLINES

3.1 Statistics Review

The Statistical Reviewer, George Kordzakhia, Ph.D. replicated the sponsor's statistical analyses and confirmed the primary efficacy results. Dr. Kordzakhia confirmed that each of the two placebo-controlled, short-term studies of Intuniv (studies 301 and 301) demonstrated the efficacy of Intuniv in the treatment of ADHD in children and adolescents between the ages of 6 and 17 years old, inclusive. The primary statistical analysis was positive for each study. The primary endpoint was the difference between the Intuniv and the placebo groups in the change in mean scores on the Attention Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV). The primary endpoint was analyzed for the entire study population by randomized treatment groups (either placebo or Intuniv 1, 2, 3, or 4 mg per day). The analysis used the ANCOVA model with

treatment group and baseline covariate by the last observation carried forward (LOCF) method.

The findings indicate that all of the guanfacine treatment arms (2mg/day, 3mg/day and 4mg/day for study 301, and 1mg/day, 2mg/day, 3mg/day and 4mg/day for study 304) were statistically significantly superior to placebo in reducing the ADHD-RS-IV total score of subjects with ADHD. Details of the efficacy findings will be discussed in the Integrated Review of Efficacy section (Section 6)

3.2 Pharmacometrics Review

The Pharmacometrics reviewer, Venkatesh Atul Bhattaram, Ph.D. conducted several analyses of the efficacy and safety data. These included explorations of a potential:

1. Dose-response relationship for efficacy
2. Dose-response relationship for QT prolongation
3. Dose-response relationship for changes in blood pressure and heart rate
4. Dose-response relationship for sedative adverse events

Dr. Bhattaram concluded that there is a positive dose-response relationship between guanfacine dose and the change in the primary efficacy measure score (ADHD-RS-IV). The relationship exists for the study population on the whole; however, Dr. Bhattaram notes that while efficacy was demonstrated in the younger subgroup (ages 6-12, inclusive), the study drug effect in adolescents (ages 13-17) was not significantly different from the effect of placebo treatment in this subgroup. This is probably related to the lower guanfacine exposures observed in the older subgroup. The Cmax and AUC were both 30% lower than those in children between the ages of 6 and 12 years old. The lower exposures appear to be directly related to the higher body weights of the older subgroup. In addition, the placebo effect appears to be greater in the older subgroup (ages 13-17) than in the younger subgroup (ages 6-12).

Similarly, there are dose- and exposure-response relationships for important safety parameters including: 1) prolongation of the QT interval; 2) decreases in systolic and diastolic blood pressure; 3) decreases in heart rate; and 4) somnolence. For every unit (ng/mL) increase in serum guanfacine concentration, two different PK/PD models predicted a 1 msec increase in the QTc interval. Dr. Bhattaram analyzed the data using QT corrections for individual subjects (QTcI), while the sponsor analyzed the QT data using population corrections (QTcP).

Higher guanfacine exposures would pose a greater risk of QT prolongation than lower exposures. Since exposure during fixed dosing depends largely on a subject's body weight, it would be important to dose patients on an mg/kg basis, in order to best manage and minimize adverse events such as QT prolongation. (Details of the QT analyses will be discussed in the Integrated Review of Safety section).

Dr. Bhattaram also notes that there is a large food effect with administration of Intuniv. With a high fat breakfast, the Cmax of guanfacine increases by 77%, and the AUC increases by 40%. Thus, in order to reduce the risk of developing adverse events such as QT prolongation, hypotension, bradycardia, and somnolence, it would be advisable for patients to take Intuniv at least one hour prior to meals.

3.3 Clinical Pharmacology Review

The final results of the clinical pharmacology review are not available currently.

3.4 Cardiorenal QT Interdisciplinary Review Team (QTIRT)

The QTIRT concluded that the concentration-QT analysis demonstrated that the guanfacine prolongs the QTc. However, the magnitude of QT prolongation cannot be adequately quantified, since four out of the seven studies (Study 104, 106, 107 and 203) were open-label studies without controls. There was inadequate data for precisely defining the relationship between the changes from baseline in the QTc interval. Hence for a clear delineation of the effect of guanfacine on the QTc interval the sponsor should conduct a thorough QT study.

The QTIRT discussed with DPP some preliminary thoughts about a thorough QT study with guanfacine. Some of the points included the following:

1. The study could be conducted in healthy adult subjects
2. The sponsor could conduct a three-way or four-way crossover study.
3. The study could use single doses of immediate-release guanfacine.
4. Possibly, IR guanfacine could be administered intravenously.
5. The study must include the active control, moxifloxacin (+8- 10 msec).
6. Exposures would need to be at least as high as those measured in pediatric subjects in the Intuniv studies.
7. The sponsor would have to include a supratherapeutic dose of guanfacine as well.
8. The sponsor would need to consider the active metabolites and metabolic pathways in properly designing the guanfacine thorough QT study.
9. The sponsor would need to consider the large food effect, especially with high-fat meals.

The QTIRT recommends that labeling include language indicating that the effect of guanfacine on the QTc interval has not been adequately studied. Labeling should also state that prolongation of the QT interval predisposes to a type of ventricular tachycardia called Torsade de pointes, which may result in syncope, seizures, and death. Therefore, reasonable precautions should be taken to mitigate the possible effects of guanfacine on the QT interval, including:

1. Checking serum potassium and magnesium since hypokalemia and hypomagnesemia can predispose to Torsade de pointes,

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

The Cardiorenal team had additional preliminary recommendations regarding risk management and potential labeling, in light of the potential QT prolongation effect. The items of discussion included obtaining careful medical history and family medical history, in order to screen patients for Long QT syndromes (QTLS). We discussed the need for careful physical examinations, as well as consideration of pre-treatment and post-treatment electrocardiogram (ECG). We discussed other potential risk factors for QT prolongation, such as electrolyte disturbances.

3.5 Office of Surveillance and Epidemiology

The final results of the consults from the Office of Surveillance and Epidemiology (OSE) are currently not available. However, preliminary results will be discussed in the Integrated Review of Safety section (Section 8) regarding cases of syncope reported during the long-term, open-label studies (Studies 303 and 305). Andrew Mosholder, M.D., Mary Ross Southworth, Pharm.D. (DDRE), and I have had a number of discussions regarding the analysis of syncopal events and postmarketing adverse associated with guanfacine treatment. In addition, Carol Pamer, RPh. has provided several consult reports regarding postmarketing guanfacine use data. All consultants from OSE have been extremely helpful during the process of this NDA review.

3.6 Pharmacology and Toxicology

The final results of the Pharmacology/Toxicology consult are currently not available. At this point, it appears unlikely that there will be new information or findings that would have an impact on the regulatory decisions.

3.7 Chemistry and Manufacturing

The final results of the CMC review have been filed. The results and recommendations currently do not have an impact on the regulatory recommendations.

3.8 Division of Medical Errors And Technical Support (DMETS) and (DDMAC)

The sponsor originally proposed the trade name (b) (4) which the Division of Medication Errors and Technical Support (DMETS) did not accept. DDMAC objected to

the proposed trade name (b) (4) "because it overstates the effectiveness of the drug product based on the information provided.

DDMAC and DMETS have accepted the proposed tradename, INTUNIV. DDMAC finds the proposed proprietary name, Intuniv, acceptable from a promotional perspective.

3.9 Division Of Scientific Investigation (DSI)

The final results of the DSI review indicate that there is no significant concern about the inspected study sites or the integrity of the data collected for the studies.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources Of Clinical Data

The table below outlines the sources of data that were reviewed.

Table 4.1 Sources of Clinical Data Reviewed

Sources of Clinical Data Reviewed	
Summary Documents	1) Summary of Clinical Efficacy; 2) Summary of Clinical Safety; 3) Summary of Clinical Pharmacology; 4) Summary of Biopharmaceutics 5) Clinical Overview; 6) Safety Update
Integrated Summary Tables and Figures (efficacy and safety)	Integrated Summary of Efficacy-Tables and ISE-Figures Integrated Summary of Safety-Tables and ISE-Figures Highlights of Clinical Pharmacology
Clinical Study Reports	1) Controlled studies: 301 and 304 2)Long-term, open-label studies: 303 and 305 3) Phase 2 studies: 201, 205,and 206
Raw Safety Data Sets (JMP files)	Studies: 301, 304, 303, and 305; Studies 201, 202, 203, 205, 206; Studies: 101, 102, 103, 104, 106, 107, 108, 109, 110
Pop PK/PD Analysis (QT and exposure analysis)	Population Pharmacokinetic and Pharmacodynamic Analysis in Pediatric Patients with Attention Deficit Hyperactivity Disorder (b) (4) contracted by Shire)
Case Report Forms	1) Specifically for cases of syncope and SAE; 2) 2) random samples
Syncope Profiles	The sponsor submitted patient safety profiles for cases of syncope (per DPP request)
FDA Consultants	• Statistics • Biopharmaceutics and Pharmacometrics • Cardiorenal QT Interdisciplinary Review Team (QTIRT) [draft] • Office of Surveillance and Epidemiology (OSE)- written communications, interdisciplinary team meetings [formal consult pending] • DDMAC, DMETS, DSI • [Pending: Clinical Pharmacology; CMC; Pharm/Tox]
Literature	Journal articles regarding:

	1) guanfacine pharmacology; 2) guanfacine treatment for ADHD and other neuropsychiatric disorders 3) Syncope in the pediatric and adult populations 4) sponsor's articles submitted
Other sources reviewed	Proposed Labeling Investigator Brochure Meeting Minutes (IND and pre-NDA phases) Correspondences with the sponsor

4.2 Tables Of Clinical Studies

4.2.1 Table of Controlled Pivotal Trials 301 and 304

Pivotal Controlled Efficacy and Safety Trials				
Study	Design	Treatment groups	Subjects	Efficacy Results
301 U.S. 48 sites 1/03 to 8/03	Multicenter, randomized, double-blind, placebo-controlled, fixed-dose, forced-titration, 8-week study in children and adolescents (ages 6-17) with ADHD Primary efficacy measure: ADHD-RS-IV	 2 mg/day 3 mg/day 4 mg/day Placebo	N = 345 N = 87 N = 86 N = 86 N = 86	 P = 0.0006* P = 0.0005* P = 0.0001*
304 U.S. 51 sites 3/04 to 7/04	Multicenter, randomized, double-blind, placebo-controlled, fixed-dose, forced-titration 9-week study in children and adolescents (ages 6-17) with ADHD Primary efficacy measure: ADHD-RS-IV	 1 mg/day 2 mg/day 3 mg/day 4 mg/day Placebo	N = 324 N = 62 N = 65 N = 65 N = 66 N = 66	 P = 0.0041* P = 0.0176* P = 0.0016* P = 0.0006*

4.2.2 Tables of All Clinical Studies in the INTUNIV Program

Table 1: Overview of SPD503 Clinical Studies

Study Title	SPD503 Protocol Number	Number of Subjects	Study Population
PHASE I			
A Pharmacokinetic Study To Assess the Bioavailability of Three Guanfacine Extended-release Test Formulations Compared to the Marketed Product Tenex® Following a Single 1mg Dose	101	12 enrolled	Healthy adults
A Phase I, Double-blind, Placebo-controlled, Randomized Safety Study of SPD503 in Young Healthy Adult Volunteers Aged 19-24	102	45 randomized	Healthy adults
A Phase I, Pharmacokinetic Study in Healthy Volunteers to Assess the Bioequivalence of SPD503 2mg and 4mg Tablets Manufactured at Pharmaceutics International Incorporated (PII) and Shire US Manufacturing, Incorporated (SUMI) Following a Single Dose Each of 2mg and 4mg	103	40 randomized	Healthy adults
A Phase I Study to Investigate the Effect of Food on the Pharmacokinetics of SPD503 in Healthy Volunteers	104	48 enrolled	Healthy adults
A Phase I, Open-Label, Single-Sequence, Crossover Study to Evaluate the Effect of Ketoconazole on the Pharmacokinetics of SPD503 in Healthy Adult Subjects	106	20 randomized	Healthy adults
A Phase I Study to Assess the Pharmacokinetics of SPD503 administered to Children and Adolescents aged 6-17 with Attention-Deficit/Hyperactivity Disorder (ADHD)	107	28 enrolled	Children and adolescents with ADHD
A Phase I, Open-label, Single-Sequence, Crossover Study to Evaluate the Effect of Rifampin on the Pharmacokinetics of SPD503 in Healthy Adult Subjects	108	20 enrolled	Healthy adults

CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The table below illustrates the differences in pharmacokinetic parameters between guanfacine immediate-release (Tenex) and guanfacine extended-release (Intuniv) when the two products were administered as single doses in adults. As expected, there was a significant difference between the two formulations for Cmax, Tmax, and $AUC_{0\text{-}t...}$ Intuniv has a lower Cmax and AUC and a longer Tmax than Tenex. The relative bioavailability of Intuniv compared to immediate-release guanfacine is 58%.

Table 5.1 PK Profile for Single-dose Guanfacine IR vs. Guanfacine ER in Adults

Guanfacine PK parameters following administration of single-dose 1 mg of Tenex (guanfacine immediate-release) or Intuniv under fasting conditions in **healthy adult** subjects		
PK Parameter	TENEX (n = 12)	Intuniv (n = 52)
C_{max} (ng/mL)	2.45 ± (0.63)	0.98 ± (.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)
$AUC0-_{inf}$ (h*ng/mL)	56.0 ± (15)	32.4 ± (8.8)
$T_{1/2}$ (h)	15.7 ± (3)	17.5 ± (3.8)
C_{24} (ng/mL)	0.85 ± (.24)	0.53 ± (.17)
F(rel) (%)		(58%)

The table below illustrates the single-dose and multiple-dose pharmacokinetic parameters of Intuniv following administration to pediatric ADHD subjects (ages 6-17)

Table 3: SPD503 Single and Repeated Dose Pharmacokinetics (Mean ± SD) in Pediatric ADHD Patients (Study SPD503-107)

Parameter	2mg, Single Dose	2mg, Repeated Dose	4mg, Repeated Dose
Children (6-12 yr)			
C_{max} (ng/mL)	2.55 ± 1.03	4.39 ± 1.66	10.15 ±7.09
t_{max} (hours)	5 ± 0	5 ± 0	5 ± 0
AUC_{last} (ng·hr/mL)	56.88 ± 22.05	70.05 ± 28.33	162.15 ± 115.56
λz (per hour)	0.0496 ± 0.0093		
$AUC_{0-\infty}$ (ng·hr/mL)	65.20 ± 23.88		
$t_{½}$ (hours)	14.4 ± 2.4		
CL/F (mL/min)	578 ± 215	552 ± 215	522 ± 212
V_z/F (L)	722 ± 326		
Adolescents (13-17 yr)			
C_{max} (ng/mL)	1.69 0 ± .43	2.86 ± 0.77	7.01 ± 1.53
t_{max} (hours)	5 ± 0	4.5 ± 0	5 ± 0
AUC_{last} (ng·hr/mL)	42.74 ± 12.85	48.19 ±16.06	116.75 ± 28.37
λz (per hour)	0.0428 ± 0.0153		
$AUC_{0-\infty}$ (ng·hr/mL)	47.25 ± 13.69		
$t_{½}$ (hours)	17.9 ± 5.8		
CL/F (mL/min)	754 ± 190	826 ± 486	607 ± 166
V_z/F (L)	1134 ± 343		

Data from Study SPD503-107. Patients received up to 28 doses.

λz, terminal elimination rate constant; AUC_{last}, area under the drug-concentration time curve from time zero to the last time point; $AUC_{0-\infty}$, area under the drug-concentration time curve extrapolated to infinity; CL/F, oral clearance; C_{max}, maximum concentration; t_{max}, time of maximum concentration; $t_{½}$, elimination half-life; SD, standard deviation; Vz/F, apparent oral volume of distribution.

Study 107 demonstrated that the pharmacokinetics of Intuniv were approximately linear after oral administration of single 2mg doses and repeated 2mg and 4mg doses in both children (6- 12 year-old subjects) and adolescents (13-17 year-old subjects) with ADHD. Plasma concentrations and concentration-related pharmacokinetic parameters in children were higher than those in adolescents. This was most likely due to the higher body weights of the adolescent subjects compared to the children.

Absorption

Based on the intravenous and oral administration of immediate-release guanfacine, absolute bioavailability ranged from 80% to 90% The relative bioavailability of Intuniv compared to guanfacine immediate-release is 58%.

Guanfacine is a weakly basic drug that has pH-dependent solubility. Guanfacine has higher solubility at acidic pH conditions than at basic pH conditions. Since the drug has a pK_a of 7.13, guanfacine exists predominantly in the lipid-soluble free base form at physiological pH. Studies utilizing Caco-2 cells demonstrated that guanfacine is a highly permeable compound with an apparent permeability coefficient (A-to-B) comparable to that of testosterone. Guanfacine is transported by a passive transcellular pathway. These properties indicate that guanfacine is likely to be well absorbed *in vivo*.

Distribution

Guanfacine is widely distributed outside the vascular compartment. Its volume of distribution is 6.3 ± 1.1 L/kg (determined after intravenous dosing). Guanfacine is moderately bound to plasma protein and to red blood cells. The plasma protein binding of guanfacine in human plasma ranges from 64-72%. Approximately 60% of guanfacine in the plasma is bound to red blood cells.

Metabolism

Cytochrome P450 3A4 is the predominant enzyme involved in the oxidative metabolism of guanfacine. Guanfacine is metabolized by oxidation of the aromatic ring, via an epoxide intermediate, to form 3-hydroxy-guanfacine. This metabolite is conjugated with glucuronic acid or sulphate, and it is then renally excreted. The glucuronide and sulfate conjugates of 3-OH-guanfacine account for approximately 50% of the radioactively labeled compound excreted in the urine. Additional routes of metabolism include conjugations with glutathione to form oxidized pre-mercapturic acids and mercapturic acid derivatives. The oxidized mercapturic acid derivatives are the only other compounds that account for a significant portion of radioactively labeled compound.

Elimination

Guanfacine is cleared hepatically and renally. Approximately one third of the total clearance is renal. The glucuronide and sulfate conjugates of 3-hydroxy guanfacine account for approximately 50% of the radioactivity excreted in the urine. Oxidized mercapturic acid derivatives are the only other metabolites that account for a significant portion of the radioactivity. Approximately 50% of the radioactive dose was excreted unchanged. The ratio of renal clearance to creatinine clearance was >2, indicating that excretion by the kidney occurs via filtration and active secretion. However, it is possible that reabsorption by the tubule also occurs.

Food Effect

There is a significant food effect on the pharmacokinetics of Intuniv. When Intuniv was administered with a high-fat breakfast, the mean exposure increased significantly. The AUC increased by approximately 40%, and the Cmax increased by approximately 77%, compared to dosing in a fasted state. The food effect could be clinically significant. Thus, one may need to consider the timing of dosing in relation to food intake, in order to minimize the increased guanfacine exposures that can occur with co-administration of food, especially with a high-fat meal.

Effect of Body Weight on Pharmacokinetics

There were inverse relationships between dose-normalized Cmax and AUC and body weight which were statistically significant. As expected from the decrease in dose-normalized AUC, there was an increase in clearance (CL/F), which was also statistically significant. The volume of distribution (Vz/F) also increased with increasing body weight. Consistent with the increases in clearance and volume of distribution, there was no change in half-life ($t_{1/2}$) with changes in body weight.

Dose Proportionality

Dose proportionality was evaluated in two studies, one after a single dose in healthy adults (Study109) and one after repeated administration in children with ADHD (Study206). In adults, mean plasma guanfacine concentrations increased in a dose-proportional manner after doses of 1mg, 2mg, and 4mg. There was a dose-proportional increase in Cmax and AUC, particularly between the 2mg and 4mg doses. Log-Log plots of Cmax and AUC versus dose were approximately linear with slopes approaching 1.0, indicating linear pharmacokinetics of guanfacine after doses of Intuniv ranging from 1mg to 4mg. In pediatric subjects with ADHD, the primary exposure parameters (Css, max and AUCss, 0-ô) increased in a dose-proportional manner across a 3-fold dose range (1-3 mg per day). Secondary exposure parameters such as Css, av and Css, min also increased progressively with dose, confirming the dose-proportional pharmacokinetics of guanfacine.

Effect of Age and Gender

Increasing age had a significant inverse relationship with dose-normalized Cmax and had a significant direct relationship with half-life ($t_{1/2}$). There were no significant relationships between age and dose-normalized AUC, clearance, or volume of distribution.

Exposure to guanfacine was higher in children (ages 6-12) compared to adolescents (ages 13-17) and adults. After oral administration of multiple doses of Intuniv 4mg, the Cmax in children (ages 6-12) and adolescents (ages 13-17) was 10ng/mL and 7ng/mL respectively, and the AUC was 162ng.h/mL and 116ng.h/mL respectively. These

differences are attributed to the lower body weight of children compared to adolescents and adults. Likewise, minor gender effects on guanfacine pharmacokinetics were considered related to bodyweight rather than gender per *se*, as male subjects tended to have higher body weight than female subjects in the studies.

Effect of Renal Impairment

The pharmacokinetics of guanfacine IR was studied in patients with impaired renal function. After intravenous administration to subjects with normal, moderately impaired, or severe renal function. In patients with impaired renal function, there was a substantial reduction in the cumulative urinary excretion of guanfacine and in renal clearance of guanfacine. The degree of the reduction in renal clearance increased as the degree of renal impairment increased.

Effect of Hepatic Impairment

The pharmacokinetics of guanfacine have not been studied in patients with hepatic impairment. Cytochrome P450 3A4 is the predominant enzyme involved in the oxidative metabolism of guanfacine. Since all subsequent metabolic steps require this initial process, it is likely that abolition of CYP3A4 activity (as might be expected in severe hepatic impairment) will result in a similar increase in guanfacine exposure.

Ketoconazole is a potent inhibitor of CYP3A4 activity. Thus, its effect on guanfacine exposure guanfacine following co-administration might be expected to approximate those in hepatic impairment. Guanfacine Cmax was essentially doubled, while AUC0-t and AUC0-inf both increased by about three-fold in the presence of ketoconazole. This suggests that there would be an approximately 2-3 fold increase in Cmax of Intuniv in patients with hepatic impairment.

Drug-Drug Interactions

CYP3A4/5 Inhibitors

Guanfacine is metabolized in vitro by cytochrome P4503A4/5. This was confirmed by in vivo drug interaction studies with ketoconazole and rifampin, which demonstrated significant inhibition and induction, respectively, of the clearance of guanfacine. There was a substantial increase in the rate and extent of guanfacine exposure when guanfacine was co-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. The mean Cmax increased from 4.14 to 7.29ng/mL and the mean AUC0- increased from 120 to 367h.ng/mL.

These results indicate that concomitant administration of Intuniv and drugs that inhibit CYP3A4 activity could result in significantly increased plasma concentrations of guanfacine, potentially leading to adverse pharmacodynamic effects. Due to the risk of QT prolongation, the use of strong inhibitors of CYP3A4/5 should be avoided.

CYP3A4 Inducers

There was a significant decrease in the rate and extent of guanfacine exposure when guanfacine was co-administered with rifampin, an inducer of the CYP3A4 system. The Cmax for guanfacine decreased by more than 50% in the presence of rifampin, while AUC0-t and AUC0-inf both decreased by 60% to 70%. The mean Cmax decreased from 3.46 to 1.64ng/mL while the AUC0- decreased from 119 to 39.9h.ng/mL.

Concomitant administration of Intuniv and drugs that induce CYP3A4 activity could result in decreased plasma concentrations of guanfacine, potentially leading to a loss of pharmacodynamic effect and loss of effectiveness. When patients are treated concomitantly with Intuniv and a CYP3A4 inducer, an increase in the dose of Intuniv (within the recommended dose range) should be considered.

Valproic Acid

Published literature indicates that co-administration of guanfacine and valproic acid can result in elevated concentrations of valproic acid. Plasma valproate levels rapidly increased when guanfacine was co-administered. Furthermore, plasma valproate concentration decreased by 41% after guanfacine was tapered and discontinued. Guanfacine may increase plasma valproate concentrations via competition for the glucuronidation pathway, as both drugs are eliminated by this pathway. However, the mechanism of this interaction has not been definitively documented. When Intuniv is co-administered with valproic acid, dosing adjustments may be required.

Psychostimulants (methylphenidate and amphetamine)

Although a formal pharmacokinetic interaction study with guanfacine and psychostimulants has not been conducted, guanfacine was co-administered with either methylphenidate or amphetamine in Study 205 as described below.

In this study, 75 patients who had been treated with a stable dose of amphetamine or methylphenidate (and had a sub-optimal response) were adjunctively with Intuniv (up to 4mg/day for 9 weeks). The sponsor states that there was no evidence of additive or unique adverse effects with the combination of Intuniv and stimulants, compared to treatment with either medication alone. Generally, that seemed to be the case. However, a relatively high proportion of subjects in the adjunctive study had psychiatric adverse events.

Guanfacine does not appear to inhibit other major human Cytochrome P450 isozymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5) in *vitro*. Guanfacine does not induce CYP1A2, CYP2B6 or CYP3A4.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication for Controlled Trials 301 and 304

The indication for the NDA under review is Attention Deficit-Hyperactivity Disorder in children and adolescents (ages 6-17).

6.2 Discussion of the Primary Endpoint for Controlled Trials 301 and 304

The primary efficacy measure used in the controlled, pivotal efficacy and safety studies is the Attention Deficit-Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV). This is a standard, well-validated instrument that is widely used and widely accepted for use as a primary efficacy endpoint in clinical trials in ADHD. The instrument is rated by clinicians. The ADHD-RS-IV consists of 18 items, each of which is rated as either none (0), mild (1), moderate (2), or severe (3). The odd-numbered items comprise the Inattentiveness subscale, and the even-numbered items comprise the Hyperactivity-Impulsiveness subscale. (Please refer to Appendix 11.1 which contains the ADHD-RS-IV).

6.3 Study Designs for Controlled Trials 301 and 304

Study 301 was a multicenter, randomized, double blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of Intuniv compared with placebo in pediatric subjects (ages 6-17) with a diagnosis of ADHD. The study used a forced dose titration design. Subjects were randomized to target doses of 2, 3, or 4mg/day of Intuniv or placebo. Double-blind assessment proceeded for 8 weeks, with weekly clinic visits scheduled for evaluation and medication dispensing. (There were 48 principal investigators in 48 U.S. study centers. The study period was January 29, 2003 to August 23, 2003).

Study 304 was a multicenter, randomized, double blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of Intuniv compared with placebo in pediatric subjects (aged 6-17) with a diagnosis of ADHD. The study used a forced dose titration design. Subjects were randomized to target doses of 1, 2, 3, or 4mg/day of Intuniv or placebo. Double-blind assessment proceeded for 9 weeks, with weekly clinic visits scheduled for evaluation and medication dispensing. (There were 45 principal investigators at 45 U.S. study sites. The study period was March 30, 2004 to October 7, 2004).

Study Objectives for Controlled Trials 301 and 304

Primary Objectives

The primary objective of this study was to assess the safety and efficacy of guanfacine compared with placebo in the treatment of children and adolescents (aged 6-17 years) with ADHD.

Secondary Objectives

The key secondary objective was to assess the duration of action of guanfacine using parent and teacher rating scales. Parents assessed the subjects using the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) administered at approximately 12, 14, and 24 hours after dosing and teachers used the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R) at approximately 4 and 8 hours after dosing.

Efficacy Measures

Primary Efficacy Measure

Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS-IV)

Secondary Efficacy Measures

Connor's Parent Rating Scale-Revised: Short Form (CPRS-R)
Connor's Teacher Rating Scale-Revised: Short Form (CTRS-R)
Clinical Global Impression-Severity Scale (CGI-S)
Clinical Global Impression-Improvement Scale (CGI-I)
Parental Global Assessment (PGA)

Subject Selection Criteria for Controlled Studies 301 and 304

Inclusion Criteria

1. Male of female patients aged 6-17, inclusive

2. Females of childbearing potential must have had a negative serum beta human chorionic gonadotropin (HCG) pregnancy test at Screening and a negative urine pregnancy test at Baseline. Females of childbearing potential must have abstained from sexual activity that could have resulted in pregnancy, or used acceptable contraceptives throughout the period of study drug exposure and for 30 days after the last dose of study drug.

3. Subject met DSM-IV-TR criteria for a primary diagnosis of ADHD (diagnostic code 314.01) combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype, based on a detailed psychiatric evaluation.

4. Subject's parent or legally authorized representative provided signature of informed consent, and there was documentation of assent by the subject indicating that they were aware of the investigational nature of the study and the required procedures and restrictions.

5. Subject was intellectually functioning at an age-appropriate level, as judged by the Investigator.

6. Subject had no concomitant illnesses that could affect efficacy, safety, or tolerability or in any way interfere with the subject's participation in the study.

7. Subject had blood pressure (BP) measurements within the 95th percentile for his/her age, gender, and height.

8. Subject's ECG results were within the normal range as judged by the Investigator in conjunction with the central reader.

9. Subject, parent, legal representative, and/or caregiver were willing and able to comply with all requirements specified in the protocol.

10. Subject's teacher was willing and able to comply with all requirements specified in the protocol.

11. Subject was able and willing to swallow intact study drug tablets.

Exclusion Criteria

1. Presence of an uncontrolled, comorbid psychiatric diagnosis (except oppositional defiant disorder) with significant symptoms such as any severe comorbid Axis II disorders or severe Axis I disorders, or other symptomatic manifestations that, in the opinion of the examining physician, contraindicated SPD503 treatment or confounded efficacy or safety assessments. Comorbid psychiatric diagnosis was established with select modules of the K-SADS-PL.

2. Weight was less than 55lb (25kg).

3. Morbid obesity (body mass index $\geq$ 35)

4. QTc interval greater than 440 milliseconds at the screening

5. Presence of a clinically significant cardiac condition or family history of cardiac disorder.

6. Hypertension [specified in Study 301].

7. Treatment with medication that could affect blood pressure or heart rate (with the exception of subject's current ADHD therapy).

8. History of seizure during the two years before the study (exclusive of febrile seizures), a tic disorder, or a family history of Tourette's disorder. Medication-induced tics were not exclusionary.

9. Treatment with any medication that was prohibited per protocol

10. A positive urine drug screen result at Screening, with the exception of subject's current stimulant therapy

11. Treatment with medication that has central nervous system (CNS) effects or that could affect test performance (e.g., sedating antihistamines and decongestant sympathomimetics). Bronchodilators were not prohibited.

12. Pregnancy or lactation

13. History of intolerance to guanfacine

14. Previous treatment with guanfacine for Attention Deficit/Hyperactivity Disorder

Dosing Regimens in the Controlled Trials

Study 301 Dosing Regimen

301 Study Drug Dosing								
	Double-blind Period							
Guanfacine dose	↑ Titration Period					↓ Tapering Period		
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
2 mg	1 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	1 mg
3 mg	1 mg	2 mg	3 mg	3 mg	3 mg	3 mg	2 mg	1 mg
4 mg	1 mg	2 mg	3 mg	4 mg	4 mg	3 mg	2 mg	1 mg

Study 304 Dosing Regimen

Study 304 Study Drug Regimen									
Group	↑Dose Titration			Dose Maintenance			↓ Dose Tapering		
	Day 1-7	Day 8-14	Day 15-21	Day 22-28	Day 29-35	Day 36-42	Day 43-49	Day 50-56	Day 57-63
placebo	placebo	placebo	placebo	placebo	placebo	placebo	placebo	placebo	placebo
1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg
2 mg	1 mg	1 mg	1 mg	2 mg	2 mg	2 mg	2 mg	2 mg	1 mg
3 mg	1 mg	2 mg	2 mg	3 mg	3 mg	3 mg	3 mg	2 mg	1 mg
4 mg	1 mg	2 mg	3 mg	4 mg	4 mg	4 mg	3 mg	2 mg	1 mg

Primary Statistical Analysis Plan

The primary endpoint was the difference between the drug and the placebo groups in the change in mean scores on the Attention Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV). The primary endpoint was analyzed for the entire study population by randomized treatment groups (either placebo or drug 1, 2, 3, or 4 mg per day). The analysis used the ANCOVA model with treatment group and baseline covariate by the last observation carried forward (LOCF) method.

Non-Pre-Specified Secondary Statistical Analyses Plan

The following analyses were performed; although, they were not specified in the Statistical Analysis Plan:

- Analysis of the primary efficacy variable by actual dose
- Analysis of the primary efficacy variable by actual dose and by age group
- Analysis of the primary efficacy variable by weight-adjusted actual dose
- Analysis of the primary efficacy variable by weight-adjusted actual dose and by age
- Analyses of the subscales of the ADHD-RS-IV by age group

6.4 Efficacy Findings: Sponsor's Analysis for Studies 301 and 304

6.4.1 Study 301 Baseline Demographics and Features of Illness

In Study 301, a total of 345 subjects were randomized to treatment with guanfacine or placebo (259 and 86, respectively). In the intent to treat population there were 247 subjects in the guanfacine group and 78 subjects in the placebo group. Subjects were between the ages of 6 and 17 years old, inclusive. The mean and median ages were 10.5 and 10 years, respectively. Among different age groups, 26%, 51%, and 23% were in the 6-8, 9-12, and 13-17 year-old categories, respectively. Male subject comprised 74%, and female subjects comprised 26% of the study population. The ethnicities were White 70%), African American 13%), Latino (10%), Asian/Pacific Islander (0.3%), Native American (0.3%), and Other (6%). The mean and median weight of subjects was 96 lbs. and 87 lbs, respectively, with a minimum and maximum weight of 54 and 271 lbs., respectively. Study 301 included subjects with ADHD Inattentive subtype (26%), Hyperactive-impulsive subtype (2%), and ADHD Combined subtype (72%). The mean and median duration of ADHD illness was 2.7 and 1.0 years, respectively. For all of the demographic variables discussed above, there were no significant differences between the guanfacine and placebo groups.

The table below illustrates the baseline severity of illness in the treatment groups, as measured by the ADHD-RS. The mean scores at baseline were comparable among the treatment groups.

Study 301 Baseline Severity of Illness (ADHD-RS-IV Score)

ADHD-RS-IV Total Score at Baseline by Randomized Dose Groups					
Baseline ADHD-RS	Placebo	Guanfacine 2 mg	Guanfacine 3 mg	Guanfacine 4 mg	Total Guanfacine
	78	84	82	81	247
Mean	38.1	36.1	36.8	38.4	37.1
Median	39	36	37.5	37	
Min, max	13, 54	11, 54	17, 54	15, 54	11, 54

6.4.2 Study 301 Disposition of Subjects

As illustrated in the table below, the proportion of subjects who discontinued from Study 301 were comparable between the guanfacine and placebo group. However, as would be expected, a higher proportion of the placebo group discontinued due to lack of efficacy, compared to the guanfacine group. Also, a considerably higher proportion of subjects in the guanfacine group discontinued due to adverse events, compared to the placebo group. Furthermore, the discontinuations due to adverse events appeared to occur in a dose-related manner.

Study 301 Subject Disposition by Randomized Dose Group					
	Placebo N = 86	Guan 2 mg N = 87	Guan 3 mg N = 86	Guan 4 mg N = 86	Total N = 345
Subject Disposition n (%)					
Enrolled (safety)	86	87	86	86	345
Randomized	86	87	86	86	345
Completed	53 (62)	58 (67)	55 (64)	49 (57)	215 (62)
Early termination	33 (38)	29 (33)	31 (36)	37 (43)	130 (38)
Intent-to-treat	78 (91)	84 (97)	82 (95)	81 (94)	325 (94)
Per-protocol	61 (71)	63 (72)	62 (72)	54 (63)	240 (70)
Reason for early termination n (%)					
Adverse event	1 (1)	9 (10)	13 (15)	20 (23)	43 (13)
Lack of efficacy	15 (17)	8 (9)	6 (7)	7 (8)	36 (10)
Subject choice	9 (11)	2 (2)	3 (4)	4 (5)	18 (5)
Lost to follow-up	3 (4)	2 (2)	4 (5)	3 (4)	12 (4)
Protocol violation	1 (1)	3 (3)	0	0	4 (1)
Other	4 (5)	5 (6)	6 (6)	3 (4)	17 (5)

6.4.3 Study 304 Baseline Demographics and Features of Illness

In Study 304, a total of 324 subjects were randomized to treatment with guanfacine or placebo (258 and 66, respectively). In the intent to treat population there were 243 subjects in the guanfacine group and 63 subjects in the placebo group. Subjects were between the ages of 6 and 17 years old, inclusive. The mean and median age was 10.5 and 10 years, respectively. Among different age groups, 75% and 25% were in the 6-12 and 13-17 year-old categories, respectively. Male subject comprised 72%, and female subjects comprised 28% of the study population. Ethnicities included White (66%), African American (17%), Latino (9%), Asian/Pacific Islander (3%), Native American (0.3%), and Other (4%). The mean and median weight of subjects was 96 and 85 lbs, respectively, with a minimum and maximum weight of 55 and 237 lbs., respectively. Study 304 included subjects with ADHD Inattentive subtype (27%), Hyperactive-impulsive subtype (2%), and ADHD Combined subtype (72%). The mean duration of ADHD illness was 1.9 years. For all of the demographic variables discussed above, there were no significant differences between the guanfacine and placebo groups.

The table below illustrates the baseline severity of illness in the treatment groups, as measured by the ADHD-RS. The mean scores at baseline were comparable among the treatment groups.

304 ADHD-RS-IV Total Score at Baseline by Randomized Dose Group					
Baseline	Placebo N= 63	Guan 1 mg N= 57	Guan 2 mg N= 63	Guan 3 mg N= 60	Guan 4 mg N= 63
Mean	39.3	41.7	39.9	39.1	40.6
Median	40	42	40	40.5	41
Min, max	24, 54	24, 54	21, 54	18, 52	25, 54

As illustrated in the table below, the proportion of subjects who discontinued from Study 304 were comparable between the guanfacine and placebo group. However, as would be expected, a higher proportion of the placebo group discontinued due to lack of efficacy, compared to the guanfacine group. A slightly higher proportion of subjects in the guanfacine group discontinued due to adverse events, compared to the placebo group. The discontinuations due to adverse events appeared to occur in a dose-related manner.

6.4.4 Study 304: Disposition of Subjects

	Placebo N = 66	Guan 1 mg N = 62	Guan 2 mg N = 65	Guan 3 mg N = 65	Guan 4 mg N= 66	Total Guan N= 258
Randomized	66	62	65	65	66	258
Safety	66 (100)	61 (98)	65 (100)	65 (100)	65 (99)	256 (99)
Completed	41 (62)	45 (73)	47 (72)	38 (59)	40 (61)	170 (66)
Early termination	25 (38)	17 (27)	18 (28)	27 (42)	26 (39)	88 (34)
Intent-to-treat	63 (96)	57 (92)	63 (97)	60 (92)	63 (96)	243 (94)
Per-protocol	41 (62)	45 (73)	48 (74)	37 (57)	41 (62)	171 (66)
Reason for Early Termination						
Adverse event	5 (8)	2 (3)	2 (3)	6 (9)	9 (14)	19 (7)
Lack of Efficacy	6 (10)	1 (2)	4 (6)	7 (11)	4 (6)	16 (6)
Withdrew consent	5 (8)	6 (10)	8 (12)	8 (12)	4 (6)	26 (10)
Lost to follow-up	4 (6)	4 (7)	1 (2)	5 (8)	8 (12)	18 (7)
Protocol violation	1 (2)	1 (2)	0	0	0	1 (0.4)
Other	4 (15)	3 (5)	1 (2)	1 (2)	2 (3)	7 (3)

6.4.5 Types of Efficacy Analyses

Efficacy results are discussed in terms of: 1) Randomized Dose Group; 2) Actual Dose Group; and 3) Actual Weight-Adjusted Dose in mg/kg within four categories (mg/kg). The randomized dose is the designated maximum dose to which a subject was randomized (ie, the maximum dose after titration was completed). Randomized doses used in Study 301 were placebo and guanfacine 2, 3, and 4mg per day. Randomized doses used in Study 304 were placebo and guanfacine 1 2, 3, and 4mg per day.

The actual dose is the dose the subject was actually taking at the time of assessment (efficacy variables, adverse events, physical examinations, vital signs, ECG, or clinical laboratory tests) or onset. The actual dose depended on both the randomization assignment and study day in relation to dose titration and tapering schemes. Actual doses in the study included placebo and 1, 2, 3, and 4mg guanfacine. The 1mg guanfacine dose is a pass-through dose that all guanfacine-treated subjects began treatment with.

Definition of Weight-adjusted Actual Dose
A subject's weight-adjusted actual dose was determined by dividing the actual dose of guanfacine that a subject received (in mg) by their weight at baseline (in kg). Pounds

were converted to kilograms by multiplying by 0.454. Subjects were categorized within one of the following five (5) groups, depending on their weight-adjusted dose:

- 0 mg/kg (placebo)
- 0.01-0.04 mg/kg
- 0.05-0.08 mg/kg
- 0.09-0.12 mg/kg
- 0.13-0.17 mg/kg

6.5 Efficacy Findings and Conclusions (FDA Statistics Reviewer Analysis)

6.5.1 Primary Analysis on the Primary Efficacy Endpoint

The statistics reviewer, George Kordzakhia, Ph.D. confirmed the sponsor's efficacy analysis results for primary endpoint, change in mean ADHD-RS-IV score. Treatment group differences were evaluated using the ANCOVA model with treatment term and baseline covariate by LOCF method. Table 1 and Table 2 list sponsor's primary efficacy results of the two studies. The findings indicate that all of the guanfacine treatment arms (2mg/day, 3mg/day and 4mg/day for study 301, and 1mg/day, 2mg/day, 3mg/day and 4mg/day for study 304) were statistically significantly superior to placebo in reducing ADHD rating scale IV (ADHD-RS-IV) total score of the patients with attention deficit/hyperactivity disorder (ADHD). In Study 301, the estimated size of the placebo-adjusted treatment effects was modest (decreases on the ADHD-RS scale of 6.5, 6.9, and 10.1 points in the 2 mg, 3 mg, and 4 mg groups, respectively). In Study 3-4, the estimated size of the placebo-adjusted treatment effects were modest as well (decreases on the ADHD-RS scale of 8.2, 5.8, 7.5, 8.7 points in the 1 mg, 2 mg, 3 mg, and 4 mg groups, respectively).

Table 1. Study 301: ADHD-RS-IV Total Score at Endpoint by Randomized Dose (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
No. patients	N=325	78	84	82	81
Baseline	Mean (SD)	38.14 (9.34)	36.10 (9.99)	36.77 (8.72)	38.40 (9.21)
Endpoint	Mean (SD)	29.28 (14.94)	20.69 (13.45)	20.98 (13.87)	19.43 (11.91)
Change from Baseline	Mean (SD)	-8.86 (12.90)	-15.40 (12.82)	-15.79 (13.00)	-18.96 (13.71)
Placebo-adjusted treatment effect:			−6.54	−6.93	−10.1
Placebo-adjusted difference	LS mean	NA	-7.42	-7.52	-9.99
	95% CI	NA	(-12.07, -2.77)	(-12.19, -2.85)	(-14.67,-5.32)
	P-Value (Dunnett)	NA	0.0006	0.0005	<0.0001

Source: Section 12.1, Table 2.1.1 of Study 301 Report (pg. 73)

Table 2. Study 304: ADHD-RS-IV Total Score at Endpoint by Randomized Dose (ITT Population)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
No patients	N=306	63	57	63	60	63
Baseline	Mean (SD)	39.25 (8.85)	41.70 (7.81)	39.92 (8.74)	39.07 (9.22)	40.60 (8.57)

Endpoint	Mean(SD)	27.1 (15.02)	21.30 (12.78)	21.9 (14.08)	19.7 (12.46)	19.7 (11.01)
Change fr. Baseline	Mean (SD)	-12.2 (12.96)	-20.4 (14.00)	-18.0 (14.88)	-19.4 (14.62)	-20.9 (11.89)
Placebo-adjusted treatment effect:			− 8.2	− 5.8	− 7.5	− 8.7
Placebo-adjusted difference	LS mean	NA	-6.75	-5.41	-7.31	-7.88
	95% CI	NA	(-11.3, -2.2)	(-9.9, -0.9)	(-11.8, -2.8)	(-12.3, -3.4)
	P-Value	NA	0.0041	0.0176	0.0016	0.0006

Source: Section 12.1, Table 2.1.1 of Study 304 Report

The reviewer also performed treatment comparisons at each visit time as an exploratory analysis for both studies. The purpose of the comparisons was to explore whether effects were consistent across the visits. The results are summarized in Table 3 and Table 4. There were significant treatment effects beginning at Week 2 in Study 301 and at Week 1 in Study 304.

Study 301

Table 3. Study 301: LS Mean Change in ADHD-RS-IV Total Score by Visit (ITT Population)

Visit (week)	Placebo Mean (SE)	SPD503 2mg Mean (SE); p-value vs. placebo	SPD503 3mg Mean (SE); p-value vs. placebo	SPD503 4mg Mean (SE); p-value vs. placebo
1 (week 1)	-5.97 (1.11)	-7.74 (1.07); 0.253	-7.31 (1.08); 0.388	-8.22 (1.09); 0.148
2 (week 2)	-8.12 (1.19)	-12.54 (1.15); 0.008	-11.20 (1.16); 0.065	-12.66 (1.17); 0.007
3 (week 3)	-8.34 (1.31)	-13.66 (1.26); 0.004	-14.59 (1.27); <0.001	-15.58 (1.28); <0.001
4 (week 4)	-8.43 (1.35)	-15.03 (1.30); <0.001	-15.05 (1.32); <0.001	-18.44 (1.33); <0.001
5 (week 5)	-8.83 (1.43)	-15.74 (1.38); <0.001	-16.03 (1.39); <0.001	-18.74 (1.40); <0.001

Source: Reviewer's results
Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

Study 304

Table 4. Study 304: LS Mean Change in ADHD-RS-IV Total Score by Visit (ITT Population)

Visit (week)	Placebo Mean (SE)	SPD503 1mg Mean (SE); p-value vs. placebo	SPD503 2 mg Mean (SE); p-value vs. placebo	SPD503 3 mg Mean (SE); p-value vs. placebo	SPD503 4 mg Mean (SE); p-value vs. placebo
1 (week1)	-5.82 (1.11)	-10.90 (1.18); 0.002	-6.67 (1.12); 0.589	-7.93 (1.13); 0.183	-9.18 (1.11); 0.033
2 (week 2)	-9.57 (1.35)	-12.86 (1.42); 0.095	-13.42 (1.36); 0.046	-15.33 (1.38); 0.003	-13.14 (1.35); 0.063
3 (week 3)	-9.38 (1.45)	-15.93 (1.53); 0.002	-13.82 (1.45); 0.031	-16.98 (1.49); <0.001	-16.63 (1.45); <0.001
4 (week 4)	-10.33 (1.51)	-18.09 (1.59); <0.001	-14.73 (1.51); 0.040	-19.39 (1.55); <0.001	-19.98 (1.51); <0.001
5 (week 5)	-12.27 (1.54)	-18.84 (1.62); 0.004	-15.52 (1.54); 0.136	-19.96 (1.58); <0.001	-19.57 (1.54); <0.001
6 (week 6)	-12.72 (1.60)	-19.43 (1.69); 0.004	-17.99 (1.60); 0.021	-19.91 (1.64); 0.002	-20.56 (1.60); <0.001

Source: Reviewer's results

Note: the reported p-values are nominal p-values and are not adjusted for multiplicity.

6.5.2 Analysis by Actual Dose on the Primary Endpoint

The sponsor performed additional analyses based on the actual dose and the weight-adjusted actual dose. The actual dose is the dose received at the time of assessment during Titration and Maintenance Phases. If a subject randomized to the 4mg SPD503 group withdrew at Week 3, then efficacy data for this subject results from an actual dose of 3mg.

Table 5 and Table 8 illustrate the actual doses used, compared to the randomized doses planned for the 1mg, 2mg, 3mg and 4mg/day groups, respectively.

The results of actual dose analysis support the primary analysis. For Study 301, the placebo-adjusted LS mean endpoint changes were numerically statistically significant for the 2mg, 3mg, and 4mg guanfacine actual doses (but not for the 1 mg group). In Study 304, all guanfacine actual doses (1mg, 2mg, 3mg and 4mg) were statistically significantly superior to placebo. Furthermore, for both studies, all weight-adjusted guanfacine doses demonstrated efficacy compared to placebo. The results of analysis by actual dose and by weight-adjusted actual dose presented below are sponsor's findings. The reviewer's results were similar.

As illustrated in the tables, the estimated size of the placebo-adjusted treatment effect increased in a dose-related manner. The effect appears to be more pronounced for the weight-adjusted, actual dose analysis.

Study 301

Table 5. Study 301: Patient Distribution by Randomized and Actual Doses

Actual Dose (highest dose actually received)	Randomized Dose			
	Placebo N=78	SPD503 2mg N=84	SPD503 3mg N=82	SPD503 4mg N=81
Placebo N=78	78	0	0	0
SPD503 1mg N=12	0	3	6	3
SPD503 2mg N=95	0	81	4	10
SPD503 3mg N=81	0	0	72	9
SPD503 4mg N=59	0	0	0	59

Source: Reviewer's results

Table 6. Study 301: ADHD-RS-IV Total Score by Actual Dose at Endpoint (ITT Population)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Endpoint	N patients	78	12	95	81	59
	Mean(SD)	29.28 (14.94)	25.50 (13.59)	22.01 (13.83)	19.81 (13.00)	17.46 (11.32)
Change from Baseline	Mean (SD)	-8.86 (12.90)	-9.50 (12.85)	-14.52 (12.31)	-16.32 (12.92)	-22.20 (13.59)
Placebo-adjusted treatment effect			− 0.64	− 5.66	− 7.46	− 13.34
Placebo-	LS mean	NA	-1.91	-6.31	-8.28	-12.73

adjusted difference	95% CI	NA	(-11.38, 7.55)	(-10.98, -1.65)	(-13.12, -3.43)	(-17.99, -7.46)
	P-Value (Dunnett)	NA	0.9699	0.0035	0.0001	<0.0001

Source: Section 12.1 Table 2.13.5 of Clinical Study 301 Report (pg. 74)

Table 7. Study 301: ADHD-RS-IV Total Score by Weight-adjusted Actual Dose at Endpoint (ITT Population) GEORGE

		Placebo	SPD503 0.01-0.04 mg/kg	SPD503 0.05-0.08 mg/kg	SPD503 0.09-0.12 mg/kg	SPD503 0.13-0.17 mg/kg
Endpoint	N patients	78	62	112	51	22
	Mean(SD)	29.28 (14.94)	22.15 (13.68)	22.65 (13.82)	15.47 (9.94)	15.14 (9.51)
Change from Baseline	Mean (SD)	-8.86 (12.90)	-11.48 (12.19)	-15.12 (13.32)	-21.71 (10.39)	-27.86 (11.63)
Placebo-adjusted treatment effect			− 2.62	− 6.26	− 12.85	− 19
Placebo-adjusted difference	LS mean	NA	-4.30	-6.40	-13.21	-17.20
	95% CI	NA	(-9.43, 0.82)	(-10.78, -2.01)	(-18.57, -7.85)	(-24.43, -9.96)
	P-Value (Dunnett)	NA	0.1308	0.0014	<0.0001	<0.0001

Source: Section 12.1 Table 2.13.1 of Clinical Study 301 Report (pg. 75)

Study 304

Table 8. Study 304: Patient Distribution by Randomized and Actual Dose

Actual Dose (highest dose actually received)	Randomized Dose				
	Placebo N=63	SPD503 1mg N=57	SPD503 2mg N=63	SPD503 3mg N=60	SPD503 4mg N=63
Placebo N=63	63	0	0	0	0
SPD503 1mg N=68	0	57	8	2	1
SPD503 2mg N=69	0	0	55	11	3
SPD503 3mg N=52	0	0	0	47	5
SPD503 4mg N=54	0	0	0	0	54

Source: Reviewer's results

Table 9. Study 304: ADHD-RS-IV Total Score by Actual Dose at Endpoint (ITT Population)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Endpoint	N patients	63	68	69	52	54
	Mean(SD)	27.1 (15.02)	23.5 (13.14)	21.2 (13.67)	17.9 (12.08)	19.1 (10.25)
Change from Baseline	Mean (SD)	-12.2 (12.96)	-17.8 (14.34)	-18.8 (14.58)	-21.7 (14.22)	-21.1 (11.66)
Placebo-adjusted treatment effect			− 5.6	− 6.6	− 9.5	− 8.9
Placebo-adjusted difference	LS mean	NA	-4.38	-6.18	-9.29	-8.33
	95% CI	NA	(-8.7, 0.0)	(-10.5, -1.8)	(-13.9, -4.6)	(-12.9, -3.7)
	P-Value	NA	0.0485	0.0053	0.0001	0.0004

Source: Section 12.1 Table 2.1.1.1 of Clinical Study 304 Report (pg. 88)

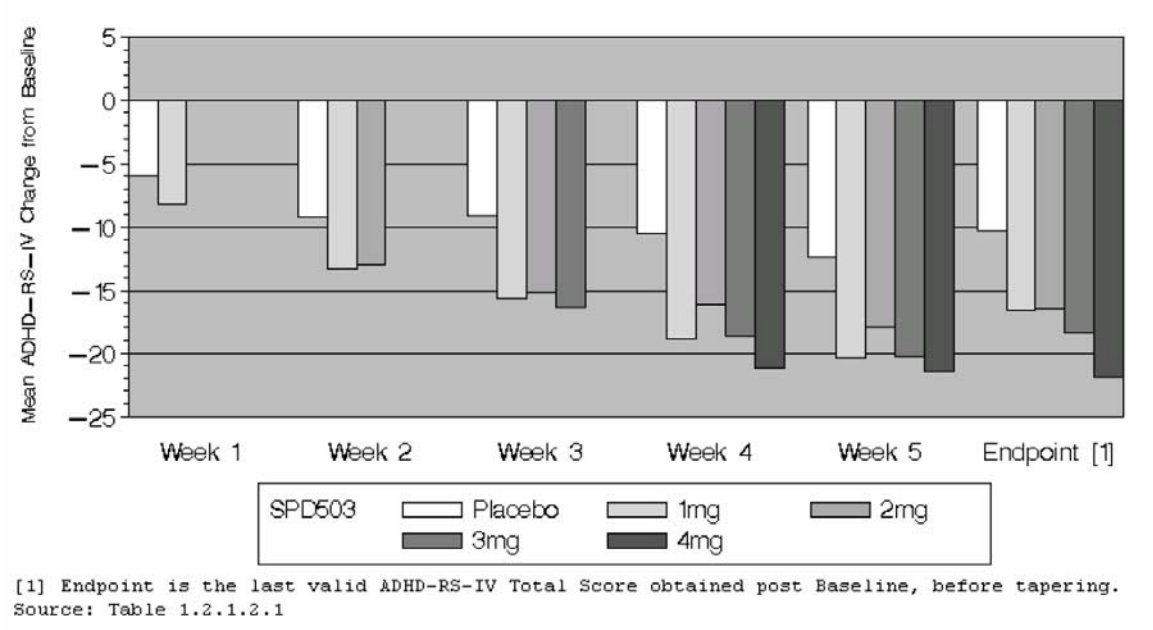
Table 10. Study 304: ADHD-RS-IV Total Score by Weight-adjusted Actual Dose at Endpoint (ITT Population)

		Placebo	SPD503 0.01-0.04 mg/kg	SPD503 0.05-0.08 mg/kg	SPD503 0.09-0.12 mg/kg	SPD503 0.13-0.16 mg/kg
Endpoint	N patients	63	112	84	33	14
	Mean(SD)	27.1 (15.02)	22.1 (13.17)	19.7 (12.44)	19.8 (11.55)	16.8 (10.47)
Change from Baseline	Mean (SD)	-12.2 (12.96)	-17.6 (14.05)	-20.0 (13.82)	-23.5 (13.35)	-24.8 (11.05)
Placebo-adjusted treatment effect			− 5.45	− 7.8	− 11.3	− 12.6
Placebo-adjusted difference	LS mean	NA	-5.13	-7.56	-8.98	-11.24
	95% CI	NA	(-9.0, -1.2)	(-11.7, -3.4)	(-14.4, -3.6)	(-18.6, -3.9)
	P-Value (Dunnett)	NA	0.0104	0.0004	<0.0012	<0.0028

Source: Section 12.1 Table 2.1.4.1 of Clinical Study 304 Report (pg. 89)

The tables below illustrate some of the efficacy results over time for the actual dose and weight-adjusted actual dose efficacy analyses. These are tables constructed by the sponsor.

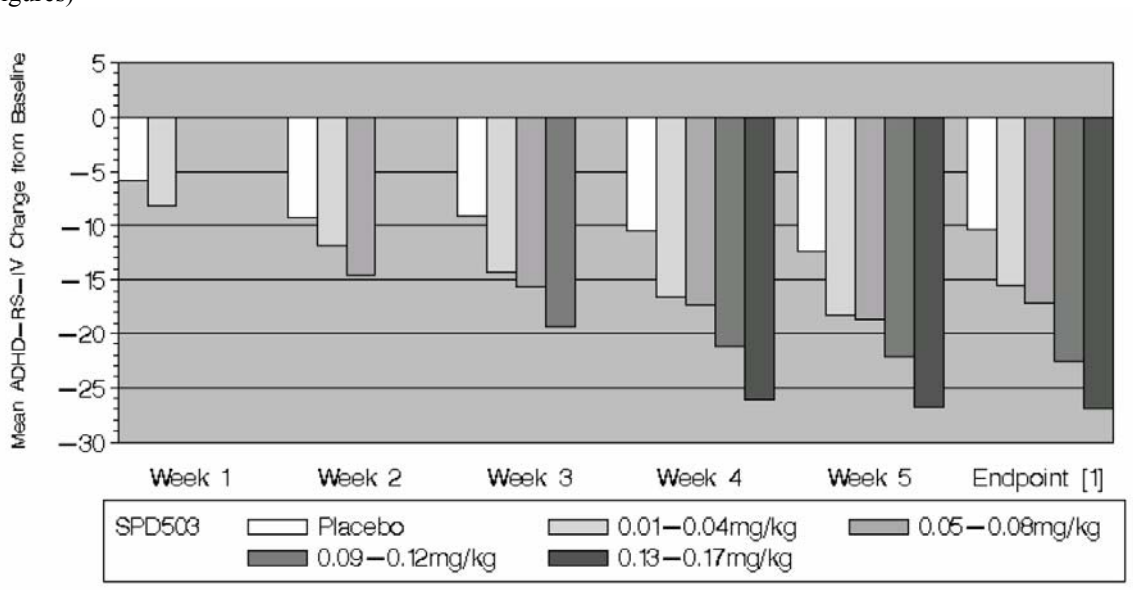
Mean ADHD-RS-IV Total Change Score by Visit for Actual Dose (Controlled Studies Combined)- Figure 1.1.1.2 of Integrated Summary of Safety Tables



[1] Endpoint is the last valid ADHD-RS-IV Total Score obtained post Baseline, before tapering.
Source: Table 1.2.1.2.1

Mean ADHD-RS-IV Total Change Score by Visit for Weight-Adjusted Actual Dose for Controlled Studies Combined. (Figure 1.1.1.3 Integrated Summary of Efficacy

Figures)



[1] Endpoint is the last valid ADHD-RS-IV Total Score obtained post Baseline, before tapering.
Source: Table 1.2.1.3.1

6.5.3 Primary Analysis on Subscale Scores of the Primary Endpoint

The eighteen ADHD-RS-IV items were grouped into two subscales: Hyperactivity/impulsivity (even numbered items) and Inattentiveness (odd numbered items). The tables below provide a summary and analysis of ADHD-RS-IV Inattentiveness and Hyperactivity/Impulsivity subscales by randomized dose groups for ITT Population. The analysis was performed by the statistics reviewer. The results confirmed sponsor's results. For both studies, all guanfacine treatment groups had a statistically significantly superior treatment effect, compared to placebo. Thus, the results suggest that treatment with guanfacine has a positive effect on symptoms consistent with inattentiveness in addition to having a positive effect on symptoms in the category of hyperactivity and impulsivity. Such findings are highly clinically significant.

Study 301

Table 11. Study 301: ADHD-RS-IV Inattentiveness Subscale Scores at Endpoint by Randomized Dose (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
No patients	326	78	84	82	81
Baseline	Mean (SD)	20.86 (4.93)	20.76 (4.85)	20.84 (4.21)	21.67 (4.18)
Endpoint	Mean (SD)	15.96 (8.04)	12.45 (7.35)	12.13 (7.06)	12.05 (7.19)
Change from Baseline	Mean (SD)	-4.90 (7.95)	-8.31 (7.28)	-8.71 (7.27)	-9.62 (7.64)
Placebo-adjusted difference	LS mean	NA	-3.47	-3.82	-4.28
	95% CI	NA	(-5.67, -1.26)	(-6.04,-1.60)	(-6.51,-2.05)
	P-Value	NA	0.0022	0.0008	0.0002

Source: Reviewer's results
Corresponds to Table 22 of Clinical Study 301 Report (pg. 85)
Note: the reported p-values and CIs are nominal and are not adjusted for multiplicity.

Table 12. Study 301: ADHD-RS-IV Hyperactivity/Impulsivity Subscale Scores at Endpoint by Randomized Dose (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
No patients	326	78	84	82	81
Baseline	Mean (SD)	17.28 (6.61)	15.33 (7.00)	15.93 (6.53)	16.73 (6.65)
Endpoint	Mean (SD)	13.00 (8.41)	8.48 (7.26)	8.84 (7.56)	7.16 (5.86)
Change from Baseline	Mean (SD)	-4.28 (6.32)	-6.86 (6.47)	-7.09 (6.96)	-9.57 (7.24)
Placebo-adjusted difference	LS mean	NA	-3.38	-3.36	-5.51
	95% CI	NA	(-5.30, -1.46)	(-5.29, -1.43)	(-7.44,-3.58)
	P-Value	NA	0.0006	0.0007	<0.0001

Source: Reviewer's results
Corresponds to Table 22 of Clinical Study 301 Report (pg. 85)
Note: the reported p-values CIs are nominal and are not adjusted for multiplicity.

Study 304

Table 13 Study 304: ADHD-RS-IV Inattentiveness Subscale score at Endpoint by Randomized Dose (ITT Population) GEORGE

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
No patients	306	63	57	63	60	63
Baseline	Mean(SD)	22.16 (4.17)	22.09 (3.79)	22.48 (4.19)	22.63 (3.56)	22.54 (3.74)
Endpoint	Mean(SD)	15.78 (7.86)	11.60 (6.68)	12.98 (7.74)	12.57 (7.86)	11.98 (6.35)
Change fr. Baseline	Mean (SD)	-6.38 (7.08)	-10.49 (7.02)	-9.49 (8.36)	-10.07 (7.77)	-10.56 (6.42)
Placebo-adjusted difference	LS mean	NA	-4.15	-2.95	-3.44	-3.98
	95% CI	NA	(-6.70, -1.59)	(-5.44, -0.46)	(-5.96, -0.92)	(-6.47,-1.49)
	P-Value	NA	0.002	0.020	0.008	0.002

Source: Reviewer's results
Corresponds to Table 19 of Clinical Study 304 Report (pg. 93)
Note: the reported p-values and CIs are nominal and are not adjusted for multiplicity

Table 14 Study 304: ADHD-RS-IV Hyperactivity/Impulsivity Subscale Score at Endpoint by Randomized Dose (ITT Population) GEORGE

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
No patients	306	63	57	63	60	63
Baseline	Mean(SD)	17.10 (6.71)	19.61 (5.01)	17.44 (6.86)	16.43 (7.08)	18.06 (6.58)
Endpoint	Mean(SD)	11.25 (8.34)	9.70 (6.87)	9.02 (8.03)	7.17 (5.72)	7.16 (5.86)
Change fr. Baseline	Mean (SD)	-5.84 (7.08)	-9.91 (7.67)	-8.43 (7.83)	-9.32 (8.05)	-10.32 (6.72)
Placebo-adjusted difference	LS mean	NA	-2.64	-2.39	-3.85	-3.93
	95% CI	NA	(-5.00, -0.28)	(-4.67, -0.11)	(-6.16, -1.54)	(-6.21, -1.64)
	P-Value	NA	0.028	0.040	0.001	0.001

Source: Reviewer's results
Corresponds to Table 21 of Clinical Study 304 Report (pg. 95)
Note: the reported p-values and CIs are nominal and are not adjusted for multiplicity.

6.5.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Age, Gender, and Ethnicity

The tables below illustrate the statistical reviewer's efficacy results from exploratory subgroup analyses by age, gender and race. The results are consistent with the sponsor's results for subgroup analysis. In both clinical trials, although the efficacy results were positive for the study population as a whole, there was not a statistically significant treatment effect for the age group 13-17 years old. From several lines of evidence, it is highly likely that one contributing factor was the lower serum guanfacine exposures observed in the Intuniv clinical program. There was an extremely strong inverse correlation between subjects' body weight and guanfacine exposure. Furthermore, the magnitude of the Intuniv treatment effect was dose-related and exposure-related. In addition, the magnitude of the placebo effect appeared to be greater for the age group 13-17 years-old, compared to the younger subgroup (ages 6-12 years).

In the subgroup analysis by gender, it is clear that Intuniv as effective in the male subject. However, for several dose groups in studies 301 and 304, the treatment effect was not statistically significant in the female subgroup. Of note, the number of female subjects was considerably smaller than the number of males in both studies. Currently the clinical significance of the subgroups analysis by gender is unclear.

Study 301

Table 15 Study 301: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and Age Subgroups (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
Age 6-8 years					
No patients		22	16	20	27
Baseline	Mean (SD)	40.41 (8.94)	37.88 (10.94)	37.00 (8.45)	41.96 (7.52)
Endpoint	Mean(SD)	36.09 (10.06)	21.88 (13.48)	19.15 (13.83)	15.63 (9.78)
Change fr. Baseline	Mean (SD)	-4.32 (9.60)	-16.00 (13.17)	-17.85 (14.41)	-26.33 (11.74)
Placebo-adjusted difference	LS mean	NA	-13.17 (3.67)	-15.53 (3.47)	-21.10 (3.20)
	95% CI	NA	(-20.48, -5.86)	(-22.44, -8.63)	(-27.48, -14.73)
	P-Value	NA	0.0006	<0.0001	<0.0001
Age 9-12					
No patients		37	51	37	39
Baseline	Mean (SD)	37.43 (10.38)	36.82 (9.98)	38.24 (8.57)	36.97 (9.90)
Endpoint	Mean(SD)	27.92 (15.75)	20.35 (14.54)	21.32 (14.85)	21.72 (12.79)
Change fr. Baseline	Mean (SD)	-9.51 (12.71)	-16.47 (12.85)	-16.92 (13.32)	-15.26 (12.32)
Placebo adjusted difference	LS mean	NA	-7.11 (2.72)	-7.20 (2.93)	-5.86 (2.89)
	95% CI	NA	(-12.49, -1.74)	(-12.98, -1.41)	(-11.57, -0.15)
	P-Value	NA	0.010	0.015	0.044
Age 13-17 years					
No patients		19	17	25	15
Baseline	Mean (SD)	36.89 (7.45)	32.24 (8.63)	34.40 (8.98)	35.67 (8.70)
Endpoint	Mean(SD)	22.79 (16.27)	21.47 (11.92)	21.92 (12.77)	19.13 (12.42)
Change fr. Baseline	Mean (SD)	-14.11 (16.00)	-10.76 (11.49)	-12.48 (11.09)	-16.53 (16.40)
Placebo adjusted	LS mean	NA	0.86 (4.42)	0.30 (3.98)	-3.08 (4.50)
	95% CI	NA	(-7.94, 9.67)	(-7.63, 8.23)	(-12.04, 5.87)

difference	P-Value	NA	0.846	0.940	0.495

Source: Reviewer's results
Corresponds to Section 12.1 Tables 2.2.2, 2.2.3, and 2.2.4 of Clinical Study 301 Report (pg. 86)
Note: the reported p-values and 95% CIs are nominal and are not adjusted for multiplicity.

Table 16 Study 301: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and Gender Subgroups (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
Males					
No patients	241	58	65	66	52
Baseline	Mean (SD)	38.90 (8.81)	36.48 (9.73)	36.55 (8.80)	37.94 (9.46)
Endpoint	Mean(SD)	31.64 (13.41)	21.23 (13.62)	20.91 (14.10)	21.17 (12.23)
Change fr. Baseline	Mean (SD)	-7.26 (12.35)	-15.25 (12.61)	-15.64 (13.16)	-16.77 (13.97)
Placebo-adjusted difference	LS mean	NA	-9.04 (2.25)	-9.40 (2.24)	-9.93 (2.37)
	95% CI	NA	(-13.47, -4.61)	(-13.82, -4.99)	(-14.59, -5.26)
	P-Value	NA	<0.0001	<0.0001	<0.0001
Females					
No patients	84	20	19	16	29
Baseline	Mean (SD)	35.95 (10.69)	34.79 (11.02)	37.69 (8.61)	39.21 (8.86)
Endpoint	Mean(SD)	21.25 (17.54)	19.63 (14.32)	21.25 (13.31)	15.69 (10.80)
Change fr. Baseline	Mean (SD)	-14.70 (14.18)	-15.16 (13.37)	-16.44 (12.71)	-23.52 (12.54)
Placebo adjusted difference	LS mean	NA	-0.92 (4.06)	-1.05 (4.25)	-7.53 (3.71)
	95% CI	NA	(-9.00, 7.16)	(-9.52, 7.42)	(-14.91, -0.14)
	P-Value	NA	0.822	0.806	0.046

Source: Reviewer's results
Note: the reported p-values and 95% CIs are nominal and are not adjusted for multiplicity.

Table 17 Study 301: ADHD-RS-IV Total Score by Randomized Dose and Race Subgroups (ITT Population)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
Caucasians					
No patients	229	57	57	56	58
Baseline	Mean (SD)	37.46 (8.96)	37.19 (10.01)	37.18 (8.90)	38.17 (9.69)
Endpoint	Mean(SD)	28.12 (15.25)	21.84 (14.41)	23.18 (13.98)	17.45 (11.74)
Change fr. Baseline	Mean (SD)	-9.33 (13.23)	-15.35 (12.50)	-14.00 (12.50)	-20.72 (14.24)
Placebo-adjusted difference	LS mean	NA	-6.12 (2.37)	-4.77 (2.38)	-11.12 (2.36)
	95% CI	NA	(-10.79, -1.44)	(-9.47, -0.08)	(-15.77, -6.46)
	P-Value	NA	0.011	0.046	<0.0001
Others					
No patients	97	21	27	26	23
Baseline	Mean (SD)	40.00 (10.30)	33.78 (9.74)	35.88 (8.43)	38.96 (8.06)
Endpoint	Mean(SD)	31.29 (15.03)	18.81 (12.11)	16.23 (12.62)	23.65 (11.62)
Change fr. Baseline	Mean (SD)	-8.71 (13.31)	-14.96 (13.36)	-19.65 (13.45)	-15.30 (11.99)
Placebo adjusted difference	LS mean	NA	-9.60 (3.64)	-13.15 (3.61)	-7.15 (3.68)
	95% CI	NA	(-16.83, -2.36)	(-20.33, -5.98)	(-14.45, 0.15)
	P-Value	NA	0.010	0.001	0.055

Source: Reviewer's results
Note: the reported 95% CIs and p-values are nominal and are not adjusted for multiplicity.

Study 304

Table 18 Study 304: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and Age Subgroups

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Age 6-12 years						
No patients	230	45	50	46	41	48
Baseline	Mean (SD)	41.33 (8.85)	42.16 (7.78)	40.57 (9.02)	41.59 (8.27)	41.50 (8.27)
Endpoint	Mean(SD)	29.82(14.86)	21.12 (12.87)	24.26 (14.57)	19.68 (13.22)	19.17 (10.35)
Change fr. Baseline	Mean (SD)	-11.51 (13.71)	-21.04 (14.45)	-16.30 (14.78)	-21.90 (13.97)	-22.33 (11.59)
Placebo-adjusted difference	LS mean	NA	-9.04	-5.25	-10.24	-10.72
	95% CI	NA	(-14.23,-3.85)	(-10.55,0.05)	(-15.69,-4.79)	(-15.96, -5.48)
	P-Value	NA	0.0007	0.052	0.0003	<0.0001
Age 13-17 years						
No patients	76	18	7	17	19	15
Baseline	Mean (SD)	34.06 (6.53)	38.43 (7.76)	38.18 (7.92)	33.63 (8.99)	37.73 (9.16)
Endpoint	Mean(SD)	20.06 (13.29)	22.57 (13.05)	16.00 (10.40)	19.95 (10.93)	21.53 (13.15)
Change fr. Baseline	Mean (SD)	-14.00 (10.95)	-15.86 (9.89)	-22.18 (14.32)	-13.68 (15.02)	-16.20 (12.01)
Placebo-adjusted difference	LS mean	NA	1.10	-5.39	0.03	0.29
	95% CI	NA	(-9.54, 11.74)	(-13.51, 2.73)	(-7.75, 7.81)	(-8.07, 8.65)
	P-Value	NA	0.837	0.190	0.994	0.946

Source: Reviewer's results
Corresponds to Section 12.1, Table 2.1.3 of Clinical Study 304 Report (pg. 92)
Note: the reported 95% CIs and p-values are nominal and are not adjusted for multiplicity.

Table 19 Study 304: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and Gender Subgroups

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Males						
No patients	220	44	37	44	44	51
Baseline	Mean (SD)	40.68 (8.41)	40.27 (8.14)	40.45 (8.33)	38.43 (9.23)	40.86 (8.35)
Endpoint	Mean(SD)	27.18 (15.24)	22.11 (12.73)	22.00 (14.52)	20.02 (13.06)	19.47 (11.03)
Change fr. Baseline	Mean (SD)	-13.50 (13.39)	-18.16 (13.90)	-18.45 (14.02)	-18.41 (14.88)	-21.39 (12.27)
Placebo-adjusted difference	LS mean	NA	-4.89	-5.08	-6.17	-7.79
	95% CI	NA	(-10.54, 0.75)	(-10.48, 0.31)	(-11.58, -0.75)	(-12.99, -2.58)
	P-Value	NA	0.089	0.065	0.026	0.003
Females						
No patients	86	19	20	19	16	12
Baseline	Mean (SD)	35.95 (9.17)	44.35 (6.53)	38.68 (9.76)	40.81 (9.24)	39.50 (9.77)
Endpoint	Mean(SD)	26.68 (14.83)	19.80 (13.08)	22.11 (13.05)	19.06 (10.94)	20.83 (11.34)
Change fr. Baseline	Mean (SD)	-9.26 (11.65)	-24.55 (13.57)	-16.58 (16.75)	-21.75 (14.34)	-18.67 (10.31)
Placebo-adjusted difference	LS mean	NA	-9.92	-5.57	-9.38	-7.14
	95% CI	NA	(-18.36, -1.49)	(-13.73, 2.59)	(-18.00, -0.75)	(-16.43, 2.16)
	P-Value	NA	0.022	0.178	0.033	0.131

Source: Reviewer's results
Note: the reported 95% CIs and p-values are nominal and are not adjusted for multiplicity.

Table 20 Study 304: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and Race Subgroups

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Caucasians						
No patients	203	38	39	40	43	43
Baseline	Mean (SD)	39.03 (9.00)	40.05 (7.81)	40.90 (8.39)	38.02 (9.01)	41.09 (8.75)
Endpoint	Mean(SD)	26.68 (15.90)	22.54 (11.41)	22.35 (14.49)	19.51 (12.85)	20.63 (11.34)
Change fr. Baseline	Mean (SD)	-12.34 (13.78)	-17.51 (12.64)	-18.55 (14.96)	-18.51 (14.63)	-20.47 (11.53)
Placebo-	LS mean	NA	-4.60	-5.17	-6.72	-6.98

adjusted difference	95% CI	NA	(-10.33, 1.12)	(-10.87, 0.53)	(-12.32, -1.13)	(-12.58, -1.38)
	P-Value	NA	0.114	0.075	0.019	0.015
Others						
No patients	103	25	18	23	17	20
Baseline	Mean (SD)	39.60 (8.78)	45.28 (6.68)	38.22 (9.27)	41.71 (9.47)	39.55 (8.29)
Endpoint	Mean(SD)	27.56 (13.81)	18.61 (15.36)	21.48 (13.37)	20.41 (11.72)	17.80 (10.28)
Change fr. Baseline	Mean (SD)	-12.04 (11.84)	-26.67 (15.12)	-16.74 (14.72)	-21.29 (15.12)	-21.75 (12.89)
Placebo-adjusted difference	LS mean	NA	-10.96	-5.59	-7.89	-9.74
	95% CI	NA	(-18.97, -2.95)	(-12.92, 1.74)	(-15.88, 0.10)	(-17.34, -2.14)
	P-Value	NA	0.008	0.133	0.053	0.013

Source: Reviewer's results
Note: the reported 95% CIs and p-values are nominal and are not adjusted for multiplicity.

EXPOSURE TO STUDY DRUG

Total Pediatric ADHD Subject Exposure in the Clinical Program

For the entire pediatric ADHD clinical program, there were 843 unique subjects exposed to guanfacine for a total exposure of 504.04 person years. There were 206 subjects exposed to placebo for a total exposure of 25.62 years.

Controlled, Short-term Pediatric ADHD Trials

There were 513 subjects exposed to Intuniv for a total of 65.02 person years.
There were 149 subjects exposed to placebo for a total of 18.39 person-years.

Long-term, Open-label Pediatric ADHD Studies

There were 446 subjects exposed to Intuniv for a total of 349.93 person years.

Pediatric ADHD Subjects in Phase 1 and 2 Studies

68 ADHD subjects ages 6-12 for 6.742 person-years of exposure to guanfacine (which included three different formulations of guanfacine).

Adults in Phase 1 Studies

There were 305 healthy adult subjects treated with guanfacine for a total exposure of 3.863 person-years.

Table 2 Lengths of Exposure to Placebo and SPD503 (All Active) – Overall Study Pool Plus Study 205 Subjects and Study 305 Subjects Enrolled from Study 205

Parameter	Placebo (N=206)	All Active (N=815)
Length of exposure (months)		
n	206	815
Mean (SD)	1.51 (0.527)	7.52 (8.402)
Median	1.60	3.33
Min, Max	0, 2.3	0, 28
Length of exposure category - n (%)		
<1 month	35 (17.0)	114 (14.0)
1 and <3 months	171 (83.0)	275 (33.7)
3 and <6 months	0	124 (15.2)
6 and <9 months	0	58 (7.1)
9 and <12 months	0	45 (5.5)
12 and <15 months	0	36 (4.4)
15 and <18 months	0	29 (3.6)
18 and <21 months	0	18 (2.2)
21 and <24 months	0	41 (5.0)
24 months	0	75 (9.2)
Total days exposed	9352	183976

7.2 Exposure To Study Drug In Controlled, Short-Term Trials

Table 6 Length of Exposure to Actual Doses – Short-Term Study Pool

Parameter	Placebo (N=149)	SPD503 1mg (N=513)	SPD503 2mg (N=424)	SPD503 3mg (N=261)	SPD503 4mg (N=122)	All Active (N=513)
Length of exposure (weeks)						
n	149	513	424	261	122	513
Mean (SD)	6.44 (2.581)	2.37 (2.369)	2.87 (1.707)	2.6 (1.203)	2.25 (0.788)	6.61 (2.608)
Median	7.00	1.43	2.14	2.14	2.00	7.14
Min, Max	0.1, 9.7	0.1, 9.6	0.1, 6.4	0.1, 5.1	0.1, 3.9	0.1, 10.4
Length of exposure category						
<1 week	8 (5.4)	65 (12.7)	17 (4.0)	10 (3.8)	7 (5.7)	20 (3.9)
≥1 and <3 weeks	12 (8.1)	339 (66.1)	259 (61.1)	147 (56.3)	80 (65.6)	47 (9.2)
≥3 and <6 weeks	21 (14.1)	58 (11.3)	102 (24.1)	104 (39.8)	35 (28.7)	82 (16.0)
≥6 and <9 weeks	75 (50.3)	18 (3.5)	46 (10.8)	0	0	243 (47.4)
≥9 weeks	33 (22.1)	33 (6.4)	0	0	0	121 (23.6)
Total days exposed	6714	8521	8529	4757	1924	23731

Controlled Trial Exposure to Intuniv

A total of 662 subjects were exposed to at least one dose of study medication in the short-term study pool. There were 513 subjects exposed to Intuniv at doses of 1, 2, 3, and 4mg daily, and there were 149 subjects exposed to placebo. Of the 513 subjects treated with Intuniv, 61 subjects (from Study 304 only) were randomized to a maximum daily dose of 1mg, 150 subjects were randomized to 2mg, 151 subjects were randomized to 3mg, and

151 subjects were randomized to 4mg. There were a total of 18.38 patient-years of exposure to placebo and 64.97 patient-years of exposure to Intuniv.

The mean length of exposure was similar across the randomized treatment groups (placebo, 2mg, 3mg, and 4mg; 6.27 to 6.74 weeks) except for a slightly longer exposure in the 1mg group (7.71 weeks) as this group is from Study 304 only, where the treatment phase was one week longer than in Study 301. For the All Active group, it was 6.61 weeks, 71% of the group received study drug for 6 to 9 weeks or more.

The majority of subjects reached the maximum dose to which they were randomized in the SPD503 2mg (94.0%), 3mg (84.1%), and 4mg (80.8%) groups. The mean daily dose received was 1.00mg in the 1mg group, 1.63mg in the 2mg group, 2.11mg in the 3mg group, and 2.44mg in the 4mg group (1.94mg for SPD503 overall) as a result of dose titration at 1mg/week increments then tapering after the maintenance period at 1mg/week decrements. The mean daily dose adjusted to body weight was 0.03mg/kg in the 1mg group, 0.04mg/kg in the 2mg group, 0.05mg/kg in the 3mg group, and 0.06mg/kg in the 4mg group (0.05mg/kg for SPD503 overall).

Analysis of the actual doses received by subjects revealed that of the 513 subjects who were exposed to SPD503 (Text Table 6), all 513 subjects received 1mg, 424 subjects received 2mg, 261 subjects received 3mg, and 122 subjects received 4mg daily at any time during the study. Due to dose escalation and tapering, the mean length of exposure was much shorter for the actual doses (2.25 to 2.87 weeks) compared with the placebo group (6.44 weeks) or SPD503 overall (6.61 weeks), which should be considered when interpreting AE results by actual dose. The total patient-years of exposure to the individual actual doses of SPD503 was 23.33 patient-years (1mg), 23.35 patient-years (2mg), 13.02 patient-years (3mg), and 5.27 patient-years (4mg).

Analysis of the weight-adjusted actual doses received by subjects showed that of the 513 subjects who were exposed to SPD503 (Text Table 7), all 513 subjects received 0.01-0.04mg/kg, 330 subjects received 0.05-0.08mg/kg, 126 subjects received 0.09-0.12mg/kg, and 38 subjects received 0.13-0.17mg/kg daily at any time during the study. Similarly to the analyses by actual dose, the mean length of exposure was much shorter for the weight-adjusted actual doses (2.21 to 3.61 weeks) compared with the placebo group (6.44 weeks) or SPD503 overall (6.61 weeks). In subjects who received SPD503, the length of exposure decreased with increasing weight-adjusted actual dose, which again should be considered when interpreting the AE results by weight-adjusted actual dose. The total patient-years of exposure to the individual mg/kg SPD503 dose categories was 35.49 patient-years (0.01- 0.04mg/kg), 21.34 patient-years (0.05-0.08mg/kg), 6.52 patient-years (0.09-0.12mg/kg), and 1.61 patient-years (0.13-0.17mg/kg).

Analysis of the length of exposure by actual dose and by the subgroups of age (6-12 years vs. =13 years), gender, or race (White, non-White) did not reveal any important differences between the various subgroups. Analysis of the length of exposure by weight-adjusted actual dose showed some differences between the subgroups of age and gender, which were probably related to differences in weight, described in Section 2.7.4.1.3.1; ie,

there was a longer exposure at the lowest SPD503 weight-adjusted dose category in subjects =13 years (5.3 weeks) compared with subjects 6-12 years (3.1 weeks), and in female subjects (4.27 weeks) compared with male subjects (3.38 weeks). No relevant difference was noted in the length of exposure by weight-adjusted actual dose and race.

7.3 Exposure To Study Drug In Long-Term, Open-Label Studies

Table 4 Length of Treatment Exposure to Actual Doses – Long-Term Study Pool

Parameter	SPD503 1mg (N=342)	SPD503 2mg (N=439)	SPD503 3mg (N=381)	SPD503 4mg (N=238)	All Active (N=446)
Length of exposure (months)					
n	342	439	381	238	446
Mean (SD)	0.47 (1.265)	2.51 (4.634)	4.06 (5.580)	6.09 (6.581)	9.55 (8.459)
Median	0.23	0.47	1.40	3.07	6.38
Min, Max	0, 12.5	0, 24.8	0, 23.7	0, 23.6	0, 25.9
Length of exposure category - n (%)					
<1 month	326 (95.3)	290 (66.1)	159 (41.7)	51 (21.4)	53 (11.9)
1 and <3 months	9 (2.6)	62 (14.1)	85 (22.3)	66 (27.7)	85 (19.1)
3 and <6 months	2 (0.6)	29 (6.6)	53 (13.9)	38 (16.0)	76 (17.0)
6 and <9 months	2 (0.6)	22 (5.0)	22 (5.8)	22 (9.2)	47 (10.5)
9 and <12 months	1 (0.3)	9 (2.1)	22 (5.8)	17 (7.1)	39 (8.7)
12 and <15 months	2 (0.6)	8 (1.8)	11 (2.9)	13 (5.5)	29 (6.5)
15 and <18 months	0	6 (1.4)	13 (3.4)	8 (3.4)	23 (5.2)
18 and <21 months	0	6 (1.4)	6 (1.6)	11 (4.6)	12 (2.7)
21 and <24 months	0	5 (1.1)	10 (2.6)	12 (5.0)	20 (4.5)
24 months	0	2 (0.5)	0	0	62 (13.9)
Total days exposed	4818	32992	46403	43512	127725

Long Term Open Label Exposure

A total of 446 subjects were exposed to at least one dose of SPD503 in the long-term study pool (Text Table 8). Text Table 8 displays data from the long-term study pool, excluding subjects who transferred into Study 305 from Study 205. This table shows exposure only during the long-term studies (in contrast to Text Table 4, which shows combined exposure from the short- and long-term studies). The most common dose that was taken prior to tapering was the protocol-allowed maximum dose, 4mg (159 subjects), followed by 3mg (150 subjects), 2mg (123 subjects), and 1mg (14 subjects). The small size of the 1mg group limits the conclusions that can be made based on the 1mg data. The mean daily dose was 1.59mg to 3.45mg (weight-adjusted: 0.04mg/kg to 0.08mg/kg) across the groups.

Approximately half the subjects in the 1mg and 2mg dose prior to tapering groups and one third of the subjects in the 3mg group had exposure to higher doses than their dose prior to tapering. For most subjects in each group, the dose prior to tapering was also the dose with the longest exposure (68.7% to 81.3% across the groups). As for maximum dose, 85.4% (381 of 446 subjects) were able to achieve doses of 3mg or 4mg. The mean length of exposure increased with dose (prior to tapering) from 3.99 months (1mg) to 9.28 months (4mg). This should be considered when interpreting the results of AE

incidence analysis, ie, dose response suggested by incidence analysis may be partly due to longer exposure to study medication (any dose) in the 3mg and 4mg dose prior to tapering groups compared with the 1mg and 2mg groups.

Mean exposure for the entire group was 7.91 months, while median exposure was 6.38 months. Two hundred and thirty-two (232) of 446 subjects (52.0%) had at least 6 months There were a total of 289.73 patient-years of exposure to SPD503 in the long-term study pool. The total patient-years of exposure to the individual actual doses of SPD503 (Text Table 9) was 10.48 patient-years (1mg), 74.96 patient-years (2mg), 105.84 patient-years (3mg), and 98.44 patient-years (4mg). Exposure to SPD503 was slightly shorter in female subjects (7.12 months) compared with male subjects (8.18 months), while no relevant differences were noted by age or race category.

Analysis of the actual doses received by the subjects revealed that of the 446 subjects who were exposed to SPD503, 342 subjects received 1mg, 438 subjects received 2mg, 381 subjects received 3mg, and 233 subjects received 4mg daily at some point(s) of the study (Text Table 9). Due to dose escalation and tapering, the mean length of exposure was much shorter for the actual doses (0.37 to 5.14 months) compared with SPD503 overall (7.91 months), and increased with actual dose, which again should be considered when interpreting the results of AE incidence analysis.

8 INTEGRATED REVIEW OF SAFETY

8.1 Safety Findings In Controlled Studies

8.1.1 Deaths

There were no deaths in the two pivotal, placebo-controlled studies. Furthermore, there were no deaths in the long-term open-label studies (303 and 305), and there were no deaths in the Phase 1 or Phase 2 studies.

8.1.2 Serious Adverse Events

Only four (4) SAE were reported in the controlled trials. None of the SAE appears to have been related to treatment with guanfacine. In Study 301, two (2) subjects treated with guanfacine had serious adverse events. One subject had an exacerbation of asthma, and another subject with a history of asthma had a pneumothorax. In Study 301, none of the subjects in the placebo group had a serious adverse event. In Study 304, one subject treated with guanfacine had a head injury, concussion, and seizure. One subject in the placebo group had a fracture of the tibia and fibula.

1. Asthma Exacerbation
Subject 119-003 was a 6 year-old white male who had a history of asthma and multiple allergies. He was randomized to Intuniv 4 mg per day. On Day 26 of study drug treatment, he was hospitalized due to difficulty breathing, and he was treated with routine care for acute asthma. The event resolved, and the subject was discharged from the hospital. The investigator considered the adverse event unrelated to study drug treatment. It appears unlikely that the adverse event was related to treatment with guanfacine.

2. Pneumothorax
Subject 148-001 was a 16 year-old male with a history of asthma. He was randomized to treatment with Intuniv 3 mg per day. On Day 6, he developed dyspnea and chest pain on exertion, while mowing the lawn. The pain fluctuated over the course of about two weeks, but became acute during wrestling. A chest radiograph revealed a left-apical pneumothorax. The subject was hospitalized, and the patient received appropriate treatment for the pneumothorax. He was discontinued from the study. On Day 27 after beginning the study, the subject recovered and was discharged from the hospital. The investigator considered the pneumothorax and respiratory symptoms unrelated to treatment with guanfacine. It appears unlikely that the adverse events were related to treatment with guanfacine.

3. Head Injury, Concussion, and Seizure
Subject 274-003 was a 12 year-old white male who was randomized to treatment with Intuniv 3 mg per day but tolerated only 2 mg per day, due to nausea. He discontinued study medication on Day 19. On Day 20 of treatment, the subject experienced a closed head injury, concussion, and seizure after an accident while riding a skateboard without a helmet. Reportedly, he struck the back of his head. He lost consciousness (duration unknown) and had a post-traumatic seizure (for approximately five minutes). He was hospitalized. A head CT scan revealed no abnormalities. The subject was discharged from the ER on the same day. He continued treatment with guanfacine for two days but discontinued from the study for reasons that are currently unclear.

4. Lower Limb Fracture
Subject 216-005 was a 13 year-old white male who was treated with placebo. On Day 23, he had a tibia and fibula fracture after being struck by a car while he was riding a bicycle. He also developed a compartment syndrome, and he required fasciotomy as well as reduction and internal fixation of the fracture. The subject continued treatment with study drug (placebo) for 20 days, but he discontinued subsequently (lost to follow-up).

8.1.3 Discontinuations due to Adverse Events in Controlled Trials

In the controlled trials, a higher proportion of subjects in the guanfacine group discontinued due to adverse events compared to the placebo group (12% and 4%, respectively). Several of the adverse events in the guanfacine group were likely related to treatment with guanfacine. These included: hypotension (6), QT interval prolongation (3), bradycardia (1), somnolence (19), sedation (11), fatigue (8), asthenia (1), lethargy

(1), dizziness (3), nightmare (1), insomnia (1), and headache (5). Adverse events leading to discontinuation that were possibly related to treatment with guanfacine included: affective lability (2), hostility (1), and depression (2).

Controlled Trials- Discontinuations due to Adverse Events					
		Guanfacine N = 513		Placebo N = 149	
Num. sub. DC	Num. of AE	61 (12%)	AE: 76	6 (4%)	AE: 11
Adverse Events leading to DC					
Cardiovascular					
Hypotension		6 (1.2)		-	
QT interval prolongation		3 (0.6)		1 (0.7)	
Sinus bradycardia		1 (0.2)		-	
Left bundle branch block		1 (0.2)		-	
Sedative events					
Somnolence		19 (3.7)		-	
Sedation		11 (2.1)		1 (0.7)	
Fatigue		8 (1.6)		-	
Asthenia		1 (0.2)		-	
Lethargy		1 (0.2)		-	
Psychiatric					
Affective lability		2 (0.4)		-	
Depression		2 (0.4)		-	
Anxiety		1 (0.2)		-	
Bradyphrenia		1 (0.2)		-	
Hostility		1 (0.2)		-	
Insomnia		1 (0.2)		-	
Nightmare		1 (0.2)		-	
Irritability		-		1 (0.7)	
Nervous System					
Headache		5 (1)		1 (0.7)	
Dizziness		3 (0.6)		1 (0.7)	
Gastrointestinal					
Abdominal pain		2 (0.4)		1 (0.7)	
Constipation		1 (0.2)		1 (0.7)	
Anorexia		1 (0.2)		-	
Other					
Petechiae		1 (0.2)		-	
Pneumothorax		1 (0.2)		-	
Enuresis		1 (0.2)		-	

8.1.4 Other Significant Adverse Events in the Controlled Trials

8.1.4.1 Psychiatric Adverse Events

Psychiatric adverse events:-some psychiatric AE were reported for a higher proportion in the guanfacine group than in the placebo group:

irritability (5%), affective lability (4%); aggression plus violent behavior (1.4% vs. 0.7%), agitation (1.4%), depressed mood (0.8%), anxiety (0.4%), and single cases of paranoia, hostility, negativism, psychomotor retardation, bradyphrenia, constricted affect, cognitive slowing, and mental status change. In controlled trials, there were no reports of suicidal ideation or suicidal behavior. There were no reports of mania or hypomania.

Table 8.1.4.1 Psychiatric Adverse Events in Controlled Trials

Adverse event	Guanfacine N= 515	Placebo N = 152
Lability	21 (4%)	4 (2.6%)
Irritability	26 (6%)	5 (3%)
Aggression*	7 (1.4)	1 (0.7)
Aggression	4 (0.8%)	1 (0.7%)
Anger	2 (0.4%)	
Agitation	7 (1.4%)	0
Violent behavior	(1.4%)	(0.7%)
Hostility	1 (0.2%)	0
Oppositional negativism	1 (0.2%)	0
Depressed mood	4 (0.8%)	0
Psychomotor retardation	1 (0.2%)	0
Constricted affect	1 (0.2%)	0
Bradyphrenia	1 (0.2%)	0
Suicidal ideation	0	0
suicidal behavior	0	0
Paranoia	1 (0.2%)	0
Mania or hypomania	0	0
Anxiety	2 (0.4%)	0
Mental status change	1 (0.2%)	0
Cognitive slowing	1 (0.2%)	0

*Aggression includes: aggression (4) anger (2), hostility (1), negativism (1)

Adverse events of psychiatric syndromes (Company)

Psychiatric syndromes were identified via a review of the database. These events were chosen as events of interest in part due to the FDA's request of Shire and other companies that study/market compounds for the treatment of ADHD. Shire therefore chose to follow a similar process to provide this information for the SPD503 program. The following are the preferred terms that, after clinical review of the SPD503 database, were judged to meet the criteria for each category suggested by the FDA:

• Psychosis or mania: formication, paranoia

• Suicidal ideation and behavior: intentional overdose, self-injurious behavior, and suicidal ideation

• Aggression and violent behavior: aggression, anger, hostility, intermittent explosive disorder, and negativism.

Miscellaneous psychiatric events consisted of the following preferred terms: feeling Abnormal, cognitive disorder, disturbance in attention, hypersomnia, memory impairment, sleep paralysis, sleep talking, abnormal behavior, abnormal dreams, adjustment disorder, affect lability, agitation, anhedonia, anxiety, bradyphrenia, depressed mood, depression, dysphoria, early morning awakening, emotional disorder,

excitability, inappropriate affect, initial insomnia, insomnia, irritability, mental status changes, middle insomnia, mood altered, mood swings, nervousness, nightmare, psychomotor retardation, restlessness, sleep disorder, sleep terror, sleepwalking, and tic.

8.1.4.3 Sedative Adverse Events

Sedative adverse events
The analysis of sedative events included the following preferred terms: somnolence, sedation, fatigue, lethargy, asthenia, and hypersomnia. In the controlled trials, sedative adverse events were more common for Intuniv (53%) compared with placebo (17%). There appeared to be a dose-response relationship for adverse events. Overall, 38 of 513 (7.4%) of subjects in the Intuniv group in the controlled trials discontinued due to sedative events. Overall, 8.6% of SPD503 subjects reported sedative events that were unresolved

Table 27 Summary of Onset and Duration of All Treatment-Emergent Sedative Events by Randomized Treatment Group – Short-Term Study Pool

	Number (%) of subjects					
Parameter	Placebo (N=149)	SPD503 1mg* (N=61)	SPD503 2mg (N=150)	SPD503 3mg (N=151)	SPD503 4mg (N=151)	All Active (N=513)
Subjects with AEs (%)	25 (16.8)	24 (39.3)	64 (42.7)	86 (57.0)	98 (64.9)	272 (53.0)
Number of events	28	28	91	123	145	387
Onset day - mean	6.8	6.4	8.0	10.3	10.6	9.5
median	4.0	2.0	3.0	7.0	8.0	7.0
range	0-36	1-23	1-50	1-42	0-55	0-55
Duration - mean	27.6	19.0	21.6	27.2	26.8	25.0
median	28.0	15.0	19.0	24.5	25.5	21.5
range	1-64	2-64	1-65	1-65	1-69	1-69
Unresolved	6 (4.0)	5 (8.2)	11 (7.3)	15 (9.9)	13 (8.6)	44 (8.6)
Mild	16 (10.7)	11 (18.0)	31 (20.7)	50 (33.1)	31 (20.5)	123 (24.0)
Moderate	8 (5.4)	12 (19.7)	32 (21.3)	29 (19.2)	55 (36.4)	128 (25.0)
Severe	1 (0.7)	1 (1.6)	1 (0.7)	7 (4.6)	12 (7.9)	21 (4.1)
Discontinued study drug	1 (0.7)	2 (3.3)	6 (4.0)	9 (6.0)	21 (13.9)	38 (7.4)

In the long-term study pool, sedative TEAEs overall occurred in 58.5% of subjects, and were less frequent in subjects who were on 4mg prior to dose tapering (47.2%) compared with subjects on 2mg (67.5%) or 3mg (67.3%). Severe sedative events were reported in 4.9% of subjects. Overall, 8.1% of subjects reported sedative events that were unresolved, and 28 of 446 subjects (6.3%) discontinued due to sedative events. Note that data from Study 305 are interim data as this study is currently ongoing.

In Study 206, sedative TEAEs overall were more commonly reported for subjects receiving SPD503 (60.3%) than placebo (28.1%). One of 80 sedative events (1.3%) in the SPD503 group was considered unresolved. Five of 80 sedative events (6.3%) in the SPD503 treatment groups were considered severe. None of the sedative events were

considered serious. One subject in the SPD503 group (0.8%) discontinued due to sedative events (fatigue and somnolence) and increased difficulty focusing.

The 5-point Pictorial Sleepiness Scale (PSS), designed to assess sleepiness in school-age children and adolescents, was used to measure sleepiness throughout the course of the day and study. Patient and observer (health care professional) reported outcomes on the PSS were similar during the daytime in a classroom setting for the guanfacine and placebo groups. However, subjects and observer (parent) scores suggested a greater degree of sleepiness in the evening hours before bedtime in the guanfacine group compared to the placebo group. These trends were consistent throughout the study.

8.1.5 Commonly Reported Adverse Events in Controlled Trials

Table 8.1.5 Common Adverse Events in Controlled Trials

Adverse event	Placebo N = 152	Guanfacine N = 513	Dose-related
General			
Fatigue	3%	14%	
Lethargy	3%	6%	
Nervous system/psychiatric			
Somnolence	7%	30%	Yes
Sedation	5%	10%	
Headache	18%	23%	
Dizziness	4%	6%	Yes
Irritability	4%	6%	
Insomnia	5%	5%	
Affective lability	1%	2%	
Nightmare	0	2%	
Gastrointestinal			
Abdominal pain, upper	7%	10%	Yes
Nausea	2%	6%	
Dyspepsia	3%	3%	
Dry mouth	1%	4%	Yes
Constipation	1%	3%	
Cardiovascular			
Hypotension	4%	6%	Yes
Blood pressure decreased	0	2%	
Other			
Sunburn (search related)*	1%	2%	
Appetite decreased	3%	5%	

*Hypotension includes the following preferred terms: hypotension, decreased blood pressure, decreased systolic blood pressure, and decreased diastolic blood pressure

(see actual dose and mg/kg Common AE tables in Appendices)

Dose-related Adverse Events:
Dose-related adverse events included hypotension, somnolence, sedation, abdominal pain, dizziness, dry mouth, constipation

8.1.6 Less Commonly Reported Drug-related Adverse Events

Less commonly reported adverse events that were probably drug-related included: bradycardia, asthenia, dyspepsia, blood pressure decreased, orthostatic hypotension, QT interval prolongation, weight increased, dizziness postural,
(consider: atrioventricular block- first degree, sinus arrhythmia, asthma exacerbation, enuresis)

Less Common- possibly drug related

Adverse event	guanfacine	Placebo
QT prolongation	3 (0.6)	0
Bradycardia	4 (0.8)	0
Atrioventricular block 1º	2 (0.4)	0
Sinus arrhythmia	2 (0.4)	0
Orthostatic hypotension	5 (1)	0
Chest pain	5 (1.0)	1 (0.7)
Asthma	4 (0.8)	0
ALT increase	3 (0.6)	0
Asthenia	4 (1)	0
Weight increased	7 (1)	0
Appetite increased	1%	1%
Dyspepsia	1%	1%
Anxiety	1	0
Middle insomnia	1	0
Crying	1	0
Postural dizziness	2 (0.4)	0
Enuresis	7 (1.4)	1 (0.7)
Pollakiuria	3 (0.6)	0
Depression	2 (0.4)	0
Aggression*	7 (1.4)	1 (0.7)
Paranoia	1 (0.2)	0

*Aggression includes: aggression (4) anger (2), hostility (1), negativism (1)

Vital Signs Findings

8.1.7.1 Blood Pressure and Heart Rate

In the controlled trials, treatment with Intuniv resulted in decreases in blood pressure and heart rate. The maximum decrease in mean systolic blood pressure was approximately 10 mm Hg at Week 4. The maximum decrease in mean diastolic blood pressure was approximately 7 mmHg in 4 mg at week 4. The maximum decrease in mean heart rate was approximately 9 bpm at Week 4.

Outliers for Vital Sign Findings of Potential Clinical Significance

The tables below illustrate findings for blood pressure and heart rate of potential clinical significance.

Parameter	Children and Adolescents
Pulse	≤50bpm or ≥100bpm
Weight	Change at ≥7% in short-term study
Seated systolic BP	6 – 12 years: <90 or >120mmHg 13 – 17 years: <100 or >140mmHg
Seated diastolic BP	6 – 12 years: <50 or >80mmHg 13 – 17 years: <60 or >90mmHg

8.1.7.2 Body Weight and Height

During the short-term, controlled trials, there were no clinically significant increases or decreases in mean body weight and height from baseline to endpoint of the study. In the placebo and guanfacine groups, there were increases in mean weight (2.2 and 3.0 lb, respectively). In the placebo and guanfacine groups, there were increases in mean height (0.35 and 0.36, respectively.

8.1.8 Electrocardiogram (ECG) Findings

8.1.8.1 Sponsor's QTcF Findings (QTcF)

There were dose-related increases in mean QTcF. The maximum increase in mean QTcF was approximately 8 msec. Analysis of the QT interval corrected for heart rate demonstrated evidence suggestive of a dose-related increase in QTcF (1.4 to 10.1msec among dose groups, 5.8 msec overall vs. 1.9msec on placebo) and, to a lesser extent, QTcP. The mean changes in QTc are likely related in part to the inability to adequately correct for changes in the heart rate that occur with SPD503. No subject had an increase of =60msec in QTcF. There was also evidence suggestive of a dose response in the incidence of heart rate =50bpm. No subject had a QRS interval =120msec, QT interval = 480msec, or a QTcP, QTcF, or QTcB interval =500msec on treatment. No other relevant treatment group differences were noted.

Table 36 Overall Mean Change from Baseline Across Visits in ECG Parameters by Actual Dose – Short-Term Study Pool

Parameter	Placebo (N=149)	SPD503 1mg (N=513)	SPD503 2mg (N=424)	SPD503 3mg (N=261)	SPD503 4mg (N=122)	All Active (N=513)
Subjects with ECGs	135	203	295	244	51	454
ECG assessments	292	341	364	258	54	1017
Mean change (SD)						
Heart rate (bpm)	-1.6 (8.30)	-1.7 (9.23)	-6.3 (10.56)	-11.6 (11.45)	-15.0 (11.75)	-7.5 (9.24)
QT (msec)	4.3 (18.39)	3.9 (19.71)	15.8 (21.89)	28.3 (26.99)	35.6 (27.73)	18.4 (21.02)
QTcP (msec)	1.5 (14.47)	0.9 (12.83)	3.5 (13.82)	4.5 (15.30)	5.5 (15.35)	3.6 (12.53)
QTcF (msec)	1.9 (14.16)	1.4 (12.71)	5.3 (13.37)	8.2 (15.36)	10.1 (15.87)	5.8 (12.57)
QTcB (msec)	0.5 (16.29)	0.0 (14.80)	-0.4 (16.32)	-2.7 (17.37)	-3.7 (17.15)	-1.0 (14.17)

The overall mean change from Baseline across visits in heart rate, QT, QTcP (population-corrected QT), QTcF, and QTcB intervals is displayed by actual dose in Text Table 36. A dose-related decrease in heart rate was observed, similarly to decreases in pulse rate described in Section 2.7.4.4.1. No relevant treatment group differences were noted for PR or QRS. The length of the uncorrected QT interval increased with increasing dose of SPD503, attributable to the effect of SPD503 on the heart rate. Analysis of the QT interval corrected for heart rate showed a pattern suggestive of a dose-related increase in QTcF of 1.4 to 10.1msec (5.8 overall) versus 1.9msec for placebo and, to a lesser extent, QTcP. Results of analyses including all ECG assessments were similar to analyses using only the first valid measurements within a time point (Study 301) or the investigator-selected measurements (Study 304). When reviewing ECG data by week, note that time points other than Baseline, Week 3, and Endpoint have limited sample size.

Table 37: ECG Parameters of Potential Clinical Significance Overall On-Therapy by Actual Dose – Short-Term Study Pool

Parameter	Number (%) of subjects					
	Placebo (N=149)	SPD503 1mg (N=513)	SPD503 2mg (N=424)	SPD503 3mg (N=261)	SPD503 4mg (N=122)	All Active (N=513)
Subjects with ECGs	135	203	295	244	51	454
Heart rate ≤50bpm	0	1 (0.5)	8 (2.7)	16 (6.6)	4 (7.8)	25 (5.5)
Heart rate ≥100bpm	4 (3.0)	7 (3.4)	4 (1.4)	2 (0.8)	0	13 (2.9)
PR ≥200msec	0	1 (0.5)	2 (0.7)	3 (1.2)	0	5 (1.1)
QRS ≥120msec	0	0	0	0	0	0
QT ≥480msec	0	0	0	0	0	0
QTcP ≥500msec	0	0	0	0	0	0
QTcF ≥500msec	0	0	0	0	0	0
QTcB ≥500msec	0	0	0	0	0	0
QTcF change from Baseline						
≥60msec	0	0	0	0	0	0
≥30 to <60msec	10 (7.4)	9 (4.4)	14 (4.7)	19 (7.8)	9 (17.6)	45 (9.9)
QTcB change from Baseline						
≥60msec	0	0	1 (0.3)	0	0	1 (0.2)
≥30 to <60msec	12 (8.9)	9 (4.4)	12 (4.1)	9 (3.7)	1 (2.0)	27 (5.9)
Abnormal, significant*	1 (0.7)	1 (0.5)	5 (1.7)	7 (2.9)	1 (2.0)	13 (2.9)

Sponsor's Criteria for ECG Abnormalities of Potential Clinical Significance

Parameter	Children and Adolescents
Heart Rate	≤50 bpm or ≥100 bpm
PR Interval	≥200 msec
QT Interval	≥480 msec
QRS Interval	≥120 msec
QTcP	≥500 msec
QTcF	≥500 msec
QTcB	≥500 msec
QTcF change from Baseline	≥30 to <60 msec or ≥60 msec
QTcB change from Baseline	≥30 to <60 msec or ≥60 msec
Investigator Overall Assessment	Abnormal, clinically significant

ECG parameters of potential clinical significance overall on-therapy are displayed by actual dose in Text Table 37. Overall 5.5% of subjects in the short-term study pool had a heart rated =50bpm some time on-therapy and the incidence increased with increasing dose from 0.5% at 1mg to 7.8% at 4mg. No subject had an increase of =60msec in QTcF. A QTcF increase of =30 to <60msec from Baseline was more common in the 4mg group (17.6%) compared with the placebo group (7.4%). No subject had a QRS interval =120msec, QT interval =480msec, or a QTcP, QTcF, or QTcB interval =500msec on

treatment. No other relevant treatment group differences were noted. Similar conclusions can be made based on analyses by randomized dose or weight-adjusted actual dose.

8.1.8.2 PK/PD QT Analysis (QTcP Contracted by Shire)

The sponsor's PK/PD analysis demonstrated that there was a clear, linear, consistent, exposure-related increase in QTcP. There was an increase in the QTcP interval of +1 msec for every ng/mL of guanfacine concentration. Individual exposures were highly correlated with subjects' body weights. Furthermore, there was no significant effect of decreased heart rate that interfered with the measurement or interpretation of QTc results. There was no QT-RR hysteresis. Therefore, the QTc results are valid and reliable.

The approximate maximum magnitude of effect was an increase of 8 msec at relevant doses/exposures. At supratherapeutic exposures and doses, there would be an increased potential risk of QT prolongation; however, the distribution analysis of individual potential increases in exposures suggests that the likelihood of potentially clinically significant QT prolongation is extremely low.

The sponsor has submitted the results of a population pharmacokinetic/pharmacodynamic (PK/PD) analysis regarding potential QT interval prolongation with guanfacine treatment. The analysis utilized guanfacine plasma concentration data and ECG data from pediatric studies 107, 203, and 206. The report is entitled "Population Pharmacokinetic and Pharmacodynamic Analysis of Guanfacine in Pediatric Patients with Attention Deficit Hyperactivity Disorder." The study was conducted by (b) (4) The report summarizes the development of a guanfacine population PK model in children and adolescents with ADHD and the development of exposure-response models to characterize the effects of guanfacine on the QT interval and heart rate.

The data used in the analysis constitutes the majority of the pharmacokinetic and related ECG data collected in the 22-037 clinical development program. The ages of subjects (6 to 17 years) and the guanfacine doses and dose/mg (1-4 mg/day and 0.05-0.17 mg/kg/day, respectively) were similar to those in the pivotal controlled trials. The database included 2,380 guanfacine plasma concentrations from 160 ADHD subjects. The PK/PD models used predictions from the population PK model and 3,498 ECG measurements from 217 subjects (160 treated with guanfacine and 57 treated with placebo.

The model characterizes a relationship between guanfacine plasma concentrations and changes in the QT interval, as well as a relationship between guanfacine plasma concentrations and changes in heart rate. For the population corrected QT interval (QTcP), an exposure-response model predicts an increase of one (1) msec from the baseline QT for every ng/mL of guanfacine plasma concentration. The model for heart rate predicts a 2.3% decrease in baseline circadian heart rate for every ng/mL of guanfacine plasma concentration.

At the highest dose tested (0.17 mg/kg/day), the exposure-response model predicts a maximum guanfacine plasma concentration (Cmax) in children of approximately 8.5 ng/mL. Thus, the model predicts a maximum QTcP prolongation of approximately 8.5 msec. The model also predicts a maximum decrease in heart rate of approximately 20% (19.55%). The sponsor notes that the highest dose tested in the model (0.17 mg/kg/day) is higher than that proposed in the label for INTUNIV. The label recommends treatment with 0.05-0.05 mg/kg/day and up to 0.12 mg/kg/day if treatment is well tolerated.

The main predictor of QTcP prolongation was guanfacine exposure, which decreased with body weight and increased with dose. This was confirmed and described using simulations of the model incorporating patient covariates, different dosages, and variability.

The report by (b) (4) included the following statements:

"A graphical evaluation of the QT-RR relationship did not reveal any consistent trends that would indicate that QT-RR hysteresis was occurring. QT-RR hysteresis can occur when there is a lag between a change in the RR interval and the detection of that change in the QT interval. Any intervention causing a rapid change in HR, e.g., certain drugs, exercise, postural changes, has the ability to result in QT-RR hysteresis. It is known that guanfacine can cause a decrease in HR via central stimulation of a2-adrenergic receptors leading to a decrease in sympathetic tone, which results in a reduction in heart rate. For this reason, it was important to determine if the HR decrease caused by guanfacine resulted in QT-RR hysteresis. The inability to detect the hysteresis may be the result of a number of factors, including the extended release characteristics of SPD503 that result in a flat PK profile (longer absorption period and lower Cmax versus immediate release), which decreases the likelihood of rapid changes in HR, the lack of closely spaced ECG measurements, which are required to capture QT-RR hysteresis, or simply the lack of the ability of guanfacine to cause this effect. The specific reason cannot be determined given the available data. Given the lack of any trend in the graphical evaluation no formal modeling of the QT-RR relationship was performed.

The ER relationship for the effect of guanfacine on QTcP was described by a linear model parameterized in terms of BQTP and SLOP. Model structural parameters and the majority of random variance parameters were estimated with good precision. Model evaluation results indicated that the model provided a good description of the data and was suitable for use as a simulation tool.

Integration of the guanfacine Population PK and PK-PD models allows for the evaluation of dosages and patient demographics relative to endpoints of interest. This integrated relationship for QTcP can be used to assess the effect of different dosage regimens and patient characteristics on QTcP changes. Weight is the main predictor of guanfacine exposure and Cmax, and guanfacine concentrations are higher for patients with lower body weights at the same guanfacine dose. PK-PD simulations showed that within the

same guanfacine dosage (mg/day), patients with lower body weights had a higher Cmax and therefore greater relative increases in QTcP.

The probabilities of changes in different QTcP metrics were examined by simulation. Scenarios were simulated looking at a representative patient population (ages > 6 years) and at a population with a low body weight with respect to the proposed indication (females, age = 6 years). Results from these simulations were consistent with the data collected from the studies (Table 16). Across a pediatric population that would represent a Phase III population, the %patients/ trial with QTcP > 480 msec was 0% after administration of either 2 or 4 mg/day of guanfacine. From these same simulations, the %patients/trial expected to see a change in QTcP from baseline of greater than or equal to 10% was predicted to be 6.3 (1.9 – 11) % when receiving 4 mg/day of guanfacine. As would be expected, the greatest changes would be expected in children with low body weights (Figures 86 and 87). The probabilities of a 10 msec change in QTcP at the maximum concentration associated with 2 mg/day guanfacine is 2%, 0%, and 0%, respectively for typical female patients weighing (approximate age) 20 kg (6 years), 50 kg (12 years), and 65 kg (17 years) (Figure 86). The probability of observing a 10 msec QTcP change following 4 mg/day guanfacine is 95%, < 1%, and ~ 0%, respectively for typical female patients weighing (approximate age) 20 kg (6 years), 50 kg (12 years), and 65 kg (17 years)(Figure 87). The median QTcP change from the simulations in typical smaller children (female, 6 y/o, 20 kg) receiving the higher 4 mg/day guanfacine dosage was 14 msec but the effect was estimated with sufficient precision to define an upper 95% CI less than 20 msec (Figure 87, top panel). Although the probability for a typical smaller child (female, 6 y/o, 20 kg, 4 mg dose) of observing a 10 msec change in QTcP is 95%, the probability associated with a 15 msec change drops to 38%, and to a probability of 1.8% for a 20 msec change. A set of simulations evaluating the effect of 2, 3, and 4 mg doses on QTcP change in a slightly larger (40 kg, age 6 – 8 year old) typical female child demonstrated that the probability of a 10 msec QTcP change is 0% for the 2 and 3 mg dose and 6.8% for the 4 mg dose (Figure 89).

(b) (4) Conclusions

A linear model was used to relate guanfacine plasma concentrations to QTcP. The estimated slope parameter (SLOP) was estimated to be 0.941 (0.627 – 1.25) msec/ng/mL. The final model would then predict an approximate 1 msec increase from baseline for every ng/mL of guanfacine in plasma. The main predictor of QTcP prolongation was guanfacine exposure, which decreased with body weight and increased with dose. This was confirmed and described using simulations of the model incorporating patient covariates, different dosages, and variability.
MINE: forget about a QT study in adults. Need whopping doses to get adequate exposures (Probably). However, see what the doses and exposures were in adults.

8.1.8.3 FDA Pharmacometrics Reviewer (QTcI Analysis)

Venkatesh Atul Bhattaram, Ph.D, the Pharmacometrics reviewer analyzed the QT and exposure data using the QT and plasma concentration data submitted by the sponsor. Essentially, Dr. Bhattaram's findings are consistent with those of the sponsor's PK/PD analysis. There was a modest dose- and exposure-related increase in the QT interval during treatment with guanfacine. The concentration-QT analysis demonstrated that guanfacine prolongs the QT interval. For every unit increase in guanfacine concentration, the QT interval would be prolonged by 1 msec. However, Dr. Bhattaram concluded that the exact risk of QT prolongation is not clear, due to methodological problems with the ECG monitoring in the clinical program. Thus, he recommends that the sponsor conduct a thorough QT study, in order to more clearly characterize the QT effect.

In addition, Dr. Bhattaram notes that there is a large food effect with guanfacine administration, particularly with a high fat meal. He recommends that patients avoid taking guanfacine with a high fat meal, since the food effect can increase the Cmax by 77% (on average) and can increase the AUC by 40%. The increase in exposure could lead to a greater risk of QT interval prolongation, compared to the effect in a non-fed condition. Preferably, the drug should be taken one hour prior to breakfast.

8.1.8.4 FDA QT Interdisciplinary Team Consult Findings

The QTIRT notes that the results submitted by the sponsor indicate that there are signals of QT prolongation. In Study 106, for the guanfacine group, the overall mean increases in QT from baseline (QTcF, msec) were 8.2, 6.0, 11.5, 8.4 and 6.5 at hours 7, 8, 9, 10, and 96, respectively. In Study 206, for three guanfacine doses combined, the mean increase in QTcF from baseline to visit 5 (msec) was 11.4 with a standard deviation of 13.49. In Study 301, for guanfacine 3 mg, the mean increase in QTcF from baseline to Week 3 was 9.1 msec with a standard deviation 16.2. However, the QTIRT team states that it is difficult to draw a firm conclusion about the QT prolonging effect of guanfacine due to the following limitations of the studies reviewed:

- Four of the seven studies (Study 104, 106, 107 and 203) were open-label studies, and they did not include controls.

- The study populations were various. Study 104 and 106 were conducted in healthy adult subjects aged 18-55. Study 107, 206, 302 and 304 were conducted in pediatric subjects (aged 6-17) with ADHD. Study 203 was conducted in children aged 6-12 with ADHD.

- The methodology of QT measurement was variable among the relevant studies. In studies 104, 106 and 107 and 203, QT intervals were measured at several time points after dosing within a three day time frame. For example, in Study 104, the

QT measurements were taken at hour -1, 0, 6, 7, 8, 10, and 96 after dosing. However, in Studies 206, 301, and 304, QT measurements were collected only once at certain visits. For example, in Study 206, QT measurements were collected at baseline, visit 5 (Study Day 28) and visit 8 (Study Day 45). No information was provided about when the QT intervals were measured in relation to Cmax.

The conclusion of the QTIRT is that there is a signal for QT prolongation, but the studies are variable and without adequate controls. The team recommends a thorough QT study in adults, in order to better characterize the QT effects.

8.1.8.5 Sponsor's Proposed Labeling

The sponsor proposes to dose Intuniv on an mg/kg basis, aiming for a specific range of exposures, recognizing the exposure-related risk of QT prolongation. The sponsor recommends limiting the dosing to within the specified range, in order to prevent serum guanfacine concentrations from rising above the threshold at which a clinically significant risk of QT prolongation could develop.

8.1.8.6 Conclusion

There appears to be a modest, consistent, exposure-related increase in QTc interval that can be managed by: 1) dosing per weight; 2) labeling properly and thoroughly; and 3) developing a risk minimization plan with the sponsor. In my opinion, the potential risk is manageable. I agree with the recommendations of the Cardiorenal QTIRT that the sponsor should conduct a thorough QT study, in order to accurately characterize the potential QT prolongation effect of guanfacine.

There were 3 discontinuations due to QT prolongation (about 30-60 msec) without clinical consequences.

8.1.9 Clinical Laboratory Findings

8.1.9.1 Mean Clinical Laboratory Findings

There were significant changes in mean clinical laboratory results for the following parameters: serum total bilirubin concentration, serum calcium concentration, and serum growth hormone concentration. Currently, the potential clinical significance of these mean changes is unclear.

Mean Serum Total Bilirubin

From baseline to endpoint, the mean serum total bilirubin increased by 9% in the guanfacine group and decreased by 1% in the placebo group. The sponsor did not provide values for direct or indirect bilirubin. There were no significant changes in mean values

for all other liver function tests. Furthermore, there were no significant changes in mean values for any other serum chemistry or hematology parameter (with the exception of calcium). There does not appear to be evidence of hemolysis, hepatic dysfunction, or other treatment-emergent effects that would explain the mean increase in serum total bilirubin. However, it would be useful to obtain information about concentrations of direct and indirect bilirubin.

Mean Serum Calcium

The mean serum calcium concentrations decreased slightly in both groups (0.07% and 0.7% in the guanfacine and placebo groups, respectively).

Mean Serum Growth Hormone

The mean serum growth hormone concentrations decreased in both groups (49% and 43% in the guanfacine and placebo group, respectively). The clinical significance of these decreases is currently unclear.

8.1.9.2 Outliers and Laboratory Abnormalities of Potential Clinical Significance

Total Bilirubin
Elevated serum total bilirubin concentrations were reported for 1.4% (7/513) of the guanfacine group and 0.7% (1/149) of the placebo group.

Calcium

Abnormally high serum calcium concentrations were reported for 9.2% (47/513) of the guanfacine group and 4% (6/149) of the placebo group. Potentially clinically significant elevations of serum calcium concentrations were reported for 5.3% of the guanfacine group and 2% of the placebo group. The highest serum calcium concentration in the guanfacine group was 10.8 mg/dL.

Urinalysis
Shifts from absent to positive urine protein were reported for 2.3% (12/513) of the guanfacine group and 1.3% (2/149) of the placebo group. Shifts from absent to positive hematuria were reported for 2.7% (14/513) of the guanfacine group and 1.3% (2/149) of the placebo group.

8.1.10 Special Safety Studies (205, 206)

8.1.10.1 Study 205

Study 205 was a multicenter, open-label, co-administration study assessing the safety and tolerability of the co-administration of Intuniv and stimulants in children and adolescents (ages 6-17) with ADHD who had suboptimal control on psychostimulants monotherapy (methylphenidate or amphetamine). The dose of Intuniv was escalated up to

4 mg/day or the maximum tolerated dose (1, 2, 3, or 4mg/day). The dosing of subjects' stimulant medication was maintained at the pre-study level.

Generally, co-administration was well tolerated. However, several psychiatric adverse events were reported relatively commonly, compared to the guanfacine monotherapy trials: irritability, anxiety, insomnia, initial insomnia, depression

There were no deaths or serious adverse events during the study. Proportions of subjects reporting adverse events were similar between the methylphenidate and amphetamine groups (98% and 85%, respectively). Overall, 6.7% (five of 75 subjects) discontinued due to adverse events (lethargy, dizziness, headache, somnolence, and rash): three of 42 (7.1%) of subjects in the methylphenidate group and two of 33 (6.1%) of subjects in the amphetamine group.

The most commonly reported adverse events were fatigue (35% of subjects), headache (33%), abdominal pain upper (32%), irritability (23%), somnolence (19%), and insomnia (16%). The proportions of these six most commonly reported TEAEs were similar between the psychostimulant groups, except for irritability, which was higher in the amphetamine group (42% of subjects as compared to 24% in the methylphenidate group). Adverse events pertaining to blood pressure, heart rate and ECG findings were infrequent.

Psychiatric Adverse Events in Study 205

Psychiatric adverse events in Study 205

Psychiatric adverse event	Methylphenidate N = 42	Amphetamine N = 33	Overall N = 75
Irritability	6 (14%)	11 (33%)	17 (23%)
Insomnia	6 (14%)	4 (12%)	10 (13%)
Anxiety	4 (10%)	3 (9%)	7 (9%)
Depressed mood	1 (2%)	3 (9%)	4 (5%)
Initial insomnia	2 (5%)	2 (6%)	4 (5%)

Sedative adverse events
Sedative events included somnolence, sedation, and fatigue. Overall, 56% of subjects reported somnolence, sedation, or fatigue. One subject treated with Intuniv discontinued due to somnolence.

ECG
Four subjects had an increase in QTcF from Screening =30-<60msec: two subjects in the methylphenidate group (one subject each at 2mg and 4mg SPD503 actual dose) and two subjects in the amphetamine group (both at the 1mg SPD503 actual dose). No subject had an increase in QTcF > 60 msec, and no subject had a QTcF > 500 msec.

Blood Pressure and Heart Rate
Mean systolic and diastolic blood pressure and pulse decreased from baseline during dose titration period, increased during the dose tapering period, and returned to slightly above titration/baseline levels at End-of-study/early termination (Visit 9). Mean changes from baseline for systolic blood pressure were -4.7 and -2.0mmHg for the methylphenidate and amphetamine groups, respectively. Mean changes from baseline for diastolic blood pressure were -1.2 and -1.6mmHg for the methylphenidate and amphetamine groups, respectively. Mean changes from baseline for pulse were -2.8 and -6.4bpm for the methylphenidate and amphetamine groups, respectively. Vital signs outliers observed in at least 50% of subjects included: systolic blood pressure less than 90mmHg in the 6 to 12 year group (53% of subjects), systolic blood pressure less than 100mmHg in the 13 to 17 year group (71% of subjects), and diastolic blood pressure less than 60mmHg in the 13 to 17 year group (76% of subjects); all three of these outliers were blood pressure decreases. Two of 74 subjects (2.7%) met the outlier criterion for diastolic postural orthostatic hypotension. The majority of subjects with vital signs findings of potential clinical significance had blood pressure decreases.

8.1.10.2 Study 206- Special Safety Studies of Cognitive Function

Study 206 was a multicenter, randomized, double blind, placebo-controlled, dose-optimization study, designed to assess the safety and tolerability of Intuniv (1mg, 2mg, and 3mg) in children and adolescents aged 6-17 diagnosed with ADHD. The primary objective was to assess the effect of Intuniv compared with placebo on a task of sustained attention: Choice Reaction Time (CRT). Secondary cognitive assessments included: Spatial Working Memory (SWM), Digit Symbol Substitution Test / Coding Test (DSST/Coding), and Permanent Product Measure of Performance (PERMP). Sedation assessments included the Pediatric Daytime Sleepiness Scale (PDSS) and the Pictorial Sleepiness Scale (PSS).

Cognitive Function Findings

The primary measure of cognitive function in Study 206 was the reaction time from the Choice Reaction Time Test (CRT). Reaction time is the time taken for the subject to release the press-pad after the stimulus has appeared on the screen. Baseline values for reaction time were similar between the treatment groups. The results are illustrated in the table below. Reaction time ranges from 100msec to 5000msec. Lower scores indicate better performance (fewer msec). The increases in reaction time from baseline in the Intuniv were small and unlikely to be clinically significant. The differences in mean reaction time between placebo were not statistically significant. Treatment with Intuniv did not impair or worsen reaction time. P-values are based on sum of squares from an ANCOVA model for the change from baseline, including treatment as a fixed effect and the baseline value as a covariate.

Study 206: Reaction Time Findings

Table 10: Change from Baseline in Reaction Time (msec) by Visit and at Endpoint by Randomized Treatment Group (Per-Protocol Set)

Time point Statistic	Placebo (N=35)	SPD503 (N=80)
Baseline		
n	35	80
Mean actual value (SD)	387.4 (73.26)	404.4 (108.80)
Visit 1 (Day 1)		
n	35	80
Mean change (SD)	3.9 (37.10)	6.8 (49.77)
P-value for treatment*		0.499
Visit 2 (Day 7)		
n	34	79
Mean change (SD)	15.5 (70.66)	8.7 (51.74)
P-value for treatment*		0.731
Visit 3 (Day 14)		
n	35	80
Mean change (SD)	24.1 (60.45)	17.3 (60.41)
P-value for treatment*		0.605
Visit 5 (Day 28)		
n	34	80
Mean change (SD)	31.3 (57.20)	17.8 (52.32)
P-value for treatment*		0.319
Visit 7 (Day 42)		
n	35	79
Mean change (SD)	21.9 (64.04)	19.3 (62.26)
P-value for treatment*		0.760
Endpoint†		
n	35	80
Mean change (SD)	21.9 (64.04)	20.7 (63.11)
P-value for treatment*		0.844

When analyzed by actual dose, optimal dose, or weight-adjusted optimal dose, there was no evidence of dose-related trends regarding reaction time. Subgroup analyses for age, gender, and ADHD subtype also did not demonstrate any notable trends. Similarly, analyses of other parameters based on the CRT including reaction time for correct responses, movement time, CRT total time, and CRT accuracy revealed no significant differences between the treatment groups, except for CRT accuracy, which improved in the Intuniv group in adolescents by Visit 7 and Endpoint.

For SWM between errors, a trend for greater improvement was observed in the Intuniv group compared with the placebo group that reached statistical significance at Visit 5 in the PPS. For SWM strategy, a small improvement was evident in the Intuniv group but not in the placebo group. These treatment group differences were slightly greater in the 13-17 years subgroup compared with the 6-12 year-old subgroup. For SWM within errors and double errors, no meaningful treatment group differences were observed. Overall, the

SWM results are consistent with the CRT, demonstrating that there was no impairment of specific cognitive functioning with Intuniv treatment.

DSST scores for subjects aged 8-17 years improved in both treatment groups, with no meaningful treatment group differences. Within the 8-12 year-old subgroup, the improvement was slightly smaller in the Intuniv group compared with the placebo group. There was no significant difference between treatment groups in the 13-17 years subgroup, indicating that treatment with Intuniv did not impair cognitive function as assessed by the DSST.

Analysis of PERMP scores revealed a greater improvement in the Intuniv group compared with the placebo group. Thus, there was no evidence of impairment of cognitive function as measured by the PERMP.

8.1.11 Drug Discontinuation (Withdrawal) Phenomena

Study 102 was a randomized, double blind, multiple dose, placebo-controlled, safety study in healthy young adults aged 19-24. The study assessed potential rebound elevations in blood pressure and heart rate, as well as other safety parameters, following abrupt cessation versus dose tapering of Intuniv at a dose of up to 4mg/day. After 17 days of daily treatment, one group underwent abrupt cessation of treatment with Intuniv. Another group underwent a gradual tapering phase from Days 17 to 32.
Abrupt cessation had their final dose on Day 16. When did they begin to have measurements after that? Day 16, 17, 18, 19

There were increases in BP and HR for the group that discontinued abruptly. Review the exact numbers. The company says in labeling that the increases were not clinically significant, but there were increases in BP up to 9 mmHg. List changes in mean and outliers for **Study 102**. Following abrupt cessation of treatment, mean systolic and diastolic values increased by 9mmHg and 8mmHg respectively on Day 19 when compared to Day 17 values.

The abrupt cessation group BP values were very similar to those of the placebo group from Day 19 through Day 46 (14 days post-study completion).
In the group that tapered from 4 mg/day, there were increases in mean BP as well: subjects in the group that tapered began taking 2mg of SPD503. Mean systolic and diastolic values in the taper group changed by +7mmHg and +3mmHg, respectively, from Day 19 to Day 21. On the morning of Day 25, subjects began taking 1mg of SPD503. Mean BP values in both the active treatment groups were very similar to those of the placebo group from Day 25 through Day 46 (14 days post-study completion).

8.1.12 Abuse Potential

Abuse potential wasn't studied. It appears that the Division did not request that the sponsor do so.

8.1.13 Human Reproduction and Pregnancy Data

There are no systematic data available regarding human reproduction or pregnancy and exposure to guanfacine. Pregnant or lactating females were excluded from participation in the clinical studies. Female subjects of child-bearing potential were required to use medically acceptable methods of contraception, or they were required to abstain from sexual intercourse. However, despite these precautions, two subjects reported pregnancies during treatment with guanfacine.

Subject 110-5034 in Study 110 was a 34-year-old Caucasian woman treated with Intuniv 2.5 mg/day. She had the serious adverse event of spontaneous abortion during the post-treatment period at 11 weeks of gestation. The event was considered possibly related to study medication. The subject noted that she had not used a double-barrier method of contraception. She became aware of her pregnancy 27 days after the last dose of guanfacine, and she experienced a spontaneous abortion 68 days after the last dose of study medication. She also underwent a D & C. An endocervical culture obtained during the procedure revealed a positive test for Group B Streptococci (Group B only), a risk factor for spontaneous abortion.

Subject 303-122 in Study 303 was a 19-year-old woman who had been treated with Intuniv 4 mg/day for 20 days when she became aware that she was pregnant. The subject noted that she had not used a double-barrier method of contraception. There were no reported complications during the pregnancy. The subject had a normal vaginal delivery of a female infant who weighed 7.0 lb. and was 19 inches long. Specific information about the infant's Apgar scores and head circumference were unavailable.

8.1.14 Assessment of Effect on Growth

The sponsor conducted a z-score analysis for body weight and height during treatment with Intuniv.

Long-term Open-label Studies

Subjects treated with Intuniv for at least 12 months in the long-term studies gained an average of 7.82 kg (17.2 lbs). Subjects treated for 15, 18, 21, and 24 months had mean increases in weight of 20.5, 23.9, 26.1, and 26.6 lb., respectively.

The Baseline mean weight Z-score at the start of the antecedent study was 0.575 suggesting that subjects were on average slightly heavier than their age- and gender-matched peers. The mean weight Z-score slightly increased to 0.702 at Week 1 of the long-term study then remained relatively stable for the rest of the treatment period, and was 0.849 at Month 12 (N=137), 0.922 at Month 18 (N=92), and 0.764 at the end of treatment (N=423). The mean height Z-score was 0.101 at the start of the antecedent study then gradually increased throughout the treatment period to 0.342 at Month 12 (N=137), 0.370 at Month 18 (N=92), up to 0.469 at Month 24 (median: 0.134, N=31).

Mean weight gain and z-scores in long-term studies

Month	N	Weight gain (lb)	Z-score for Weight
1	396	+4.5	0.691
3	304	+7.4	0.719
6	213	+10.6	0.743
9	169	+14.5	0.808
12	137	+17.2	0.849
15	112	+20.5	0.847
18	92	+23.9	0.922
21	77	+26.1	0.920
24	31	+26.6	0.759

Generally, it appears that, on average, there was significant weight gain associated with long-term, open-label treatment with guanfacine. The z-scores seem to increase out of proportion to what one might expect. It is possible that previous use of stimulants and subsequent discontinuation of stimulant use might have such an effect, and it would be useful to perform such an analysis, if possible. The apparent weight gain is a safety finding that will require further analysis.

8.1.15 Overdosage Experience

Overdosage Experience in the Clinical Studies

The highest dose studied in the Intuniv clinical development program was 4mg/day. (An accidental or intentional overdose was defined as):

Overdosage was reported for three (3) subjects during the Intuniv clinical development program. All three cases occurred in the long-term, open-label studies. In the controlled, short-term trials, there were no reported cases of overdosage, and there were no serious adverse events or discontinuations due to adverse events that were related to intentional or unintentional Intuniv overdoses. In the long-term studies, two cases of accidental overdoses were considered serious adverse events.

Subject 155-003 in Study 303 was a 9-year-old white male who had the SAE of accidental overdose in Month 7 of long-term, open-label treatment while assigned to treatment with Intuniv 3mg per day. The accidental overdose, per the subject's parent, consisted of the subject taking a total of 9 mg of Intuniv. The event was considered not related to study drug treatment, which was interrupted due to the event. The subject continued in the study. (The case is discussed in CSR Section 7.2.2.5).

Subject 224-002 in Study 305 was a 12-year-old White male who experienced the SAE of accidental overdose in Month 2 of treatment while assigned to treatment with Intuniv 4mg per day. The accidental overdose consisted of the subject taking a total of 16 mg. The event was considered not related to study drug treatment, which was interrupted due

to the event. The subject continued in the study. (This case is discussed in CSR Section 7.3.5.2).

Subject 223-999, a maternal aunt of a subject enrolled in Study 305, was a 38-year-old White female who experienced the SAE of intentional overdose. She attempted suicide by taking five 3mg tablets of Intuniv and other medications. She was hospitalized for the event. She had a history of three previous suicidal attempts. (A narrative for this subject is provided in the CSR This subject is discussed in CSR Section 7.3.5.4).

The sponsor notes that a study examined the epidemiology and toxicity of pediatric guanfacine exposures reported to poison control centers. Between 1993 and 1999 there were 870 guanfacine exposures reported in children less than 19 years of age. The majority (674) of exposures were acute. Most children (546, 62.8%) had no symptoms reported in association with the exposures. In symptomatic children (324, 37.2%), the most common adverse effects were drowsiness or lethargy (occurring in 249 children or 76.8%), bradycardia (97 children, 30%), and hypotension (84 children 25.8%). Miosis was reported in seven (7) children. There were no guanfacine-related deaths reported via poison control centers during this interval.

Three (3) cases of overdose were reported. Details of two of these cases are included in the current package insert for Tenex (guanfacine immediate-release). In one case, a 25-year-old woman intentionally ingested 60mg of guanfacine. She presented with severe drowsiness and bradycardia (45 bpm). Gastric lavage was performed, and an infusion of isoproterenol was administered at a concentration of 0.8mg over a period of 12 hours. She recovered quickly without sequelae. In the second case, a 28-year-old woman ingested 30-40mg of guanfacine. She developed lethargy, was treated with activated charcoal and a cathartic, was monitored for 24 hours, and she was discharged in good condition.

The third case involved a 2-year-old boy who ingested 4mg of guanfacine and presented with lethargy 35 minutes after ingestion. Upon admission to the emergency room, his blood pressure was 100/60mmHg with a heart rate of 83 beats per minute. Gastric lavage was performed and he was administered activated charcoal, I.V. infusion, and cardiac monitoring for 24h. Approximately 18h after admittance, his systolic blood pressure was in the range of 58-68 mmHg with a heart rate as low as 66 beats per minute. The child recovered normally with no additional AEs. Assuming the 4mg ingestion is accurate, that would amount to a dose of 0.35mg/kg, approximately 30 times the normal adult dose. Blood levels for guanfacine were measured at admittance and after 2h. Levels were 39.5 and 16.9 ng/ml, respectively.

The sponsor recommends that management of guanfacine overdosage should include monitoring for and treatment of hypotension, bradycardia, lethargy, and respiratory depression. Children and adolescents who develop lethargy should be observed for the development of more serious toxicity including coma, bradycardia, and hypotension for up to 24 hours, due to the possibility of the delayed onset of hypotension. Guanfacine is not dialyzable in clinically significant amounts.

8.2 SAFETY FINDINGS IN SAFETY UPDATE AND LONG-TERM STUDIES

Description of Study Designs for Studies 303 and 305

Study 303 was a multicenter, open-label, long-term extension safety study designed to evaluate the safety and efficacy of Intuniv for up to 12 months in pediatric subjects with ADHD. This study was later amended to extend open-label treatment for up to 24 months. All subjects who completed at least 2 weeks of double-blind participation in Study 301 and met eligibility criteria for Study 303 were eligible to enroll. Subjects were treated for a 4-week dose-optimization phase followed by a 24-month maintenance phase. Subjects visited the site weekly during the dose-optimization phase and monthly during the maintenance phase.

Study 305 is a multicenter, open-label, safety study designed to evaluate the safety and efficacy of Intuniv treatment for 24 months in pediatric subjects with ADHD. Subjects who completed all study visits through Visit 9 of Study 304 or Study 205, or withdrew due to lack of efficacy after completing visit 4 of Study 304 were eligible to for Study 305. Subjects were treated with Intuniv during a 4-week dose-optimization phase followed by a 24-month maintenance phase. Subjects visited the site weekly during the dose-optimization phase and monthly during the maintenance phase.

Safety Findings in the Long-Term, Open-Label Studies

8.2.1 Deaths

There were no deaths in the two long-term, open-label studies (303 and 305).

8.2.2 Serious Adverse Events

There were a number of serious adverse events reported during the long-term studies that were probably or possibly related to treatment with Intuniv. Approximately 5.6% (25/446) of subjects in the long-term study population had an SAE. The majority of these SAE were reported for subjects treated with either 3 mg/day or 4 mg/day of Intuniv. Of the SAE that were probably or possibly related to study drug treatment, seven (7) cases were reported as syncope. One case reported as loss of consciousness was possibly a syncopal episodes. One case of orthostatic hypotension was probably related to study drug treatment. There were two cases of seizures. There were two (2) accidental medication overdoses and one (1) intentional medication overdose. In 12 cases, subjects discontinued from the study due to the SAE.

A number of the reported SAE were probably not related to treatment with guanfacine. In 14 of the 25 subjects with SAE in the long-term studies, it is highly unlikely that the SAEs were related to study drug treatment.

Table 9 Listing of All Serious Adverse Events – Long-Term Study Pool

Study/ Subject	Gender/ Age/ Race	Actual Dose	Preferred Term	Month Occurred	Drug Relationship	Severity	Effect on Dosing
303/ 102-003	M/8/W	2mg	Orthostatic hypotension	Month 1	Related	Severe	Discontinued
303/ 124-006	F/10/W	4mg	Syncope	Month 2	Possibly related	Moderate	Discontinued
303/ 124-008	M/13/H	4mg	Intermittent explosive disorder	Month 15	Not related	Moderate	Discontinued
303/ 131-005	M/9/W	2mg	Syncope	Month 1	Possibly related	Mild	None
303/ 142-001	M/9/W	3mg	Gastrointestinal injury	Month 12	Not related	Severe	Interrupted
		3mg	Intestinal stoma complication	Month 13	Not related	Severe	Interrupted
303/ 147-005	M/7/B	3mg	Lymphoma	Month 8	Not related	Severe	Discontinued
303/ 152-003	M/12/W	4mg	Empyema	Month 7	Not related	Severe	None
		4mg	Pneumonia	Month 7	Not related	Severe	None
303/ 155-003	M/9/W	3mg	Accidental overdose	Month 7	Not related	Moderate	Interrupted
303/ 156-001	M/9/B	3mg	Convulsion	Month 2	Not related	Moderate	Discontinued
305/ 208-005	F/16/W	4mg	Syncope	Month 2	Related	Moderate	Discontinued
305/ 208-013	F/14/W	2mg	Syncope vasovagal	Month 21	Possibly related	Severe	Discontinued
305/ 218-011	M/6/W	2mg	Suicidal ideation	Month 15	Not related	Moderate	Interrupted
305/ 224-002	M/12/W	4mg	Accidental overdose	Month 2	Not related	Moderate	Interrupted
305/ 224-004	M/7/W	4mg	Syncope vasovagal	Month 11	Possibly related	Mild	Discontinued
305/ 226-010	M/13/W	4mg	Peritonitis	Month 7	Not related	Severe	None
		4mg	Appendicitis	Month 7	Not related	Severe	Discontinued
305/ 238-003	M/9/W	4mg	Aggression	Month 9	Possibly related	Severe	Discontinued
305/ 238-005	F/9/W	4mg	Slipped femoral epiphysis	Month 4	Not related	Severe	None
305/ 242-001	M/14/H	3mg	Post concussion syndrome	Month 10	Not related	Moderate	Interrupted
		3mg	Spinal compression fracture	Month 10	Not related	Moderate	Interrupted
305/ 254-004	F/12/W	4mg	Suicidal ideation	Month 10	Not related	Severe	Discontinued
305/ 268-002	M/10/W	3mg	Loss of consciousness	Month 6	Possibly related	Mild	None
		3mg	Loss of consciousness	Month 8	Possibly Related	Moderate	Discontinued
305/ 276-002	M/9/H	3mg	Syncope	Month 10	Related	Severe	None
305/ 279-001	F/11/B	4mg	Simple partial seizures	Month 9	Not related	Moderate	None
305/ 280-006	F/9/W	2mg	Syncope	Month 5	Possibly related	Mild	None

Table 10 Listing of Additional Serious Adverse Events – Study 305 Subjects Originating from Study 205 (not in Long-Term Pool)

Study/ Subject	Gender/ Age/ Race	Actual Dose	Preferred Term	Month Occurred	Drug Relationship	Severity	Effect on Dosing
305/552-005*	M/12/W	4mg	Head injury	Month 4	Not related	Severe	None
305/581-004*	M/14/W	3mg	Epidural Hematoma	Post-Tx	Not related	Severe	Discontinued
		3mg	Head Injury	Post-Tx	Not related	Severe	Discontinued
		3mg	Loss of Consciousness	Post-Tx	Not related	Severe	Discontinued

* Subjects originated from Study 205 and were taking concomitant psychostimulants.
Source: Interim CSR for Study 305 and narratives submitted in the NDA.

Discontinuations Due to Adverse Events

Discontinuations due to Adverse Events in Long-term Open-label Studies	
Adverse event	Number (%) N= 446
All DC due to AE	80 (18%)
Somnolence	3.4%
Weight increased	2%
Depression	1.6%
Fatigue	1.6%
Syncope	0.9%
Hypotension	0.9%
Sedation	0.9%
Headache	0.9%
Lethargy	0.7%
Irritability	0.4%
Aggression	0.4%

Syncope in the Long-term Studies

There were ten (10) pediatric subjects who had a total of 11 events of syncope. One subject had two distinct episodes. Approximately 1.2% of the entire pediatric population exposed to guanfacine had a syncopal episode. This is higher than the background rate of syncope in the general pediatric population. Several of these patients sought medical attention for the syncopal events. The rate of those seeking medical attention due to syncope in the guanfacine clinical program exceeds the relevant background rate estimated by Driscoll et. al. in an epidemiologic study of pediatric syncope.

It is likely that exposure to guanfacine was a factor contributing to syncope in at least some of these cases, given the drug's effect on blood pressure and heart rate. Of note, all of these cases of syncope occurred in the long-term, open-label phase of treatment, long after subjects were first exposed to guanfacine. In many of the syncope cases, another factor appeared to at least contribute to the syncopal event. These specific factors

included: dehydration, exercise, pain, injury, sight of blood, heat, acute psychosocial stressors, gastrointestinal illness, and previous history of presyncopal episodes.

All of these syncopal events occurred in the two long-term Studies, 303 and 305. Higher mg/kg doses of SPD503 do not appear to be associated with a higher incidence of syncope (subjects with syncope had doses ranging from 0.05mg/kg to 0.13mg/kg). The syncopal events were of short duration and were not associated with persistently altered mental

The tables below illustrate some of the details of the syncope cases in the Intuniv clinical program.

Table 13 Summary of Subjects with Syncope and Syncopal-like Adverse Events in All SPD503 Clinical Trials

Study/ Subject Number	Demography	Time in Study	SPD503 Dose or Treatment Group	Dose (mg/kg)	Adverse Event (Study Day of AE)	Seriousness/ Relationship to Study Drug	Duration of AE	Outcome
AS OF 30 JUN 2006 DATA CUT-OFF								
Healthy volunteers								
101/ 009*	33-year-old White female healthy volunteer	Subject completed study SPD503-101: 1 Dose of 3 Different Test Formulations of Extended Release SPD503 (1mg) and Tenex® 1mg	Dosed with 1mg Tenex® on day of event	.02	Syncope approximately eight hours after dosing during Treatment Period 2 (Day 1 of exposure to Tenex® 1mg)	Non-Serious*/ Mild/Almost Certainly Related†	3 minutes	Resolved after subject was placed in the supine position with her knees elevated.
104/ 1008	26-year-old Hispanic female healthy volunteer	3 days in SPD503-104	4 x 1mg (at date of AE) Fasted Treatment Group	.06	Syncope (Day 1)	Serious/ Probably Related‡	<1 day	Subject discontinued from the study. Event resolved.
ADHD Subjects Receiving SPD503								
303/ 102-003	8-year-old White male	47 days in SPD503-301 35 days in SPD503-303	Placebo Treatment Group 2mg/day (at date of AE)	.06	Orthostatic hypotension (Day 27)	Serious/ Related§	<1 day	Subject discontinued from the study. Event resolved.
303/ 124-006	10-year-old White female	49 days in SPD503-301 106 days in SPD503-303	4mg/day Treatment Group 4mg/day (at date of AE)	.13	Syncope (Day 52)	Serious/ Possibly Related§	<1 day	Subject discontinued from the study. Event resolved.

Study/ Subject Number	Demography	Time in Study	SPD503 Dose or Treatment Group	Dose (mg/kg)	Adverse Event (Study Day of AE)	Seriousness/ Relationship to Study Drug	Duration of AE	Outcome
303/ 131-005	9-year-old White male	30 days in SPD503-301 (Discontinued due to lack of efficacy) 143 days in SPD503-303 (Discontinued due to weight gain of 15lbs)	2mg/day Treatment Group 2mg/day (at date of AE)	.05	Syncope (Day 2)	Serious/ Possibly Related§	<1 day	Event resolved.
303/ 156-001#	9-year-old Black male	49 days in SPD503-301 40 days in SPD503-303	2mg/day Treatment Group 3mg/day (at date of AE)	.09	Syncope (Day 33)	Serious#/ Related§,*	<1 day	Event resolved.
305/ 208-005	16-year-old White female	64 days in SPD503-304 69 days in SPD503-305	4mg/day Treatment Group 4mg/day (at date of AE)	.06	Syncope (Day 59)	Serious/ Related‡	<1 day	Subject discontinued from the study. Event resolved.
305/ 208-013	16-year-old White female (at date of AE)	63 days in SPD503-304 615 days in SPD503-305	4mg/day Treatment Group 2mg/day (at date of AE)	.03	Vasovagal syncope	Serious/Possibly Related	<1 day	Subject discontinued from the study. Event resolved.
305/ 224-004	8-year-old White male	63 days in SPD503-304 306 days in SPD503-305	3mg/day Treatment Group 4mg/day (at date of AE)	.13	Syncope (Day 369)	Serious/ Possibly Related‡	<1 day	Subject discontinued from the study. Event resolved.

Study/ Subject Number	Demography	Time in Study	SPD503 Dose or Treatment Group	Dose (mg/kg)	Adverse Event (Study Day of AE)	Seriousness/ Relationship to Study Drug	Duration of AE	Outcome
305/ 268-002	11-year-old White male	63 days in SPD503-304 178 days in SPD503-305	Placebo Treatment Group 3 mg/day (at date of AE)	.10	Loss of consciousness (Day 178)	Serious/ Possibly Related	<1 day	Event resolved.
305/ 268-002	11-year-old White male	63 days in SPD503-304 211 days in SPD503-305	Placebo Treatment Group 3 mg/day (at date of AE)	.10	Loss of consciousness (Day 211)	Serious/ Related‡	<1 day	Subject discontinued from the study. Event resolved.
305/ 276-002	10-year-old Hispanic male	64 days in SPD503-304 302 days in SPD503-305	2mg/day Treatment Group 3mg/day (at date of AE)	.11	Syncope (Day 364)	Serious/ Related	<1 day	Event resolved. Subject continues in the study.
305/ 280-006	10-year-old White female	63 days in SPD503-304 152 days in SPD503-305	Placebo Treatment Group 2mg/day (at date of AE)	.06	Syncope (Day 127)	Serious/ Possibly Related‡	<1 day	Event resolved.
ADHD Subject receiving immediate release guanfacine								
202/ 104-007*	12-year-old White male	Subject completed study: 35 Days of Treatment in SPD503-202	Randomized to SPD503IR	0 (Subject Off Drug at Time of Event)	Syncope (Day 42 – Off Drug)	Non-Serious*/ Mild/ Not Related**	<1 day	Resolved same day.

Consult Findings From the Office of Surveillance and Epidemiology

Andrew D. Mosholder, M.D., M.P.H., Epidemiologist and Mary Ross Southworth, Pharm.D., Safety Evaluator Division of Drug Risk Evaluation, Office of Surveillance and Epidemiology performed a consult regarding postmarketing adverse event reports with guanfacine as well as the cases of syncope in the Intuniv clinical program.

Dr. Mosholder states the following:

"Rates of syncope requiring medical attention in pediatric populations have been estimated at 126 to 300 per 100,000 per year in relevant literature studies (see section 7.0 ESTIMATES OF PEDIATRIC SYNCOPE for details). In the guanfacine data set, there were four cases of syncope requiring medical attention out of an exposure of 504.04 patient-years, representing a rate of 794 such cases per 100,000 per year. This represents an approximate 2 to 6 fold increase in the rate of syncope in the guanfacine treated group over what would be expected. If it were feasible to adjust the comparison for the fact that the guanfacine clinical trial subjects were predominantly males, this margin would be even higher.

Another source of data on rates of syncope in a pediatric population comes from the Strattera (atomoxetine) development program; Strattera has information about syncope in the PRECAUTIONS section of labeling.2 The rate of syncope in controlled and open label pediatric ADHD trials for atomoxetine was 8.1 per 1000 patient-years, or one case of syncope in every 124 patient years of exposure. In controlled and open label pediatric ADHD trials with guanfacine, the rate of syncope was 21.8 per 1000 patient-years, or one case of syncope per 46 patient-years. While comparisons of adverse event rates between different development programs must be made cautiously, it appears that the syncope rate in the guanfacine development program was nearly three times that observed in the atomoxetine development program.

There was no discernable pattern among the syncopal events in the clinical studies with respect to duration of exposure or other risk factors, and in fact no cases occurred in the short term trials. It could be postulated that guanfacine treatment affects the "syncope threshold" via its effects on the cardiovascular system, but that another event such as dehydration or emotional stress is necessary for syncope to occur; this might explain the apparently random pattern with respect to exposure time."

OSE Conclusions and Recommendations:

1. The rate of cases of syncope are several times higher than the background rate in a pediatric population and the rate of syncope observed in pediatric trials with atomoxetine. [Dr. Mosholder and I have reviewed cases and literature regarding syncope, and we agree on these points].

2. Postmarketing surveillance data for guanfacine did not disclose any new signals of significant adverse reactions in the pediatric population. There were postmarket cases of mania and hallucinations. [These will be included in labeling].

3. "Although concerns about cardiovascular adverse effects associated with other drugs for ADHD (atomoxetine, stimulant therapies) have lead to the inclusion of such information in their labeling, none of these drugs have been associated with a signal for syncope of the magnitude present in the guanfacine ADHD data set."

4. An independent assessment of the syncope signal by a pediatric cardiologist is recommended. It would be helpful to obtain advice on how this signal should be further investigated.

5. Specific risk management measures could reduce the risk of syncope (staying hydrated, avoid over-heating). FDA and the sponsor should consider means of communication and education of patients and caregivers.

7. "A full analysis of the risks and benefits of guanfacine in the treatment of ADHD is beyond the scope of this consult. However, in our view, approval for the NDA for guanfacine in the treatment of ADHD would need to be based on a compelling clinical benefit that outweighs the signal for syncope. Guanfacine is marketed in an immediate-release formulation, so that if there is a clinical need for a child to be treated with guanfacine, it is currently available with off-label use. The principle impact of an approval of the pending NDA for ADHD would be to allow promotion of this use as FDA-approved."

8." If approved, the risk of syncope would need to be very prominently labeled, and communicated to parents and children through a patient information sheet, Medguide, or similar mechanism. A safety signal in children with a risk of 1% in clinical trials will not be "rare" when projected to large numbers of children post-licensure. Prior to initiating treatment, parents and caregivers would need to know that "fainting" is a common adverse event on this drug, and take necessary precautions when their child is on this therapy (although we are not optimistic that it will be feasible to keep young boys from climbing, etc.). We would point out that all other ADHD treatments have Medguides discussing cardiovascular events as well as drug-induced psychosis and mania; both categories of adverse events would be relevant for a guanfacine ADHD Medguide. Also, if the NDA is approved, the sponsor should be asked to conduct whatever additional investigations of the syncope signal are deemed necessary as Phase IV commitments."

9. The sponsor should incorporate the data from the American Association of Poison Control Centers publication on pediatric guanfacine overdosages in the labeling."

Generally, I agree with Dr. Mosholder's and Dr. Southworth's findings and recommendations, except for item 7. In my opinion, the efficacy of guanfacine was soundly demonstrated in these trials. While there are significant potential safety concerns, I conclude that they are manageable through proper labeling, communication, education, and development of risk minimization and risk management plans, and conducting further safety evaluations. Furthermore, treatment with guanfacine would proceed most safely if the drug was used as approved and as labeled. I agree with all of the specific suggestions related to risk management activities.

Common Adverse Events in the Long-term, Open-label Studies (303 and 305)

Commonly Reported Adverse Events in Long-term Open-label Studies (303 and 305)	
Adverse event	All doses of Intuniv N= 446
Somnolence	34%
Headache	26%
Fatigue	15%
Sedation	13%
Abdominal pain (upper)	11%
Hypotension	10%
Vomiting	9%
Dizziness	7%
Weight increased	7%
Nausea	7%
Irritability	6%
Weight increased	

ECG in Long-Term, Open-Label Studies (303 and 305)

Table 38 Overall Mean Change from Baseline Across Visits in ECG Parameters by Actual Dose – Long-Term Study Pool

Parameter	SPD503 1mg (N=342)	SPD503 2mg (N=438)	SPD503 3mg (N=381)	SPD503 4mg (N=233)	All Active (N=446)
Subjects with ECGs	30	107	172	150	331
ECG assessments	35	203	331	295	864
Mean change (SD)					
Heart rate (bpm)	-2.4 (11.94)	-6.9 (8.45)	-8.6 (10.90)	-10.3 (12.47)	-8.0 (10.39)
QT (msec)	0.6 (24.07)	12.6 (19.10)	17.4 (25.56)	20.0 (28.23)	15.6 (24.25)
QTcP (msec)	-3.4 (13.79)	-1.1 (14.87)	-0.3 (14.80)	-1.1 (15.01)	-0.8 (13.80)
QTcF (msec)	-2.9 (13.89)	0.9 (14.33)	2.4 (15.10)	2.0 (15.26)	1.7 (14.04)
QTcB (msec)	-5.0 (14.86)	-5.5 (17.13)	-5.7 (16.49)	-7.6 (17.34)	-5.8 (15.51)

Table 39: ECG Parameters of Potential Clinical Significance Overall On-Therapy by Actual Dose – Long-Term Study Pool

Parameter	Number (%) of subjects				
	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg	All Active
Subjects with ECGs	30	107	172	150	331
Heart rate ≤50bpm	0	3 (2.8)	14 (8.1)	11 (7.3)	25 (7.6)
Heart rate ≥100bpm	3 (10.0)	2 (1.9)	6 (3.5)	4 (2.7)	15 (4.5)
PR ≥200msec	0	1 (0.9)	1 (0.6)	1 (0.7)	2 (0.6)
QRS ≥120msec	0	0	0	0	0
QT ≥480msec	0	0	2 (1.2)	0	2 (0.6)
QTcP ≥500msec	0	0	0	0	0
QTcF ≥500msec	0	0	0	0	0
QTcB ≥500msec	0	0	0	0	0
QTcF change from Baseline					
≥60msec	0	0	0	0	0
≥30 to <60msec	2 (6.7)	6 (5.6)	13 (7.6)	12 (8.0)	32 (9.7)
QTcB change from Baseline					
≥60msec	0	0	0	0	0
≥30 to <60msec	0	6 (5.6)	10 (5.8)	6 (4.0)	22 (6.6)
Abnormal, significant*	0	1 (0.9)	2 (1.2)	2 (1.3)	5 (1.5)

8.3 POSTMARKETING SAFETY DATA (Sponsor)

Postmarketing Experience with Guanfacine (company)

Postmarketing experience with guanfacine was summarized based on data available to Shire: U.S. prescription data; worldwide sales data; postmarketing spontaneous adverse events data reported to FDA; and in published literature. 1986, guanfacine immediate-release (TENEX) was approved for the treatment of hypertension in adults and adolescents (12-17). There has considerable off-label use of guanfacine for the treatment of ADHD, Tourette's, Tic, OCD, other psychiatric disorders.

Summary of Exposure (see Carol Pamer's note about possible over-estimation)
The sponsor states that the total exposure to guanfacine has been approximately 2.4 million patient-years. This number is based on the calculation that there have been (b) (4) prescriptions (TENEX and guanfacine generics) for the period January 1987 to September 2005. This data was obtained through IMS Health MIDAS Database. It should be noted that this estimated total exposure is probably an overestimate, since this was based on the number of prescriptions written, as opposed to the number of prescriptions actually dispensed.

The largest proportion (46.3%) of estimated exposure has been for the age group 3-19 years old. Ages 3-9 account for approximately 22% of the guanfacine exposure, and ages

10-19 years account for approximately 24.4% of the exposure. The two most common indications for guanfacine treatment were hypertension (46.9%) and ADHD (26.5%), followed by tics (6.1%), OCD (3.6%), and other emotional disorders (2.6%). ADHD was the most common indication for the age groups: 0-2, 3-9, and 10-19 years old. In this age group, the general cluster of 'psychiatric exposure accounted for 38.8% of use. The tables below illustrate the estimated guanfacine use by age group and by diagnosis.

Guanfacine Use by Age Groups

Age group	Percent of indications
0-2 years	0.2%
3-9	21.9%
10-19	24.4%
20-39	3.3%
40-59	14.3%
60-64	5.3%
65-74	12.5%
75-84	11.8%
85+	2.8%
unspecified	3.7%

Guanfacine Use by Diagnosis

Diagnosis	Percent of indications
Hypertension	46.9%
Attention Deficit/Hyperactivity (ADHD)	26.5%
Tic disorder	6.1%
Obsessive Compulsive Disorder (OCD)	3.6%
Other Emotional Disorder	2.6%
All other indications	14.3%

Postmarketing Adverse Events Reported with Guanfacine Treatment

The following data was obtained from the sponsor's review of ADRS and AERS databases of all postmarketing spontaneous adverse events reported to FDA for the use of Tenex and other guanfacine products for the period January 1, 1969 to March 31, 2005. For patients 17 years old or younger, there were 955 adverse events reported for 309 patients. The most commonly reported adverse events included: somnolence (22 events), drug ineffective (19), aggression (18), fatigue (15), weight increased (15), abnormal behavior (12), tic (12), nausea (11), anger (10), disturbance in attention (10), mania (10), sedation (10), agitation (9), condition aggravated (9), insomnia (9), lethargy (9), vomiting (9), and weight decreased (9).

Special Interest Categories

1. Deaths in 0-24 age group (4 deaths)

- One patient (21 y.o.) had the following adverse events reported: arrhythmia, convulsion, overdose, and stupor.
- One patient (13 y.o.) had pneumonia and stupor.
- One patient (13 y.o.): had convulsions, cardiac arrest, heart failure, and pneumonia.
- One patient (9 y.o.) had cardiac arrest, cardiac failure, diarrhea, drug hypersensitivity, dyspnea, and lethargy.

2. Potentially life-threatening events (36 events)
The most commonly reported adverse events in the category were: convulsion (18), loss of consciousness (7), depressed level of consciousness (4), and stupor (3).

3. Cardiovascular events (24 events)
Cardiovascular adverse events included: cardiac arrest (2), cardiac failure (2), myocardial infarction (2), syncope (3), and chest pain (4)

4. Neuropsychiatric events (209)
The most commonly reported neuropsychiatric adverse events were: aggression (18), abnormal behavior (12), tic (12), attention disturbance (10), mania (10), agitation (9), hostility (8), irritability (7), mood swings (7), psychomotor hyperactivity (7), movement disorder (3).

5. Hypersensitivity events (129).
Commonly reported hypersensitivity adverse events included: edema (facial), urticaria, allergic reaction, dermatitis-exfoliative, rash-maculopapular, hypersensitivity, rash-vesicular, bullous. In the pediatric population, the most commonly reported were: hypersensitivity (7), rash generalized (3), and rash macular (2).

Review of Literature
From review of the literature, the most commonly reported adverse events with guanfacine treatment have been: sedation, tiredness, fatigue, headache, abdominal pain, appetite decreased, nocturnal enuresis, and irritability. Some reports of hypotension and rebound hypertension after discontinuation of treatment. Syncope was reported for four (4). Other postmarketing cases have included: mania, hypersensitivity, and drug interactions with guanfacine treatment.

OSE Consult Cindy Kortepeter, Pharm.D. (June 12, 2000)

OPDRA Postmarketing Safety Review/Consult:
Drug: Tenex/Guanfacine - NDA# 19-032
Events: Selected cardiovascular events and sudden death in the pediatric population

From Dr. Kortpeter's review and analysis, the most frequently reported postmarketing adverse events for guanfacine in all age groups were cardiovascular and nervous system disorders. In the 0-17 year-old age range, the most frequently reported events were nervous system disorders (convulsions NOS, sedation), psychiatric disorders (mania),

cardiac disorders (bradycardia), and injury & poisoning (accidental overdose). A search of the AERS database identified 7 cases in the 0-17 year-old age range using the terms specified in the consult (falls, rebound hypertension, hypotension, cardiac function diagnostic procedures which includes QT prolongation, and ventricular arrhythmia and cardiac arrest which includes torsade de pointes and sudden death). There were no reports of falls, rebound hypertension, QT prolongation, ventricular arrhythmia, Torsade de Pointes, or sudden death. There was one death, which was attributed to pneumonia, sepsis, acute respiratory distress, CHF, and an acid/base disorder in a 13 year-old asthmatic who suffered a cardiac arrest. There were four (4) cases of intentional or accidental overdose. In one case, it was difficult to determine whether guanfacine was responsible for the memory deficits of a 13 year-old male who received 3 mg rather than 1 mg daily for 3 to 4 days. The other three overdose cases show that adverse overdose effects of guanfacine can manifest as altered mental status, including lethargy and somnolence, hypotension, bradycardia, and paradoxical hypertension (which would not be unexpected since direct stimulation of peripheral alpha-adrenergic receptors can occur). Bradycardia and hypotension were delayed adverse events, occurring at 16 hours post-ingestion in a 2 year-old and 22 hours post-ingestion in a 15 year-old. These adverse events are consistent with the labeling and/or are well recognized in Poisindex. There was one case of asymptomatic ECG changes in a 10 year-old. The remaining case of a 6 year-old on propranolol with symptoms of decreased respiratory and heart rates and increased blood pressure was excluded since her glucose was 30 mg/dl and she responded immediately to intravenous D50.

Drug usage data showed that of all guanfacine appearances, less than 15% were in the 0-17 year-old age range; yet, greater than 95% of the projected number of total drug uses for ADD/ADHD is in 0-17 year-olds with the highest (77.1%) in the 5-12 year-old age group. Nevertheless, aside from accidental or intentional ingestions, there were no apparent significant adverse cardiovascular events reported for the 0-17 year-old population.

9 ADDITIONAL CLINICAL ISSUES

9.1 DOSING REGIMEN AND ADMINISTRATION

Intuniv™ is an extended-release tablet and should be dosed once daily. The dosage strengths include 1, 2, (b) (4) 3, and 4 mg tablets. Tablets should not be crushed, chewed, or broken before swallowing, because this will increase the rate of guanfacine release. Patients should begin treatment with a dose of 1 mg per day. The dose should be increased in increments of no more than 1 mg per week. The dose should be maintained within the range of 1mg to 4 mg per day, depending on clinical response and the emergence of adverse events. The clinician should consider dosing on an mg per kg basis, in order to balance the exposure-related potential benefits and risks of treatment. There was a strong inverse correlation between body weight and serum guanfacine concentration in clinical trials. Clinical improvements were observed beginning at doses

in the range 0.05-0.08 mg/kg/day. Generally, efficacy increased with increasing weight-adjusted dose (mg/kg). If well tolerated, doses up to 0.12 mg/kg/day were demonstrated to provide additional benefit. Doses above 4 mg have not been studied.

There is a significant food effect on the absorption of Intuniv. When administered with a large high-fat meal, the mean exposures increased significantly. The AUC increased by approximately 40%, and the Cmax increased by approximately 77%, compared to dosing in a fasted state. The food effect could be clinically significant, because many of the important adverse effects of Intuniv occurred in a dose-related or exposure-related manner. Thus, to minimize the potential risks, patients should take Intuniv without food or with a light meal, and they should avoid taking Intuniv with a large or high-fat meal.

Treatment with Intuniv should not be discontinued abruptly, since patients may develop transient increases in blood pressure and heart rate. To minimize the risk of developing these effects, the dose should be tapered in decrements of no greater than 1 mg every 3 to 7 days.

9.2 DRUG INTERACTIONS

CYP3A4/5 Inhibitors

Guanfacine is metabolized in vitro by cytochrome P4503A4/5. There was a substantial increase in the rate and extent of guanfacine exposure when guanfacine was co-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. These results indicate that concomitant administration of Intuniv and drugs that inhibit CYP3A4 activity could result in increased plasma concentrations of guanfacine, potentially leading to adverse pharmacodynamic effects. When patients are treated concomitantly with Intuniv and a CYP3A4/5 inhibitor, the dose of Intuniv should be reduced appropriately.

CYP3A4 Inducers

There was a significant decrease in the rate and extent of guanfacine exposure when guanfacine was co-administered with rifampin, an inducer of the CYP3A4 system. The Cmax for guanfacine decreased by more than 50% in the presence of rifampin, while AUC0-t and AUC0-inf both decreased by 60% to 70%. Concomitant administration of Intuniv and drugs that induce CYP3A4 activity could result in decreased plasma concentrations of guanfacine, potentially leading to a loss of pharmacodynamic effect and loss of effectiveness. When patients are treated concomitantly with Intuniv and a CYP3A4 inducer, an increase in the dose of Intuniv (within the recommended dose range) should be considered.

Valproic Acid

Published literature indicates that co-administration of guanfacine and valproic acid can result in elevated concentrations of valproic acid. Plasma valproate levels rapidly

increased when guanfacine was co-administered. Furthermore, plasma valproate concentration decreased by 41% after guanfacine was tapered and discontinued. Guanfacine may increase plasma valproate concentrations via competition for the glucuronidation pathway, as both drugs are eliminated by this pathway. However, the mechanism of this interaction has not been definitively documented. When Intuniv is co-administered with valproic acid, dosing adjustments may be required.

9.3 SPECIAL POPULATIONS

Renal Impairment

The pharmacokinetics of guanfacine immediate-release was studied in patients with impaired renal function. After intravenous administration to subjects with normal, moderately impaired, or severely impaired renal function. In patients with impaired renal function, there was a substantial reduction in the cumulative urinary excretion of guanfacine and in renal clearance of guanfacine. The degree of the reduction in renal clearance increased as the degree of renal impairment increased. The clinician should consider adjusting the dose of Intuniv in patients with impairment of renal function.

Hepatic Impairment

The pharmacokinetics of guanfacine have not been studied in patients with hepatic impairment. Cytochrome P450 3A4 is the predominant enzyme involved in the oxidative metabolism of guanfacine. Since all subsequent metabolic steps require this initial process, it is likely that abolition of CYP3A4 activity (as might be expected in severe hepatic impairment) will result in a similar increase in guanfacine exposure. Ketoconazole is a potent inhibitor of CYP3A4 activity. Thus, its effect on guanfacine exposure guanfacine following co-administration might be expected to approximate those in hepatic impairment. Guanfacine Cmax was essentially doubled, while AUC0-t and AUC0-inf both increased by about three-fold in the presence of ketoconazole. This suggests that there would be an approximately 2-3 fold increase in Cmax of Intuniv in patients with hepatic impairment. The clinician should consider adjusting the dose of Intuniv in patients with impairment of hepatic function.

Effect of Body Weight on Pharmacokinetics

There were inverse relationships between dose-normalized Cmax and AUC and body weight which were statistically significant. As expected from the decrease in dose-normalized AUC, there was an increase in clearance (CL/F), which was also statistically significant. The volume of distribution (Vz/F) also increased with increasing body weight. Consistent with the increases in clearance and volume of distribution, there was no change in half-life ($t_{1/2}$) with changes in body weight.

Effect of Age and Gender

Increasing age had a significant inverse relationship with dose-normalized Cmax and

had a significant direct relationship with half-life ($t_{1/2}$). There were no significant relationships between age and dose-normalized AUC, clearance, or volume of distribution.

Exposure to guanfacine was higher in children (ages 6-12) compared to adolescents (ages 13-17) and adults. After oral administration of multiple doses of Intuniv 4mg, the Cmax in children (ages 6-12) and adolescents (ages 13-17) was 10ng/mL and 7ng/mL respectively, and the AUC was 162ng.h/mL and 116ng.h/mL respectively. These differences are attributed to the lower body weight of children compared to adolescents and adults. Likewise, minor gender effects on guanfacine pharmacokinetics were considered related to bodyweight rather than gender per *se*, as male subjects tended to have higher body weight than female subjects in the studies.
The pharmacokinetics and dose-proportionality of guanfacine after single- and multiple dose administration of SPD503 have been examined in children (6-12 years) and adolescents (13-17 years) with ADHD. The pharmacokinetics of guanfacine has been studied in subjects with impaired renal function, the elderly, and patients with hypertension. In vivo drug interaction studies with ketoconazole and rifampin were conducted to examine the impact of inhibition and induction of cytochrome P4503A4/5 on the pharmacokinetics of guanfacine administered as SPD503.

9.4 PEDIATRICS

The sponsor has studied the efficacy and safety of Intuniv in children and adolescents between the ages of 6 and 12 years-old, inclusive. At this point, the sponsor will not be required to study Intuniv in children below the age of 6 years-old. The Division will discuss with the sponsor any additional required pediatric studies.

9.5 LITERATURE REVIEW BY SPONSOR

The sponsor submitted a number of relevant journal articles about guanfacine and ADHD but did not perform a literature review.

9.6 POSTMARKETING RISK MANAGEMENT PLAN

The sponsor has not submitted a proposal for a postmarketing risk management plan. I recommend that the Division require the sponsor to submit a risk management plan pertaining to potential adverse events not limited to the following: sedation, syncope, QT interval prolongation, hypotension, bradycardia, psychiatric adverse events, and weight gain.

10 OVERALL ASSESSMENT

10.1 CONCLUSIONS

Efficacy Findings

Two adequate and well controlled trials demonstrated the efficacy of Intuniv in ADHD. Each was positive separately for the primary efficacy endpoint: change in mean ADHD-RS scores for the randomized (intended fixed dose). In addition to being statistically significant, the reductions in mean ADHD-RS in the Intuniv groups, compared to the placebo groups, were clinically significant. The placebo-adjusted changes in mean ADHD-RS scores ranged from − 6.5 to − 10.1 points for the primary efficacy analysis. The results were also positive for the non-pre-specified efficacy analyses: change in mean ADHD-RS in both the actual-dose analysis and the weight-adjusted actual-dose analyses.

Furthermore, the efficacy of Intuniv was dose-related and exposure-related. For the actual-dose and weight adjusted actual-dose analyses, the Intuniv treatment effects were larger than those in the randomized dose analysis. The greatest placebo-adjusted treatment effects in these analyses ranged from − 8.9 to − 19 points on the ADHD-RS scale, all of which are clinically significant.

Inattention and Hyperactivity-Impulsivity Subscales- the studies were positive for the non-prespecified analyses of: 1) Inattention Subscale of ADHD-RS; and 2) Impulsivity-Hyperactivity Subscale of ADHD-RS.

Safety Findings

Treatment with Intuniv was reasonably safe and well tolerated. There were no deaths in the clinical program. There were few serious adverse events in the placebo-controlled trials. None of them were drug-related: Only four (4) SAE were reported in the controlled trials. None of the SAE appears to have been related to treatment with guanfacine. In Study 301, two (2) subjects treated with guanfacine had serious adverse events. One subject had an exacerbation of asthma, and another subject with a history of asthma had a pneumothorax. In Study 301, none of the subjects in the placebo group had a serious adverse event. In Study 304, one subject treated with guanfacine had a head injury, concussion, and seizure. One subject in the placebo group had a fracture of the tibia and fibula.

There were a number of discontinuations due to adverse events, most of which were probably drug-related. In the controlled trials, a higher proportion of subjects in the guanfacine group discontinued due to adverse events compared to the placebo group (12% and 4%, respectively). Several of the adverse events in the guanfacine group were likely related to treatment with guanfacine. These included: hypotension (6), QT interval

prolongation (3), bradycardia (1), somnolence (19), sedation (11), fatigue (8), asthenia (1), lethargy (1), dizziness (3), nightmare (1), insomnia (1), and headache (5). Adverse events leading to discontinuation that were possibly related to treatment with guanfacine included: affective lability (2), hostility (1), and depression (2).

Adverse events were most commonly reported for the following categories: nervous system, psychiatric, and gastrointestinal. The most commonly reported specific adverse events in the Intuniv group were: somnolence (30%), headache (23%), fatigue (14%), sedation (10%), abdominal pain (10%), hypotension (6%), dizziness (6%), lethargy (6%), irritability (6%), nausea (6%), and insomnia (5%). It is likely that all of these types of adverse events were related to treatment with Intuniv, based on the pattern of AE reports (compared to placebo) and the previous clinical experience with guanfacine. The following adverse events were dose-related or exposure-related in the clinical trials: hypotension, somnolence, sedation, abdominal pain, dizziness, dry mouth, and constipation.

Sedative adverse events were quite commonly reported in the controlled trials. Sedative adverse events included somnolence, sedation, hypersomnia, fatigue, lethargy, and asthenia. In the Intuniv group in the controlled trials, 53% of subjects reported sedative adverse events, compared to 17% of the placebo group. Sedative events were dose-related overall (combining all sedative type events).

Less commonly reported adverse events that were probably drug-related included bradycardia, asthenia, dyspepsia, blood pressure decreased, orthostatic hypotension, QT interval prolongation, weight gain, and postural dizziness. It is possible that the following adverse events were related to treatment with guanfacine: atrioventricular block-first degree, sinus arrhythmia (unspecified), enuresis, and Pollakiuria.

Psychiatric adverse events were reported for a higher proportion in the Intuniv group than in the placebo group. These included: irritability (5%), affective lability (4%); aggression (1.4% vs. 0.7%), agitation (1.4%), depressed mood (0.8%), and anxiety (0.4%). There were single cases of paranoia, psychomotor retardation, bradyphrenia, constricted affect, cognitive slowing, and mental status change. In controlled trials, there were no reports of suicidal ideation or suicidal behavior. There were no reports of mania or hypomania.

Other important findings that were dose-related included decreased blood pressure and decreased heart rate. There were also transient rebound increases in blood pressure and heart rate upon abrupt discontinuation of treatment with Intuniv. In addition, QT interval prolongation occurred in an exposure-related manner.

Syncope was reported for ten (10) pediatric subjects in the Intuniv clinical program. One subject had two episodes. These subjects represented approximately 1.2% of the entire pediatric population exposed to guanfacine. All of these cases of syncope occurred during the long-term, open-label phases of the studies, relatively long after subjects were first exposed to guanfacine. The rate of syncope in the clinical program was higher than the estimated background rate of syncope in the general pediatric population. Several of

these patients sought medical attention for the syncopal events. The rate of those seeking medical attention due to syncope in the guanfacine clinical program exceeds the relevant estimated background rate of pediatric patients seeking or reaching medical attention for syncope. It seems likely that exposure to guanfacine was a factor contributing to syncope in at least some of these cases, given the drug's effect on blood pressure and heart rate. In many of the syncope cases, another factor appeared to at least contribute to the syncopal event. These specific factors included: dehydration, heat, exercise, pain, injury, sight of blood, acute psychosocial stressors, gastrointestinal illness, and previous history of presyncopal episodes.

10.2 RECOMMENDATION ON REGULATORY ACTION

I recommend that the Division of Psychiatry Products take an Approvable action for NDA 22-037. In my opinion, the sponsor has demonstrated the efficacy and safety of Intuniv (guanfacine extended-release) in the treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in children and adolescents (ages 6-17 years-old). Studies 301 and 304 were adequate and well-controlled trials that demonstrated the efficacy of Intuniv, as measured by the change in mean Attention Deficit-Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) scores. There was a statistically and clinically significant difference in the treatment effect of Intuniv compared to placebo in both placebo-controlled trials. Furthermore, the treatment effect was dose-related and exposure-related.

In my opinion, treatment with Intuniv was reasonably safe and well tolerated in the trials. While there were clinically significant adverse events in the trials, many of the potential safety concerns can be managed largely through rational dosing on an mg/kg basis. For, a considerable portion of the common and significant adverse events appear to be dose-related and exposure-related. Guanfacine exposures were highly correlated (inversely) with subjects' body weights. Furthermore, the sponsor used fixed doses, instead of dosing per body weight in the trials.

10.3 RECOMMENDATION ON POSTMARKETING ACTION

10.3.1 Required Postmarketing Commitments

- The sponsor should conduct a dedicated, thorough QT study of guanfacine in healthy adult subjects. (Preliminary details will be discussed below in the Cardiorenal QT Interdisciplinary Review Team consult).
- The sponsor should conduct a controlled trial in adolescent subjects with ADHD, in order to confirm that treatment with Intuniv is safe and effective in this population.
- The sponsor should conduct a controlled trial of adjunctive treatment with guanfacine stimulant medications in children and adolescents with ADHD.
- The sponsor should continue to collect ECG data in ongoing pediatric trials.

- The sponsor should conduct a placebo-controlled maintenance trial to assess the long-term efficacy and safety of guanfacine in children and adolescents with ADHD. This should probably be a placebo-controlled randomized withdrawal study.
- The sponsor should conduct a separate long-term safety study, focusing on the following safety concerns: growth, weight gain, metabolic effects, QT interval prolongation, syncope and other cardiovascular safety parameters, seizures, sedative adverse events, cognitive performance, and effects on growth hormone and bilirubin concentrations.

10.3.2 Risk Management Activity

The sponsor should submit a detailed Risk Management Plan that focuses on managing the potential cardiovascular risks of QT prolongation, syncope, hypotension, and bradycardia. Risk management should also focus on the common sedative adverse events. The plan should include a detailed discussion of the exposure-related and dose-related risks and a dosing and titration plan based on body weight.

In addition, it would be useful for the sponsor to develop a Med Guide or similar form of communication for educating patients, parents, and caregivers about the potential safety concerns listed above. In developing a Risk Management Plan, the sponsor should probably consult with pediatric cardiologists.

Finally, the sponsor should incorporate should incorporate the data from the American Association of Poison Control Centers publication on pediatric guanfacine overdosages in the labeling for Intuniv™.

10.3.3 Other Phase 4 Requests

We will consider recommending that the sponsor conduct specific drug interaction studies, including guanfacine interactions with: valproic acid and moderate inhibitors of the CYP3A4/5 system.

26 pages withheld immediately after this page as B4 (draft labeling)

11 APPENDIX

APPENDIX 11.1: Attention Deficit Hyperactivity Disorder Rating Scale-IV

	None	Mild	Moderate	Severe
1. Fails to give close attention to details or makes careless mistakes in work	0	1	2	3
2. Fidgets with hands or feet or squirms in seat	0	1	2	3
3. Has difficulty sustaining attention in tasks or play activities	0	1	2	3
4. Leaves seat in classroom or in other situations in which seating is expected	0	1	2	3
5. Does not seem to listen when spoken to directly	0	1	2	3
6. Runs about or climbs excessively in situations in which it is inappropriate	0	1	2	3
7. Does not follow through on instructions and fails to finish work	0	1	2	3
8. Has difficulty playing or engaging in leisure activities quietly	0	1	2	3
9. Has difficulty organizing tasks and activities	0	1	2	3
10. Is "on the go" or acts as if "driven by a motor"	0	1	2	3
11. Avoids tasks (e.g., schoolwork, homework) that require sustained mental effort	0	1	2	3
12. Talks excessively	0	1	2	3
13. Loses things necessary for tasks or activities	0	1	2	3
14. Blurts out answers before questions have been completed	0	1	2	3
15. Is easily distracted	0	1	2	3
16. Has difficulty awaiting turn	0	1	2	3
17. Is forgetful in daily activities	0	1	2	3
18. Interrupts or intrudes on others	0	1	2	3

APPENDIX 11.2: Schedule of Assessments in Controlled Trials

Assessments	Scr	Bas										F/U

Visit number	−1	0	1	2	3	4	5	6	7	8	9	10
Assessment day		0	7	14	21	28	35	42	49	56	59	86
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomit Meds		X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Weight, height	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X			X				X		X	
Clinical labs	X										X	
ADHD-RS-IV		X	X	X	X	X	X					
CGI-S	X	X										
CGI-I			X	X	X	X	X					
Drug accountab.			X	X	X	X	X	X	X	X		

APPENDIX 11.3: Prohibited and Permitted Concomitant Medications

Prohibited Medications:

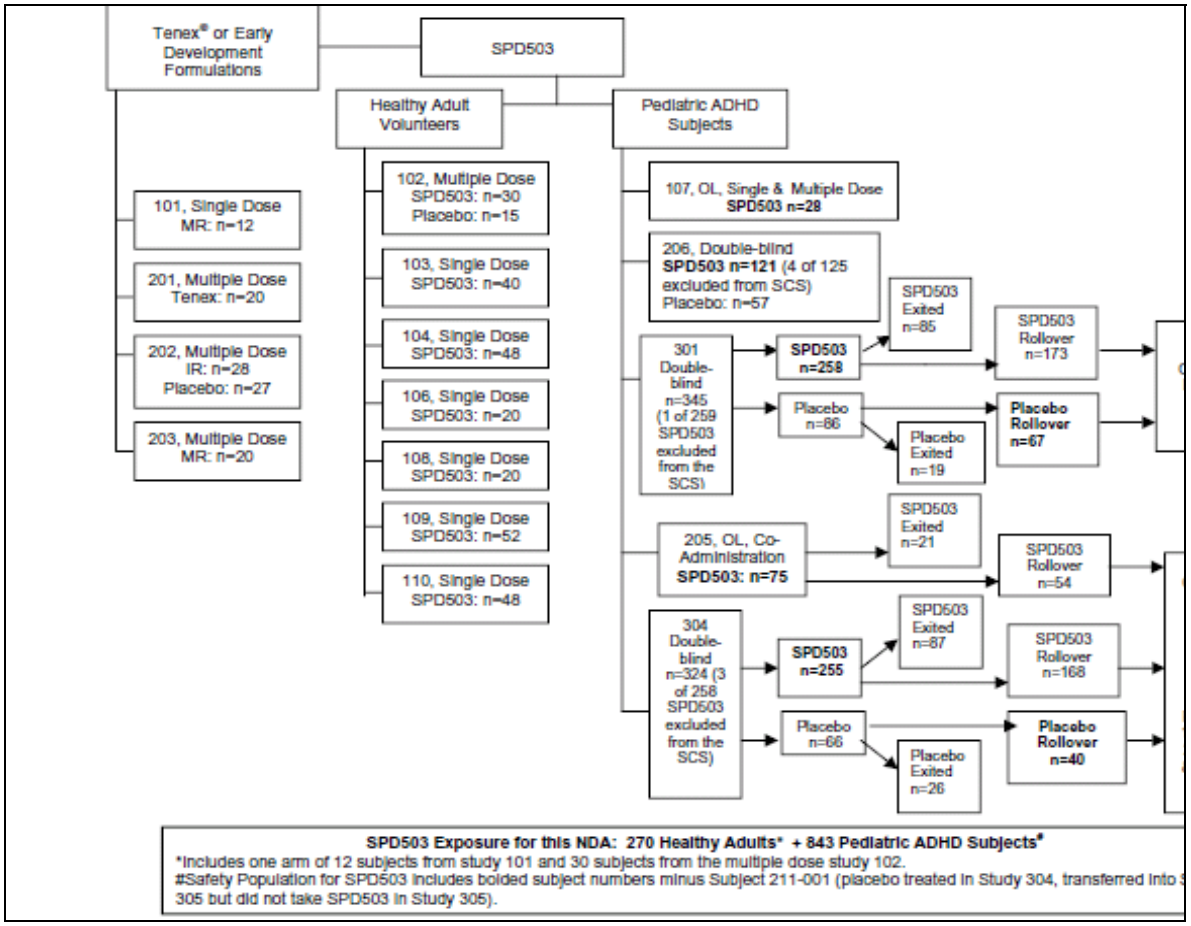
- Methylphenidate, amphetamines, sympathomimetic, appetite suppressants, modafenil, pemoline
- Clonidine
- Antidepressants: tricyclics, tetracyclics, Trazadone, bupropion, Fluoxetine, sertraline, paroxetine, citalopram, venlafaxine, nefazodone
- Monoamine oxidase
- Anticonvulsants and mood stabilizers
- Antipsychotics
- Benzodiazepines and benzodiazepine derivatives, sedative-hypnotics

- Sedating antihistamines; (non-sedating antihistamines were permitted).
- digoxin, antihypertensive medications, any investigational medications

Permitted Concomitant Medications
Bronchodilators, antibiotics, over the counter medications that did not affect blood pressure, heart rate, or CNS function.

APPENDIX 11.4

Flow Chart for the Clinical Program



APPENDIX 11.5

Table 11 Demographic and Disease Characteristics by Randomized Treatment Group – Short-Term Study Pool

Parameter	Placebo (N=149)	SPD503 1mg* (N=61)	SPD503 2mg (N=150)	SPD503 3mg (N=151)	SPD503 4mg (N=151)	All Active (N=513)
Age (years)						
n	149	61	150	151	151	513
Mean	10.7	9.3	10.5	10.9	10.3	10.4
SD	2.76	2.14	2.55	2.84	2.73	2.69
Median	11.0	9.0	10.0	11.0	10.0	10.0
Min, Max	6, 17	6, 13	5, 17	6, 17	6, 17	5, 17
Age Category						
6-12 years	110 (73.8)	54 (88.5)	116 (77.3)	104 (68.9)	120 (79.5)	394 (76.8)
≥13 years	39 (26.2)	7 (11.5)	34 (22.7)	47 (31.1)	31 (20.5)	119 (23.2)
Gender						
Male	107 (71.8)	41 (67.2)	111 (74.0)	117 (77.5)	110 (72.8)	379 (73.9)
Female	42 (28.2)	20 (32.8)	39 (26.0)	34 (22.5)	41 (27.2)	134 (26.1)
Ethnic Origin						
White	102 (68.5)	42 (68.9)	99 (66.0)	104 (68.9)	106 (70.2)	351 (68.4)
Black	22 (14.8)	11 (18.0)	30 (20.0)	16 (10.6)	22 (14.6)	79 (15.4)
Hispanic	14 (9.4)	3 (4.9)	11 (7.3)	20 (13.2)	14 (9.3)	48 (9.4)
Asian/Pacific Islander	1 (0.7)	3 (4.9)	2 (1.3)	0	4 (2.6)	9 (1.8)
Native American	0	0	0	1 (0.7)	1 (0.7)	2 (0.4)
Other	10 (6.7)	2 (3.3)	8 (5.3)	10 (6.6)	4 (2.6)	24 (4.7)
Weight (lb)						
n	149	61	150	151	151	513
Mean	96.5	77.2	99.1	100.1	96.8	96.1
SD	34.04	16.67	36.16	37.94	36.59	35.74
Median	90.0	75.0	92.0	89.0	84.0	85.0
Min, Max	55, 237	55, 109	55, 275	55, 220	53, 204	53, 275
Weight Category (lbs)						
<75	49 (32.9)	30 (49.2)	46 (30.7)	51 (33.8)	53 (35.1)	180 (35.1)
≥75 - <110	50 (33.6)	31 (50.8)	50 (33.3)	43 (28.5)	51 (33.8)	175 (34.1)
≥110	50 (33.6)	0	54 (36.0)	57 (37.7)	47 (31.1)	158 (30.8)
Height (in)						
n	149	61	150	151	151	513
Mean	57.38	54.23	57.85	57.98	56.85	57.16
SD	6.433	4.495	6.219	6.849	6.055	6.285
Median	57.00	53.30	57.90	57.00	56.00	56.30
Min, Max	40.7, 73.3	47.4, 63.7	46.5, 72.7	44, 72	45.8, 70.5	44, 72.7
ADHD Subtype						
Inattentive	41 (27.5)	12 (19.7)	42 (28.0)	35 (23.2)	41 (27.2)	130 (25.3)
Hyperactive	3 (2.0)	1 (1.6)	4 (2.7)	2 (1.3)	2 (1.3)	9 (1.8)
Combined	105 (70.5)	48 (78.7)	104 (69.3)	114 (75.5)	108 (71.5)	374 (72.9)
Not available	0	0	0	0	0	0

Parameter	Placebo (N=149)	SPD503 1mg* (N=61)	SPD503 2mg (N=150)	SPD503 3mg (N=151)	SPD503 4mg (N=151)	All Active (N=513)
Years since ADHD diagnosis						
n	149	61	150	151	151	513
Mean	2.556	1.483	2.071	2.683	2.245	2.232
SD	3.2675	2.1627	2.7645	2.8908	3.0017	2.8275
Median	1.150	0.170	0.840	2.140	0.390	0.850
Min, Max	0, 11.5	0, 8.89	0, 12.18	0, 14.75	0, 12.13	0, 14.75

APPENDIX 11.6:

Study 301 Baseline Demographics

Characteristics	Placebo N= 78	Guan 2 mg N= 84	Guan 3 mg N= 82	Guan 4 mg N= 81	Total N= 325
Age					
Mean	10.6	10.6	10.8	10.1	10.5
Median	10	10	11	10	10
Min, Max	6, 17	6, 16	6, 17	6, 17	6, 17
Age category					
6-8	23 (27)	18 (21)	21 (24)	29 (34)	91 (26)
9-12	43 (50)	51 (59)	39 (45)	41 (48)	174 (50)
13-17	20 (23)	18 (21)	26 (30)	16 (19)	80 (23)
Gender					
Male	64 (74)	67 (77)	69 (80)	57 (66)	257 (75)
Female	22 (26)	20 (23)	17 (20)	29 (34)	88 (26)
Ethnic origin					
White	63 (73)	59 (68)	58 (67)	62 (72)	242 (70)
Black	8 (9)	17 (20)	10 (12)	11 (13)	46 (13)
Hispanic	7 (8)	6 (7)	13 (15)	8 (9)	34 (10)
Asian, P.I.	1 (1)	0	0	1 (1)	2 (1)
Native Amer.	0	0	1 (1)	0	1 (<1)
Other	7 (8)	5 (6)	4 (5)	4 (5)	20 (6)
Weight (lb)					
Mean	94	99	98	93	96
Median	88	92	91	79	87
Min, Max	55, 175	55, 271	55, 197	54, 207	54, 271
Height (in)					
Mean	57	58	58	56	57
Median	57	57	57	55	56
Min, Max	46, 73	47, 73	44, 71	46, 71	44, 73
ADHD subtype					
Inattentive	19 (22)	28 (32)	20 (23)	23 (27)	90 (26)
Hyperac-imp.	0	4 (5)	1 (1)	2 (2)	7 (2)
Combined	67 (78)	55 (63)	65 (76)	61 (71)	248 (72)
Years since Dx					
Mean	2.7	2.3	3	2.4	2.6
Median	0.7	1.0	3.0	0.2	1.0
Min, Max	0, 12	0, 13	0, 10	0, 13	0, 13

APPENDIX 11.7

Table 4: Demographics and Disease Diagnosis by Randomized Treatment Group (Study SPD503-304 ITT Population)

Characteristics	Placebo N=63	SPD503 1mg N=57	SPD503 2mg N=63	SPD503 3mg N=60	SPD503 4mg N=63	Total N=306
Age (y)						
Mean (SD)	10.7 (2.92)	9.2 (2.17)	10.7 (2.76)	11.1 (2.76)	10.6 (2.55)	10.5 (2.71)
Median	11.0	9.0	10.0	10.5	10.0	10.0
Min, Max	6, 17	6, 13	6, 17	6, 17	6, 16	6, 17
Age category (y), n (%)*						
6-12	45 (71.4)	50 (87.7)	46 (73.0)	41 (68.3)	48 (76.2)	230 (75.2)
13-17	18 (28.6)	7 (12.3)	17 (27.0)	19 (31.7)	15 (23.8)	76 (24.8)
Gender, n (%)						
Male	44 (69.8)	37 (64.9)	44 (69.8)	44 (73.3)	51 (81.0)	220 (71.9)
Female	19 (30.2)	20 (35.1)	19 (30.2)	16 (26.7)	12 (19.0)	86 (28.1)
Ethnic origin, n (%)						
White	38 (60.3)	39 (68.4)	40 (63.5)	43 (71.7)	43 (68.3)	203 (66.3)
Black	14 (22.2)	10 (17.5)	13 (20.6)	6 (10.0)	10 (15.9)	53 (17.3)
Hispanic	7 (11.1)	3 (5.3)	5 (7.9)	6 (10.0)	6 (9.5)	27 (8.8)
Asian or Pacific Islander	1 (1.6)	3 (5.3)	2 (3.2)	0	3 (4.8)	9 (2.9)
Native American	0	0	0	0	1 (1.6)	1 (0.3)
Other	3 (4.8)	2 (3.5)	3 (4.8)	5 (8.3)	0	13 (4.2)
Weight (lb)						
Mean (SD)	98.37 (37.90)	76.61 (16.62)	99.25 (31.79)	101.10 (38.15)	101.51 (37.72)	95.68 (34.69)
Median	90.0	74.0	98.0	85.5	88.0	85.0
Min, Max	55.0, 237.0	55.0, 109.0	55.0 183.0	57.0, 220.0	55.0, 185.0	55.0, 237.0
Height (in)						
Mean (SD)	57.56 (6.38)	54.10 (4.60)	57.76 (6.20)	57.99 (6.08)	57.69 (6.07)	57.07 (6.05)
Median	57.5	52.5	58.9	57.5	57.8	57.0
Min, Max	40.7, 71.0	47.4, 63.7	47.0, 71.3	48.0, 72.0	47.5, 68.3	40.7, 72.0
ADHD subtype, n (%)						
Inattentive	22 (34.9)	12 (21.1)	14 (22.2)	15 (25.0)	18 (28.6)	81 (26.5)
Hyperactive/ impulsive	3 (4.8)	1 (1.8)	1 (1.6)	1 (1.7)	0	6 (2.0)
Combined	38 (60.3)	44 (77.2)	48 (76.2)	44 (73.3)	45 (71.4)	219 (71.6)

Table 4: Demographics and Disease Diagnosis by Randomized Treatment Group (Study SPD503-304 ITT Population)

Characteristics	Placebo N=63	SPD503 1mg N=57	SPD503 2mg N=63	SPD503 3mg N=60	SPD503 4mg N=63	Total N=306
Years since ADHD diagnosis						
Mean (SD)	2.3 (3.03)	1.2 (1.97)	1.9 (2.72)	2.0 (2.31)	2.1 (3.02)	1.9 (2.67)
Median	1.0	0	0	1.5	1.0	0
Min, Max	0, 11	0, 8	0, 12	0, 9	0, 11	0, 12

APPENDIX 11.8

Table 35 Criteria Used Significance to Identify ECG Abnormalities of Potential Clinical

Parameter	Children and Adolescents	Healthy Adult Volunteers
Heart Rate	≤50 bpm or ≥100 bpm	≤50 bpm or ≥100 bpm
PR Interval	≥200 msec	≥200 msec
QT Interval	≥480 msec	≥480 msec
QRS Interval	≥120 msec	≥120 msec
QTcP	≥500 msec	≥500 msec
QTcF	≥500 msec	≥500 msec
QTcB	≥500 msec	≥500 msec
QTcF change from Baseline	≥30 to <60 msec or ≥60 msec	≥30 to <60 msec or ≥60 msec
QTcB change from Baseline	≥30 to <60 msec or ≥60 msec	≥30 to <60 msec or ≥60 msec
Investigator Overall Assessment	Abnormal, clinically significant	

APPENDIX 11.9

Table Criteria Used to Identify Laboratory Abnormalities of Potential Clinical Significance

	Children and Adolescents		Healthy Adult Volunteers	
Laboratory Parameter	Lower Limit	Upper Limit	Lower Limit	Upper Limit
Hematology:				
Hemoglobin (g/dL)				
Male	<11	>16.5	<11	>16.5
Female	<11	>16.5	<9.8	>16.5
Hematocrit (%)				
Male	<32	>45	<32	>45
Female	<32	>45	<30	>45
MCV (fL)	<70	>110	<70	>110
MCHC (g/dL)	<28	>41	<28	>41
Erythrocytes (x106/µL)				
Male	<2.5	NA	<2.5	NA
Female	<2.0	NA	<2.0	NA
WBC (x103/µL)	<2.80	>14.00	<2.80	>14.00
Neutrophils (%)	<15	NA	<15	NA
Lymphocytes (%)	NA	>80	NA	>80
Monocytes (%)	NA	>40	NA	>40
Eosinophils (%)	NA	>10	NA	>10
Basophils (%)	NA	>15	NA	>15
Platelet Count (x103/µL)	<100	>600	<100	>600
Bands (abs) (x103/µL)	NA	> 0.27	NA	>0.27
Neutrophils, Bands (%)	NA	> 5	NA	>5
Clinical Chemistry:				
Alkaline Phosphatase (U/L)	NA	3 x ULN	NA	3 x ULN
SGOT (AST) (U/L)	NA	3 x ULN	NA	3 x ULN
SGPT (ALT) (U/L)	NA	3 x ULN	NA	3 x ULN
GGT	NA	3 x ULN	NA	3 x ULN
Total Bilirubin (mg/dL)	NA	>2.0	NA	>2.0
LDH	NA	> 3x ULN	NA	>3 x ULN
Glucose (mg/dL)	<45	>160	<45	>160
Urea Nitrogen (mg/dL)	NA	>30	NA	>30
Creatinine (mg/dL)	NA	>1.5	NA	>1.5
Sodium (mmol/L)	<130	>150	<130	>150
Potassium (mmol/L)	<3	>5.8	<3	>5.8
Chloride (mmol/L)	<90	>115	<90	>115
Albumin (g/dL)	<2.4	>7.0	<2.4	>7.0
Calcium (mg/dL)	<8	>10.5	<8	>10.5
Serum Bicarbonate (mmol/L)	<15.5	>33	<15.5	>33
Total Protein (g/Dl)	<6.1	>8.4	<6.1	>8.4
Cortisol (serum) (ug/dL)	<3	>23	-	-
TSH (uIU/mL)	<0.35	>6	-	-
HGH (ug/dL)		>10	-	-
Urinalysis:				
Protein/Albumin	Positive Value	Positive Value	NA	1+ or greater

Glucose/Sugar	Positive Value	Positive Value	NA	Positive Value
Hemoglobin/Blood	Positive Value	Positive Value	NA	Positive Value*
Ketones	Positive Value	Positive Value	NA	do not list
Bilirubin	Positive Value	Positive Value	NA	Positive Value
Leukocyte Est	Positive Value	Positive Value	NA	Positive Value
Nitrites	Positive Value	Positive Value	NA	do not list

APPENDIX 11.10

Table 5 Demographic and Disease Characteristics by Dose Prior to Tapering – Long-Term Study Pool

Parameter	SPD503 1mg (N=17)	SPD503 2mg (N=121)	SPD503 3mg (N=147)	SPD503 4mg (N=161)	All Active (N=446)
Age (years)					
n	17	121	147	161	446
Mean	10.3	10.6	10.0	10.9	10.5
SD	2.64	2.71	2.52	2.67	2.65
Median	10.0	10.0	10.0	11.0	10.0
Min, Max	7, 15	6, 17	6, 17	6, 17	6, 17
Age Category - n (%)					
6-12 years	13 (76.5)	95 (78.5)	120 (81.6)	111 (68.9)	339 (76.0)
13 years	4 (23.5)	26 (21.5)	27 (18.4)	50 (31.1)	107 (24.0)
Gender - n (%)					
Male	12 (70.6)	82 (67.8)	115 (78.2)	123 (76.4)	332 (74.4)
Female	5 (29.4)	39 (32.2)	32 (21.8)	38 (23.6)	114 (25.6)
Ethnic Origin - n (%)					
White	7 (41.2)	88 (72.7)	105 (71.4)	109 (67.7)	309 (69.3)
Black	6 (35.3)	11 (9.1)	18 (12.2)	25 (15.5)	60 (13.5)
Hispanic	2 (11.8)	13 (10.7)	14 (9.5)	16 (9.9)	45 (10.1)
Asian/Pacific Islander	1 (5.9)	1 (0.8)	3 (2.0)	3 (1.9)	8 (1.8)
Native American	0	0	0	1 (0.6)	1 (0.2)
Other	1 (5.9)	8 (6.6)	7 (4.8)	7 (4.3)	23 (5.2)
Weight (lb)					
n	17	121	147	161	446
Mean	89.5	96.2	89.2	103.0	96.1
SD	34.13	33.48	32.05	38.26	35.24
Median	76.0	90.0	80.0	96.0	88.0
Min, Max	55, 149	55, 199	53, 220	55, 275	53, 275
Weight Category (lbs) - n (%)					
<75	8 (47.1)	39 (32.2)	62 (42.2)	44 (27.3)	153 (34.3)
75 - <110	3 (17.6)	50 (41.3)	50 (34.0)	56 (34.8)	159 (35.7)
110	6 (35.3)	32 (26.4)	35 (23.8)	61 (37.9)	134 (30.0)
Height (in)					
n	17	121	147	161	446
Mean	57.16	56.77	55.98	58.47	57.14
SD	6.706	5.834	6.003	6.293	6.164
Median	57.00	56.00	55.00	59.00	56.70
Min, Max	49.7, 68	40.7, 71.3	45.8, 70.5	46.5, 72.7	40.7, 72.7
ADHD Subtype - n (%)					
Inattentive	3 (17.6)	34 (28.1)	41 (27.9)	36 (22.4)	114 (25.6)
Hyperactive	0	2 (1.7)	4 (2.7)	2 (1.2)	8 (1.8)
Combined	14 (82.4)	85 (70.2)	102 (69.4)	123 (76.4)	324 (72.6)
Not available	0	0	0	0	0

Table 5 Demographic and Disease Characteristics by Dose Prior to Tapering – Long-Term Study Pool

Parameter	SPD503 1mg (N=17)	SPD503 2mg (N=121)	SPD503 3mg (N=147)	SPD503 4mg (N=161)	All Active (N=446)
Years since ADHD diagnosis					
n	17	121	147	161	446
Mean	1.145	2.010	2.189	2.480	2.206
SD	1.2050	2.9167	2.7089	2.9918	2.8378
Median	1.140	0.390	0.810	1.290	0.710
Min, Max	0, 3.21	0, 12.17	0, 10	0, 12.18	0, 12.18

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/s/

Robert Levin
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Clin Review