CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-037/SE1-S002
Priority or Standard	Standard
Submit Date(s)	April 28, 2010
Received Date(s)	April 28, 2010
PDUFA Goal Date	February 28, 2011
Division / Office	DPP/ODE1
Reviewer Name(s)	Silvana Borges, M.D.
Review Completion Date	January 19, 2011
Established Name	Guanfacine
Trade Name	Intuniv®
Therapeutic Class	Selective α2 agonist
Applicant	Shire Pharmaceuticals
Formulation(s)	Extended-release tablets (1 mg, 2 mg, 3 mg and 4 mg strengths)
Dosing Regimen	1 to 4 mg QD
Indication(s)	Adjunctive therapy for ADHD
Intended Population(s)	Children and adolescents

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that this supplement be approved. In my opinion, the sponsor has demonstrated the efficacy and reasonable safety of Intuniv (guanfacine extended-release) as an adjunctive therapy to oral psychostimulants in the treatment of Attention Deficit-Hyperactivity Disorder (ADHD) in children and adolescents (ages 6-17 years-old).

1.2 Risk Benefit Assessment

Intuniv is a selective α2 agonist that is approved as monotherapy for the treatment of ADHD in children and adolescents. Despite the effectiveness of ADHD medications, some patients have a suboptimal response or have side effects that limit their ability to reach an optimal dose. An option for these patients is adjunctive therapy. Although there are no FDA-approved adjunctive therapies for ADHD, these are not uncommon in clinical practice. Given that psychostimulants remain the mainstay of ADHD treatment, it was expected that Intuniv would be used as an adjunctive therapy in patients with a suboptimal response to stimulants. Therefore, the study of the efficacy and safety of such adjunctive therapy was deemed critical and was included as a postmarketing requirement for Intuniv upon its approval as ADHD monotherapy.

In my opinion, based on the Study 313 results, Intuniv administered as adjunctive therapy to an oral psychostimulant (amphetamine or methylphenidate) showed significantly greater improvement compared with placebo plus oral psychostimulant of ADHD symptoms as measured by the ADHD-RS-IV Total score. This was shown for both morning and evening administration of Intuniv, and in both children (6-12 years) and adolescents (13-17 years). These are important findings because they represent a treatment alternative for patients with suboptimal response to psychostimulants and provide useful dosing information. The positive results in adolescents are also relevant since the efficacy of Intuniv in adolescents with ADHD was not thoroughly determined in the Intuniv monotherapy trials. Additionally, two drug interaction studies concluded that there were no drug interactions between Intuniv and methylphenidate following co-administration of 4 mg of Intuniv and 36 mg of CONCERTA, and between Intuniv and lisdexamfetamine following co-administration of 4 mg of Intuniv and 50 mg of VYVANSE.

Intuniv plus psychostimulant was well tolerated and reasonably safe in this study population. No new safety signals emerged from the administration of Intuniv as adjunctive therapy to amphetamine or methylphenidate products compared with Intuniv or psychostimulants administered alone. Furthermore, although not thoroughly

demonstrated, data from Study 313 suggest that the effect of the adjunctive therapy on heart rate, blood pressure and sedative events could be less marked than that observed with Intuniv or psychostimulants administered alone. The most frequently reported Treatment-Emergent Adverse Events (TEAEs) was headache, which occurred in a higher proportion of subjects receiving Intuniv plus psychostimulant (21.2%) compared with subjects receiving placebo plus psychostimulant (13.1%). Other TEAEs occurring in a significant larger proportion of subjects in the Intuniv group compared with the placebo group were somnolence, fatigue, insomnia, abdominal pain, and dizziness. These TEAEs are generally known to be reported with Intuniv or psychostimulant treatment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This review identified no new major risks that would merit a Risk Evaluation and Mitigation Strategy.

1.4 Recommendations for Postmarket Requirements and Commitments

In the approval letter of Intuniv as monotherapy treatment for ADHD dated September 02, 2009, the following pediatric studies were required:

- A long-term maintenance study of efficacy and safety of guanfacine as monotherapy for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients ages 6 to 17.
- An efficacy and safety study of guanfacine in adolescent patients ages 12 to 17.

No additional postmarketing studies are deemed necessary.

2 Introduction and Regulatory Background

2.1 Product Information

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 four dose strengths: 1, 2, 3, and 4 mg. The product is intended for once daily dosing. The trade name of the product is Intuniv. Thus, Intuniv is an oral, extended-release tablet formulation of guanfacine hydrochloride.

2.2 Currently Available Treatments for Proposed Indications

For many years, the mainstay of approved treatment for ADHD has been the stimulants, methylphenidate and amphetamines. Included in this category are dexmethylphenidate,

lisdexamfetamine, dextroamphetamine, methamphetamine, and amphetamine single and mixed salts. Non-stimulant drugs approved for the treatment of ADHD include atomoxetine (Strattera), a selective norepinephrine reuptake inhibitor, the referred guanfacine (Intuniv), and clonidine (Kapvay), both selective α2-adrenergic receptor agonists. As listed below, there are numerous immediate-release and extended-release formulations of drugs available for the treatment of ADHD:

- Adderall (mixed salts of amphetamine/dextroamphetamine) Tablets
- Adderall XR (mixed salts of amphetamine/dextroamphetamine) 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
- Vyvanse (lisdexamfetamine: a pro-drug of amphetamine) Capsules
- Guanfacine (Intuniv) Extended-Release Tablets
- Clonidine (Kapvay) Extended-Release Tablets

Although not approved for the indication, several other drugs are thought to be effective in treating some patients with ADHD. These include bupropion (Wellbutrin), and tricyclic antidepressants (e.g., imipramine and desipramine).

2.3 Availability of Proposed Active Ingredient in the United States

Guanfacine is currently approved and marketed in the U.S. for the treatment of hypertension. Guanfacine in its extended-release formulation (Intuniv) is being marketed in the US for the treatment of ADHD following its approval in September 2009.

2.4 Important Safety Issues With Consideration to Related Drugs

Clonidine is the prototypic α2 adrenergic receptor agonist. Clonidine activates α2 receptors in the autonomic control centers in the CNS, thus decreasing discharges in sympathetic fibers in the splanchnic and cardiac nerves. As a result, clonidine decreases blood pressure and heart rate, and causes some undesired effects in the

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

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 Summary of Presubmission Regulatory Activity Related to Submission

Guanfacine was approved in 1986 for the treatment of hypertension in patients > 12 years old. Shire opened IND 60,019 (guanfacine HCl immediate-release) on 03/13/2000 and **IND 63,551 (guanfacine HCl extended-release) on 10/26/2001** to support the development of Intuniv (guanfacine HCl extended-release tablets) for the treatment of ADHD. Highlights of regulatory interactions between Shire and FDA (DNPDP and DPP) are described below:

- **10/08/2002 - End-of-Phase 2 Meeting:** FDA agreed with the generalities of the proposed pediatric ADHD pivotal trials.

- **01/28/2004 - Type C Meeting:** FDA and Shire had discussions on pivotal study 301 preliminary results and 304 study plans.

- **10/18/2004 through 02/23/2005:** FDA and Shire had discussions about pivotal Study 304 and other aspects of the Intuniv clinical development plan.

- **05/18/2005 - End of Phase 3 Meeting:** FDA stated the following conclusions:
  - 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
  - The available data should be sufficient to assess heart rate and QT 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

- FDA requested that data describing CYP2C8 inhibition, induction of CYP450 and interaction with P-glycoprotein be provided in the NDA

- **08/03/2005:** Based on FDA's preliminary view of the pivotal data, it was noted that the Pediatric Written Request 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 Intuniv with stimulants, since alpha-2 agonists are often used with stimulants in ADHD treatment
  3. Placebo-controlled evening vs. morning dosing study (mono- or adjunct-therapy), since Guanfacine IR is used mostly in the evening as adjunctive therapy to stimulants during the day.
  4. A randomized withdrawal study to evaluate long-term efficacy

- **08/24/2006**: Shire submitted a **505(b) (2) type NDA for Intuniv (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 clinical review concluded that 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 could be managed largely through rational dosing on an mg/kg basis. A considerable portion of the common and significant adverse events appeared to be dose and exposure related.

- **09/02/2009 - Approval:** Intuniv (guanfacine extended-release tablets) was approved with the following postmarketing requirements:
  1) A long-term maintenance study of efficacy and safety of Intuniv as monotherapy in children and adolescents with ADHD
  2) An efficacy and safety study of Intuniv in adolescents.
  3) An efficacy and safety study of Intuniv as adjunctive treatment with oral psychostimulants.
  4) A cardiac toxicity study in rats
  5) A reproductive toxicity assessment in juvenile rats

On **04/28/10**, this application was submitted as a **supplement (SE1-002) to NDA 22037** to support a claim for the adjunctive use of Intuniv with oral psychostimulants for the treatment of ADHD in pediatric patients ages 6 to 17 years, and to fulfill the corresponding postmarketing commitment included in the 2009 Approval Letter. This submission contains three clinical studies (SPD503-313: efficacy and safety study; SPD503-114 and SPD503-115: PK studies), and two toxicology studies.

2.6 Other Relevant Background Information

A Filing Meeting was held on 06/08/2010 and concluded that the application could be filed. It was also decided that this application would be granted standard review status. The Action Due Date was established as 02/28/2011.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

I audited a sample of case report forms (CRFs) to evaluate the consistency of adverse event information across the CRF, corresponding narrative summary, and adverse event tabulation. A total of 12 CRFs were selected for this audit, with the following patient identification numbers: 02-016, 09-009, 14-003, 23-009, 25-012, 26-003, 29-013, 31-001, 33-011, 40-008, 54-007, and 62-003. Forty-eight adverse events were reported in these CRFs. In general, the adverse event information was found to be consistent across the above documents. Two adverse events (blood pressure decreased and seasonal allergies) were reported in the CRFs but not included in the adverse events file. However, these discrepancies are considered to be minor and unlikely to affect the overall safety results.

I also audited the coding of adverse event investigator terms to preferred terms. In study 313, the sponsor used MedDRA coding. The adverse event tabulations for study 313 were examined, comparing the variables AE versus PT. No coding deficiencies were detected.

Dr. Ishida, the Statistical Reviewer, detected missing data of concomitant medication records in one of the submitted tabulation data sets, named *cm*. The *cm* data set contained the CRF record data of stimulant medications and was one of the data sets used in the primary efficacy analysis. We asked the sponsor to validate and resubmit the referred data set and to validate all other submitted data sets to ensure data integrity. The sponsor acknowledged the existence of the referred missing data, validated and resubmitted the cm data set, and stated that, upon validation of all other data sets, failed to find any additional discrepancies.

3.2 Compliance with Good Clinical Practices

The Division of Scientific Investigations (DSI) was consulted to inspect two of the clinical sites with the highest subject enrollment from study 313: Site #07 (Howard Ilivicky, MD of St. Charles, MO) and Site#40 (J. Mark Joyce, MD of Jacksonville, FL). A Clinical Inspection Summary was completed by Anthony Orencia, M.D., Good Clinical Practice Branch II, DSI on 11/05/2010. At Dr. Ilivicky's site, subjects #7, #9 and #16 were found to have previous or current histories of suicidal thoughts or ideation or post traumatic

stress disorder (PTSD) which were exclusion criteria. Some discrepancies in concomitant medication calendar dates and the ADHD-RS-IV scale score were found, although they were considered insignificant. A minor regulatory violation with respect to incomplete record keeping deficiency was also noted. No deficiencies were noted at Dr. Joyce's site. As a result of these inspections, DSI recommended exclusion of subjects #7, #9, and #16 from this study since these subjects had history of previous or current suicidal risk or PTSD. The statistical reviewer checked the efficacy data of these subjects, concluding that there was almost no impact of these subjects on the analysis results.

The DSI inspection also documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations, and the data are considered reliable in support of the application.

According to the study 313 report, this clinical study was conducted in compliance with the ethical principles of the Declaration of Helsinki and in accordance with all ICH Good Clinical Practice guidelines.

Shire has certified that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

3.3 Financial Disclosures

The sponsor submitted the certification of financial disclosure of clinical investigators participating in studies 313, 114 and 115 in compliance with 21 CFR part 54. One investigator in study 313 reported "significant payments of other sorts" from the sponsor: (b) (6) (principal investigator (b) (6) received approximately $50,000 during 2007 and 2008. However, given that (b) (6) study 313 was conducted under double-blind conditions, it is unlikely that this investigator would have produced data that could have biased the study results in favor of Intuniv.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The current submission includes a regulatory notification from the sponsor to agree with the Agency's recommendation for adopting a final regulatory specification for drug product dissolution (b) (4)

4.2 Clinical Microbiology

None.

4.3 Preclinical Pharmacology/Toxicology

Two additional toxicology studies in the neonatal/juvenile rat were submitted in this application:

1. A preliminary oral toxicity study in neonatal/juvenile rats (Shire Ref. No. R01525M-SPD503) to investigate the influence of guanfacine and methylphenidate administered either alone or concurrently for 15 days.
2. An oral (gavage) developmental toxicity study in neonatal/juvenile rats (Shire Ref. No. R01587M-SPD503) to investigate the influence of guanfacine and methylphenidate administered either alone or concurrently for 53 days.

Daily oral administration of guanfacine at doses up to 1mg/kg/day or methylphenidate at doses up to 50mg/kg/day (either alone or as adjunctive treatments) to juvenile CD rats from Day 7 of age for 53 days was well tolerated. Treatment of males and females with guanfacine and/or methylphenidate was associated with reduced mean body weight gain compared with control. There was no clear effect of treatment on the attainment of sexual maturity or on hormone levels on the day of attainment of sexual maturity. There was no effect on mean organ weights, and no observed macro or micropathological changes. Toxicokinetic evaluations indicated that when 1mg/kg/day guanfacine was co-administered with 50mg/kg/day methylphenidate, higher systemic exposure was achieved than when 1mg/kg/day guanfacine was administered alone. However, the concomitant use of guanfacine and methylphenidate at high doses was considered unlikely to have any long-term detrimental effect and had no adverse effect on fertility or embryonic survival.

The sponsor concluded that a dose level of 1mg/kg/day guanfacine and 50mg/kg/day methylphenidate, administered either alone or as adjunctive treatment, represented the NOAEL for male and female juvenile CD rats.

Dr. Ikram Elayan is the assigned pharmacology/toxicology reviewer for this efficacy supplement. At the time of completion of this clinical review, the pharm/tox review has not been finalized yet. There seem to be no major safety findings in these submitted juvenile animal studies.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Guanfacine is a centrally acting selective α2-adrenergic receptor agonist. 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. Activation of the α2-adrenergic receptor has been shown to increase blood flow in the prefrontal cortex, which in turn enhances executive function, working memory, attention, and behavioral inhibition. This modulation of prefrontal cortical cognitive functions is thought to be guanfacine's mechanism of action in ADHD.

4.4.2 Pharmacodynamics

This supplement contains no new information on the pharmacodynamics of Intuniv.

4.4.3 Pharmacokinetics

This submission includes two drug interaction studies: one with CONCERTA (Study 114), and the other with VYVANSE (Study 115). The two drug interaction studies concluded that there are no drug interactions between guanfacine and methylphenidate following co-administration of 4 mg of Intuniv and 36 mg of CONCERTA, and between guanfacine and lisdexamfetamine following co-administration of 4 mg of Intuniv and 50 mg of VYVANSE. According to the approved labeling, the pharmacokinetics of guanfacine is dose-proportional within the range of 1–4 mg. Thus, the conclusion for these drug interaction studies could be applied to all doses. Although 19% increase in guanfacine Cmax and 7% increase in guanfacine AUC following co-administration of Intuniv and VYVANSE was observed, it is not clinically meaningful to be interpreted as drug-drug interaction. Dr. Lee, clinical pharmacologist, from the Office of Clinical Pharmacology completed her review of PK findings from these two drug interaction studies.[1]

1See Dr. Lee's Clinical Pharmacology Review and Evaluation dated 11/02/2010

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study 313, which examined the efficacy and safety of Intuniv as adjunctive treatment in ADHD, is the primary focus of this supplement. Also, safety data from two drug interaction studies in healthy adults that were completed after the original ADHD monotherapy application (NDA 22037) are examined in this review. All three studies are summarized in Table 1 below.

Table 1: ADHD and Drug interaction studies

Study Number	Study Description[2]
313	9-week double-blind, randomized, placebo-controlled study of Intuniv as adjunctive therapy to psychostimulants in patients aged 6-17 yrs with ADHD. N = 455.
114	open-label, randomized, 3-period crossover, drug-drug interaction study of Intuniv 4 mg alone, CONCERTA (methylphenidate HCl) 36 mg alone and their adjunctive use in healthy adults (mean age 30.8 yrs). N = 38.
115	open-label, randomized, 3-period crossover, drug-drug interaction study of Intuniv 4mg alone, VYVANSE (lisdexamfetamine dimesylate) 50 mg alone and their adjunctive use in healthy adults (mean age 30.5 yrs). N = 42.

5.2 Review Strategy

This review consisted of an examination of relevant background clinical information from the original ADHD application (NDA 22037), efficacy and safety data from study 313, and a limited review of safety data (deaths, non-fatal serious adverse events, and dropouts due to adverse events) from studies 114 and 115.

6 Review of Efficacy

Efficacy Summary

The efficacy of Intuniv 1-4 mg/day as adjunctive treatment to psychostimulants for ADHD was demonstrated in one 9-week study (study 313). No significant difference was found between Intuniv administered in the morning and Intuniv administered in the evening as adjunctive therapy for ADHD. Additionally, two drug interaction studies

2 N represents number of subjects who received at least one dose of study drug

concluded that there are no drug interactions between Intuniv and methylphenidate following co-administration of 4 mg of Intuniv and 36 mg of CONCERTA, and between Intuniv and lisdexamfetamine when following co-administration of 4 mg of Intuniv and 50 mg of VYVANSE.

6.1 Studies Pertinent to the Adjunctive Therapy for ADHD Claim

6.1.1 Rationale for Selection of Studies for Review

The sponsor conducted a single trial (study 313) of adjunctive treatment with Intuniv in patients with ADHD partially responsive to standard therapy. This study forms the basis for the adjunctive efficacy claim.

6.1.2 Study Summaries

Study 313

Methods/Study Design/Analysis Plan

This was a 9-week, double-blind, randomized, placebo-controlled, dose-optimization study conducted in 59 sites in the USA.

Primary objective

The primary objective was to assess the efficacy of optimized Intuniv (1, 2, 3, and 4mg/day) compared to placebo, when co -administered with psychostimulants, in the treatment of children (6-12 years) and adolescents (13-17 years) with ADHD, with a partial response to psychostimulants.

Inclusion criteria

- Males or females, 6-17 years of age with a diagnosis of ADHD according to the DSM-IV-TR criteria
- Receiving one of the **pre specified psychostimulants**: ADDERALL XR (mixed salts of a single-entity amphetamine product), VYVANSE (lisdexamfetamine dimesylate), CONCERTA (methylphenidate HCl), FOCALIN XR (dexmethylphenidate HCl), RITALIN LA (methylphenidate HCl extended-release), METADATE CD (methylphenidate HCl), or FDA-approved generic equivalents
- Suboptimal response to current psychostimulant treatment. A **suboptimal response** was defined as treatment with a stable dose of psychostimulant for at least 4 weeks with improvement; however, mild to moderate ADHD symptoms remain present as defined by ADHD RS IV ≥24 and CGI-S ≥3 at Screening and Baseline

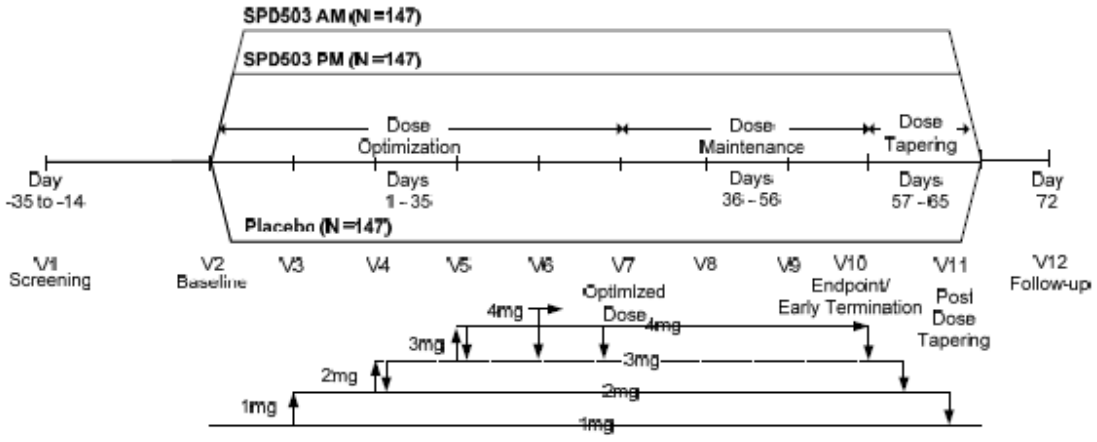
Exclusion criteria

- Other current psychiatric diagnosis (except Oppositional Defiant Disorder)
- History of substance abuse or dependence
- Risk for suicide
- History or presence of cardiac abnormalities
- Weight less than 55 lbs or greater than 176 lbs
- Pregnancy
- Concomitant medication that affect blood pressure, heart rate, or the central nervous system, or prolong the QT/QTc interval (except pre specified psychostimulants)
- Concomitant medications known to be CYP3A4/5 inducers or inhibitors prohibited after Baseline visit. However, if use was planned for the duration of the study, and a stable dose was established for at least 14 days prior to Baseline, the treatment could be given concomitantly throughout the study, with no planned changes in use.

Study design

Eligible patients entered the trial in the **screening phase** (visit 1, days -35 to -14) for verification of inclusion/exclusion criteria and screening tests, including medical and medication history, physical examination, vital signs, ECG, clinical labs, urine drug and alcohol test, pregnancy test (for females of childbearing potential) and psychiatric assessments, following the study schema shown below.

Figure 1 Study Design Diagram



The **first phase** of the study was the **Dose-optimization Period**, which lasted 5-weeks. At Visit 2 (Baseline), patients were randomized to receive Intuniv or matching placebo (1mg/day) and received 1 active or placebo tablet every morning and 1 active or placebo tablet every evening. Subjects were to maintain their current, stable dose of psychostimulant treatment taken each morning. Subjects returned to the site weekly for

evaluation of ADHD symptoms and possible side effects, and were titrated to their optimal dose based on tolerability and response to study drug. At each visit, the Investigator decided to maintain the current dose, increase the dose (1mg weekly increments), or decrease the dose (by 1mg increments after Visit 3, week 1). During the study only 1 dose reduction was permitted. Visit 7 (week 5) was the last opportunity to make any changes to dose level prior to the Dose-maintenance Phase.

During the **Dose-maintenance Phase**, subjects were maintained on their optimal dose for an additional 3 weeks. The final efficacy evaluation occurred at Visit 10 (end of week 8). During this phase, the Investigator could down-titrate a subject by 1mg, to ensure the subject's safety, if the dose was not already decreased during optimization.

A **Dose-tapering Period** of up to 9 days followed, allowing down titration of study drug with follow-up safety assessments after dose tapering.

Study evaluations

Patients were evaluated during the dose optimization and dose maintenance phases at weeks 1, 2, 3, 4, 5, 6, 7 and 8 following randomization. There was also an evaluation on day 65 for patients who entered the dose-tapering period, and a final follow-up visit on day 72. **Safety assessments** included weekly vital signs, clinical monitoring of adverse events and concomitant medications; physical examination (Visits 1 and 10); pregnancy tests (Visits 1, 2, and 12); hematology, clinical chemistry, urinalysis, height, and weight (Visits 1, 2, and 10); and ECGs (Visits 2, 4, 6, and 8). **Efficacy assessments** included weekly ADHD-RS IV, Conners' Global Index – Parent (CGI-P), Clinical Global Impressions – Severity (CGI-S) and –Improvement (CGI-I), and Post-Sleep Questionnaire (PSQ); Before-school Functioning Questionnaire (BSFQ) on Visits 8, 10 and 11; Parent's Global Assessment (PGA), and Oppositional subscale of the Conners' Parent Rating Scale-Revised: Long Version (CPRS-R:L) on Visits 10 and 11.

Efficacy analysis

The **primary efficacy variable** for each subject was defined as the change from Baseline to Endpoint on the ADHD-RS-IV Total score. Endpoint was defined as the last on-therapy, post randomization treatment week, prior to any dose taper at which a valid ADHD-RS-IV Total score was collected. The last observation carried forward (LOCF) approach was used as an imputation method for missing data of the primary efficacy endpoint. The **efficacy Intention-to-treat (ITT) population** or full analysis set (FAS) consisted of all subjects who receive at least 1 dose of any study drug during this study.

The mean ADHD RS-IV Total score and change from Baseline score were summarized for each visit and for Endpoint by treatment group. The **primary efficacy analysis** was performed using the LOCF ANCOVA model with treatment group and psychostimulant type (amphetamine or methylphenidate) as model factors, and baseline score as a

covariate. The null hypothesis was that there was no difference between optimized Intuniv AM and placebo, or between optimized Intuniv PM and placebo. The hypothesis test was conducted for 2-sided, overall 0.05% type I error rate. Dunnett's adjustment for multiple comparisons was used to control the overall significance level in the analysis.

There were **no pre-specified key secondary efficacy variables**. However, the Hyperactivity/Impulsivity subscale Total score and Inattentiveness subscale Total score of the ADHD-RS-IV, CGI-P Total score, CPRS-R:L oppositional subscale and BSFQ parent-rated items were analyzed using an ANCOVA as for the analysis. The CGI-I, CGI-S and PGA were each analyzed using a Cochran-Mantel-Haenzsel test stratified by psychostimulant type (amphetamine or methylphenidate). There was **no interim analysis** for this study.

An initial **sample size** of 399 patients (133 subjects in each of the Intuniv and placebo groups) was calculated to provide 90% power and a significance level of 0.05 (2-sided) with a 1:1:1 (Intuniv AM:Intuniv PM:placebo) allocation ratio to detect an effect size of 0.4 between either Intuniv group and placebo (equivalent to a standard deviation of 10 points and a difference between active and placebo of approximately 4 points on the ADHD-RS-IV total score). To account for drop-outs, 441 subjects needed to be enrolled. Enrollment planned to recruit approximately 25% females and 25% adolescents. Randomization was stratified to balance pre-specified oral psychostimulant type (amphetamine or methylphenidate).

Results

Demographics

Demographics for each treatment group are displayed in Table 2 below. The mean age was 10.8 years, 71.6% of subjects were male, and 67.7% were white. The study enrolled 79.3% children and 20.7% adolescents. Approximately 53% of subjects received methylphenidate products and 47% of subjects received amphetamine products. The largest proportion of subjects received CONCERTA (45.3%) as their concomitant psychostimulant followed by VYVANSE (29.5%) and ADDERALL XR (17.8%).

Baseline Characteristics

The Intuniv PM group had somewhat lower weight at Baseline than the Intuniv AM and placebo groups. There were no other major differences between double-blind treatment groups regarding age, height, ADHD subtype and length of diagnosis, concomitant psychostimulant, and baseline ADHD-RS-IV total score.

Table 2 Summary of Demographic Characteristics

	Placebo + Stimulant (N = 153)	SPD503 AM + Stimulant (N = 150)	SPD503 PM + Stimulant (N = 152)	Overall SPD503 + Stimulant (N = 302)	Total (N = 455)
Age, years					
Mean (SD)	10.8 (2.3)	11.0 (2.6)	10.6 (2.3)	10.8 (2.5)	10.8 (2.4)
Median	11.0	11.0	10.0	11.0	11.0
Min, Max	6, 17	6, 17	6, 17	6, 17	6, 17
Categories, n (%)					
6-12 years	123 (80.4)	114 (76.0)	124 (81.6)	238 (78.8)	361 (79.3)
13-17 years	30 (19.6)	36 (24.0)	28 (18.4)	64 (21.2)	94 (20.7)
Sex, n (%)					
Male	112 (73.2)	108 (72.0)	106 (69.7)	214 (70.9)	326 (71.6)
Female	41 (26.8)	42 (28.0)	46 (30.3)	88 (29.1)	129 (28.4)
Race, n (%)					
White	102 (66.7)	104 (69.3)	102 (67.1)	206 (68.2)	308 (67.7)
Black or African American	35 (22.9)	28 (18.7)	37 (24.3)	65 (21.5)	100 (22.0)
Native Hawaiian or other Pacific Islander	1 (0.7)	1 (0.7)	1 (0.7)	2 (0.7)	3 (0.7)
Asian	1 (0.7)	2 (1.3)	3 (2.0)	5 (1.7)	6 (1.3)
American Indian or Alaska Native	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.2)
Other	14 (9.2)	14 (9.3)	9 (5.9)	23 (7.6)	37 (8.1)
Height, in					
Mean (SD)	57.65 (5.5)	58.10 (6.0)	57.05 (5.4)	57.57 (5.7)	57.60 (5.6)
Median	57.00	57.80	56.60	57.05	57.00
Min, Max	47.6, 70.0	46.0, 73.7	46.4, 71.0	46.0, 73.7	46.0, 73.7
Weight, lbs					
Mean (SD)	89.14 (27.9)	90.76 (29.7)	85.40 (26.5)	88.06 (28.2)	88.43 (28.1)
Median	85.50	83.00	76.20	79.75	81.40
Min, Max	55.0, 164.0	55.0, 175.0	55.0, 164.0	55.0, 175.0	55.0, 175.0
BMI					
Mean (SD)	18.39 (3.0)	18.37 (2.8)	18.06 (2.9)	18.21 (2.9)	18.27 (2.9)
Median	17.62	17.84	17.41	17.59	17.62
Min, Max	13.7, 27.0	14.2, 28.2	13.4, 28.3	13.4, 28.3	13.4, 28.3
Concomitant Psychostimulant, n (%)					
Adderall XR	27 (17.6)	26 (17.3)	28 (18.4)	54 (17.9)	81 (17.8)
Concerta	69 (45.1)	69 (46.0)	68 (44.7)	137 (45.4)	206 (45.3)
Focalin XR	9 (5.9)	9 (6.0)	9 (5.9)	18 (6.0)	27 (5.9)
Metadate CD	2 (1.3)	2 (1.3)	1 (0.7)	3 (1.0)	5 (1.1)
Ritalin LA	1 (0.7)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.4)
Vyvanse	45 (29.4)	43 (28.7)	46 (30.3)	89 (29.5)	134 (29.5)

Note: Corresponds to Table 3 in Study 313 report document

Patient Disposition

In study 313, 59 centers in the US randomized patients. No foreign sites were used in the study. A total of **461 subjects were randomized** into the study; 6 subjects did not receive study drug. The **full analysis set** then consisted of **455 patients** (153 placebo

patients, 150 patients on Intuniv AM and 152 patients on Intuniv PM). In addition, there were 6 subjects who had no post-baseline efficacy assessment. The sponsor's **primary efficacy analysis** was conducted on the set of the **449 subjects** (LOCF subjects). A total of 386 subjects are reported to complete the study through Visit 10 - end of week 8 (Endpoint).

However, the sponsor excluded 7 of the 386 subjects from the set of Visit 10 completers because they had their Visit 10 efficacy assessment after their last non-tapering dose date. In addition, 3 subjects who terminated their study early at Visit 10 were included in the efficacy analysis set of completers through Visit 10 because they had a valid efficacy assessment for Visit 10 before the last non-tapering dose date. Therefore, **382 (83 %) subjects were included as completers through Visit 10** in the actual analysis data set that the sponsor used for the primary efficacy analysis (see Table 2.1.1.1 of Study 313 report). **Sixty-seven** subjects (449 minus 382) terminated the study prior to Visit 10 and were considered as **early termination patients** in the sponsor's efficacy assessment. There were minor differences in the reasons for early termination among the treatment groups. However, these differences are considered unlikely to affect the overall results of the study. According to the statistical review, the dropout rate was about 15% and there was no evidence suggesting that the dropouts and missing data impacted on the primary efficacy analysis to the extent that the study result should be questioned.

Concomitant Medication Use

More patients were on atomoxetine and dexamphetamine in the placebo group (10.5 and 39.2 %, respectively) than in the Intuniv AM (8 and 33.3 %, respectively) and PM (7.9 and 34.9 %, respectively) groups prior to entering the study. No other clinically important differences were found across the treatment groups regarding the prior, concomitant, or post-treatment medications received.

The most frequent concomitant medication, other than the concomitant psychostimulants included in the study, was acetaminophen, which was received by 15.7% of subjects in the placebo group, 14.0% of subjects in the Intuniv AM group, and 11.2% of subjects in the Intuniv PM group. Two subjects (67-003 and 30-022) were noted to have received concomitant guanfacine; however, the guanfacine was started after the last dose of taper medication and before the final follow-up visit. Thus, it seems unlikely that this use would have biased the study results in favor of Intuniv. Urine drug screens to monitor for the use of possible confounding medication during the double-blind phase were done only at the time of randomization. Thus, it is possible that a larger number of patients took unreported prohibited medication during the double-blind phase.

Important Protocol Violations

Sixteen (3.5%) subjects were discontinued from the study for protocol violations. The most frequent protocol violation leading to discontinuation was non-compliance (8 subjects, 1.8%), followed by violation of inclusion/exclusion criteria which occurred or were noted after randomization (6 subjects, 1.3%). Two subjects were discontinued for other protocol violations (one patient was out of town, unwilling to come to the required visits, and another patient needed a prohibited medication).

The protocol stated that subjects were to remain on their current, stable dose of psychostimulant throughout the study. Four subjects had a change in dose of their concomitant psychostimulant. Three subjects increased their dose: Subject 34-006 (Intuniv AM, terminated from the study); Subject 13-015 (placebo, completed the study); Subject 22-003 (Intuniv AM, completed the study). One patient (Subject 34-001, Intuniv AM) had his dose decreased; the subject was terminated from the study. Subject 37-007 (Intuniv AM) stopped the stimulant dose for 3 days because of an episode of tachycardia at Visit 12 (final follow-up visit). The sponsor asserts that no other significant protocol deviations likely to impact the data analysis were noted.

Dosing

The mean daily doses of Intuniv are displayed in Table 3 below.

Table 3 Summary of Optimal Dose of SPD503 (Safety Population)

	SPD503 AM+ Stimulant (N=150)	SPD503 PM+ Stimulant (N=152)	All SPD503+ Stimulant (N=302)
Optimal Dose, mg (n)	135	136	271
Mean (SD)	3.3 (1.0)	3.2 (1.0)	3.2 (1.0)
Median	4.0	3.0	4.0
Min, Max	1, 4	1, 4	1, 4
Subjects Receiving, n (%)			
1mg	8 (5.3)	8 (5.3)	16 (5.3)
2mg	22 (14.7)	27 (17.8)	49 (16.2)
3mg	26 (17.3)	35 (23.0)	61 (20.2)
4mg	79 (52.7)	66 (43.4)	145 (48.0)
Weight-adjusted Optimal Dose, mg/kg			
Mean (SD)	0.088 (0.04)	0.089 (0.03)	0.088 (0.04)
Median	0.090	0.090	0.090
Min, Max	0.02, 0.16	0.01, 0.16	0.01, 0.16
Subjects Receiving, n (%)			
0.01 - 0.04mg/kg	21 (14.0)	14 (9.2)	35 (11.6)
0.05 - 0.08mg/kg	46 (30.7)	51 (33.6)	97 (32.1)
0.09 - 0.12mg/kg	49 (32.7)	48 (31.6)	97 (32.1)
0.13 - 0.16mg/kg	19 (12.7)	23 (15.1)	42 (13.9)

Note: Corresponds to Table 17 in Study 313 report document

The mean optimal dose and mean weight-adjusted optimal dose were similar across treatment groups. It is of note that the mean weight-adjusted dose (approximately 0.09mg/kg) was in the middle of the range found to be efficacious in the monotherapy pivotal studies (0.05-0.12mg/kg). However, the median optimal dose was lower in the Intuniv PM group (3mg) than the Intuniv AM group (4mg). In other words, more patients in the Intuniv AM group (52.7 %) received a 4 mg dose than in the Intuniv PM group (43.4 %). Conversely, more patients in the Intuniv PM group (67.8 %) were exposed to Intuniv for >65 days compared to the Intuniv AM group (51.3 %), as shown in Table 4 below.

The mean actual and weight-adjusted doses at Endpoint for subjects with an ADHD-RS-IV Total score at Endpoint were also similar across treatment groups. A higher proportion of subjects in the Intuniv AM group received a weight-adjusted dose of 0.01-0.04mg/kg compared with the Intuniv PM group (24.0% vs.12.5%, respectively). A possible explanation may be that the weight at Baseline was slightly higher in the Intuniv AM group than in the Intuniv PM group. Therefore, these differences in drug exposure between treatment groups appear to cancel themselves out and are, in this reviewer's opinion, unlikely to affect the overall study results.

Table 4 Summary of Drug Exposure

	Placebo+ Stimulant (N=153)	SPD503 AM+ Stimulant (N=150)	SPD503 PM+ Stimulant (N=152)	All SPD503+ Stimulant (N=302)	Total+ Stimulant (N=455)
Length of Exposure (wks)					
Mean (SD)	8.4 (2.0)	8.3 (2.1)	8.3 (2.2)	8.3 (2.1)	8.4 (2.1)
Median	9.0	9.0	9.0	9.0	9.0
Min, Max	1, 10	0, 11	0, 11	0, 11	0, 11
Days Exposed, n (%)					
1-7	1 (0.7)	2 (1.3)	3 (2.0)	5 (1.7)	6 (1.3)
8-14	3 (2.0)	4 (2.7)	3 (2.0)	7 (2.3)	10 (2.2)
15-21	4 (2.6)	1 (0.7)	3 (2.0)	4 (1.3)	8 (1.8)
22-28	3 (2.0)	2 (1.3)	3 (2.0)	5 (1.7)	8 (1.8)
29-35	3 (2.0)	4 (2.7)	2 (1.3)	6 (2.0)	9 (2.0)
36-42	0 (0.0)	2 (1.3)	3 (2.0)	5 (1.7)	5 (1.1)
43-49	0 (0.0)	4 (2.7)	2 (1.3)	6 (2.0)	6 (1.3)
50-56	4 (2.6)	3 (2.0)	1 (0.7)	4 (1.3)	8 (1.8)
57-65	40 (26.1)	51 (34.0)	29 (19.1)	80 (26.5)	120 (26.4)
>65	95 (62.1)	77 (51.3)	103 (67.8)	180 (59.6)	275 (60.4)
Total Days Exposed	9439	9136	9301	18437	27876
Total Years Exposed	25.8	25.0	25.5	50.5	76.3

Note: Corresponds to Table 16 in Study 313 report document

Efficacy Results

As displayed in Table 5 below, results of the protocol-specified primary efficacy analysis demonstrated statistical superiority of Intuniv over placebo when added to a psychostimulant, with a least squares mean difference in the ADHD-RS-IV Total score change from baseline between groups of -4.5 (p=0.002) for Intuniv AM and -5.3 (p<0.001) for Intuniv PM. This result was confirmed by the Statistical Reviewer, Dr. Eiji Ishida.[3]

The primary efficacy analysis showed Intuniv to be superior to placebo regardless of the time of administration (AM or PM). The sponsor also conducted some secondary analyses whose results seem to indicate that Intuniv administered in the evening could be more beneficial than its administration in the morning:

Table 5 Summary of Change from Baseline in ADHD-RS-IV Total Score at Endpoint - LOCF (FAS)

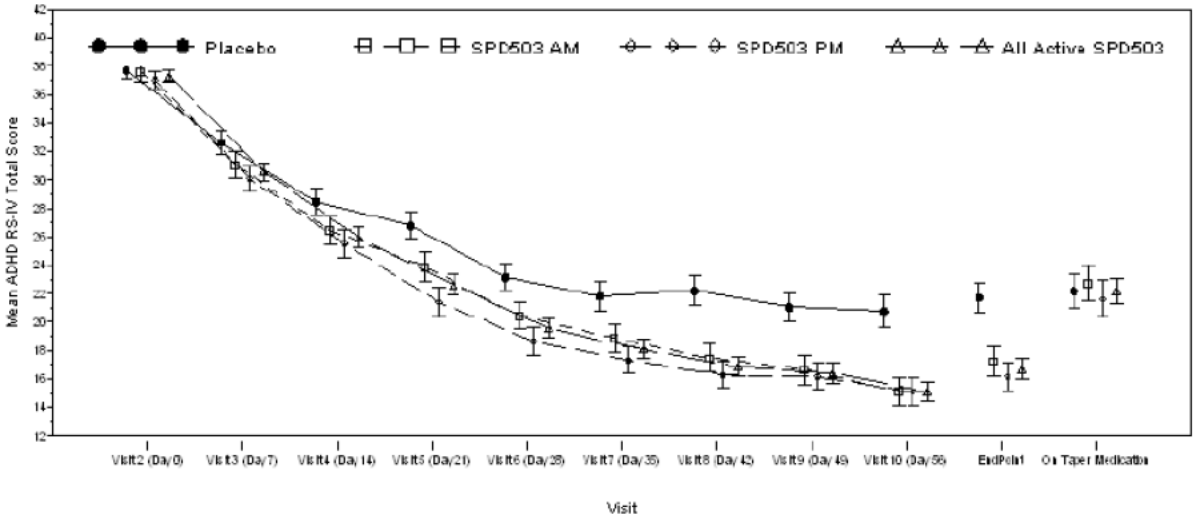
	Placebo+ Stimulant (N=153)	SPD503 AM+ Stimulant (N=150)	SPD503 PM+ Stimulant (N=152)	All SPD503+ Stimulant (N=302)
Baseline				
n	153	150	152	302
Mean (SD)	37.7 (7.75)	37.6 (8.13)	37.0 (7.65)	37.3 (7.89)
Endpoint[a]				
n	152	149	148	297
Mean (SD)	21.7 (12.98)	17.3 (12.86)	16.1 (11.84)	16.7 (12.35)
Change from Baseline				
Mean (SD)	-16.0 (11.77)	-20.4 (12.77)	-21.0 (12.39)	-20.7 (12.56)
LS mean	-15.9	-20.3	-21.2	-20.7
Placebo-adjusted difference[b]				
LS mean	NA	-4.5	-5.3	-4.9
(95% CI)	NA	(-7.5, -1.4)	(-8.3, -2.3)	(-7.2, -2.6)
Effect Size	NA	0.377	0.447	0.412
p-value		0.002[c]	<0.001[c]	<0.001[d]

- In the analysis of ADHD-RS-IV total score Over Time, Intuniv PM was consistently superior to placebo from Visit 4 (2 weeks on treatment, p=0.035) while Intuniv AM showed improvement over placebo from Visit 7 (5 weeks on treatment, p=0.026) (Figure 2).
- There was a significantly greater proportion of responders (response defined as a reduction from Baseline in the ADHD-RS-IV Total score of ≥25% at Endpoint) in the Intuniv PM group (83.1 %) compared with the placebo group (69.7 %) (p=0.007). However, the Intuniv AM group did not achieve significance compared with placebo (p=0.062).

3 See Dr. Ishida's Statistical Review and Evaluation dated 12/28/2010

However, the above mentioned variables were not part of the study primary endpoints and the validity of those findings cannot be ascertained.

Figure 2. Mean ADHD-RS-IV Total Score by Visit



ADHD-RS-IV total score analysis by weight-adjusted Dose

For the Intuniv AM dose at Endpoint, significant improvement from Baseline was shown for the 0.05-0.08 (p=0.007) and 0.09-0.12mg/kg subgroups (p=0.009) compared with placebo. For the Intuniv PM dose at Endpoint, significant improvement from Baseline was shown for the 0.01-0.04 (p=0.02) and 0.05-0.08mg/kg subgroups (p<0.001) compared with placebo. It is of note that no statistically significant improvement was shown in the 0.13-0.16 mg/kg subgroups in neither Intuniv treatment group (AM or PM). Because of the limitations of a dose-optimized design in evaluating dose response, no meaningful conclusions can be made from these results.

Analyses were also performed on a number of **secondary efficacy variables**. Both Intuniv treatment groups (AM and PM) had significantly greater improvement on the Hyperactivity/Impulsivity and Inattentive subscales of the ADHD-RS-IV, the CGI-I, the CGI-P (morning and evening assessments), the BSFQ (parent ratings only, no difference for subject ratings), the PGA, and the oppositional subscale of the CPRS-R:L compared with the placebo group.

At Endpoint, the Connor's Global Index-Parent (CGI-P) scores were significantly reduced in the Intuniv groups compared with the placebo group. For the CGI-P morning assessment, the change from baseline was -8.4 in the Intuniv AM group, -9.6 in the Intuniv PM group, and -6.9 in the placebo group. The CGI-P evening assessment showed similar results (-8.2, -8.8, and -6.0 for Intuniv AM, Intuniv PM, and placebo, respectively). Although the sponsor is proposing to include reference to these findings in

labeling, it is of note that the CGI-P was not a pre-specified key secondary efficacy variable.

6.1.3 **Crosscutting Issues**

Subgroup Analyses

Demographic Subgroups

The sponsor examined the effects of demographic variables on efficacy by conducting the exploratory analyses on demographic subgroups. Subgroups were age (6-12 and 13-17 years), gender (male and female), race (white and non-white), and psychostimulant type (methylphenidate or amphetamine). These analyses revealed the following relevant findings (Table 6 and 7):

- both children (6-12 years) and adolescents (13-17 years) in both the Intuniv AM and PM groups showed significant improvement from Baseline compared with placebo

- males in both Intuniv groups (AM and PM) had a significantly greater improvement from Baseline compared with males in the placebo group. This difference did not hold in the female subgroup. It is of note that the power to detect such difference could have been decreased in females since they represent only 28.4 % of participants

- non-white subjects receiving Intuniv (AM or PM) did not seem to show significant improvement from Baseline compared with non-white subjects receiving placebo

- subjects receiving Intuniv plus concomitant methylphenidate showed significant improvement from Baseline compared with subjects receiving placebo plus methylphenidate regardless of time of administration (AM or PM), while only subjects in the Intuniv PM group who were receiving concomitant amphetamine showed significantly greater improvement from Baseline compared with subjects receiving amphetamine alone.

Dose Response

Study 313 utilized a flexible dosing regimen. Therefore, no conclusions regarding dose-response for adjunctive therapy can be drawn from this study.

Key Secondary Variables

There were no pre-specified key secondary efficacy variables in this study.

Table 6: Study 313 Subgroup Analyses of ADHD-RS-IV Total Score			
	Placebo	**Intuniv AM**	**Intuniv PM**
Age 6-12 years			
N	123	114	124
Mean Baseline ADHD-RS-IV Total Score	38.6	38.2	37.6
LSM Change from baseline	-16.7	-20.3	-21.8
p-value	N/A	0.023	0.001
Age 13-17 years			
N	30	36	28
Mean Baseline ADHD-RS-IV Total Score	34.1	35.5	34.4
LSM Change from baseline	-12.3	-20.5	-18.6
p-value	N/A	0.003	0.033
Gender Male			
N	112	108	106
Mean Baseline ADHD-RS-IV Total Score	37.6	37.5	37.6
LSM Change from baseline	-15.7	-20.3	-21.2
p-value	N/A	0.004	0.001
Gender Female			
N	41	42	46
Mean Baseline ADHD-RS-IV Total Score	37.9	37.9	35.7
LSM Change from baseline	-16.4	-19.8	-20.8
p-value	N/A	0.199	0.091
Race White			
N	102	104	102
Mean Baseline ADHD-RS-IV Total Score	37.6	37.6	36.6
LSM Change from baseline	-14.2	-18.9	-20.9
p-value	N/A	0.003	<0.001
Race Non-White			
N	51	46	50
Mean Baseline ADHD-RS-IV Total Score	37.8	37.7	37.9
LSM Change from baseline	-19.3	-23.6	-21.4
p-value	N/A	0.085	0.389

Table 7: Study 313 Analysis of ADHD-RS-IV Total Score by Psychostimulant Type			
	Placebo	**Intuniv AM**	**Intuniv PM**
Concomitant Methylphenidate			
N	81	81	78
Mean Baseline ADHD-RS-IV Total Score	37.4	38.2	37.6
LSM Change from baseline	-15.9	-21.1	-21.2
p-value	N/A	0.006	0.005
Concomitant Amphetamine			
N	72	69	74
Mean Baseline ADHD-RS-IV Total Score	38.1	36.8	36.5
LSM Change from baseline	-15.9	-19.4	-21.0
p-value	N/A	0.083	0.011

Effect Size

The difference in the ADHD-RS-IV Total Score between adjunctive Intuniv and placebo was, on average, -4.9 points (95% confidence interval -7.2, -2.6). This effect size is smaller than placebo-adjusted changes in mean ADHD-RS scores from the positive monotherapy trials of Intuniv in ADHD which ranged from − 6.5 to − 10.1 points. This is consistent with the general expectation that gains from adjunctive treatment tend to be small compared to those achieved with monotherapy.

Long-Term Efficacy

Study 313 cannot provide any data to establish the safety and efficacy of Intuniv beyond 9 weeks as adjunctive therapy in patients with ADHD. An adequately designed study to produce data on the longer term use of Intuniv should be conducted and is included as a post marketing requirement in the Approval Letter for Intuniv as monotherapy for ADHD dated 09/02/2009.

Pediatric Development

Study 313 constitutes a post marketing requirement under the Pediatric Research Equity Act (PREA) as described in the Approval Letter for Intuniv as monotherapy for ADHD dated 09/02/2009. Other post marketing requirements under PREA include an efficacy and safety study of Intuniv in adolescents with ADHD, and a long-term maintenance study of efficacy and safety of Intuniv as monotherapy in children and adolescents with ADHD.

6.1.4 **Efficacy Conclusions Regarding the Adjunctive Therapy Claim**

Study 313 demonstrated a statistically significant effect produced by adding Intuniv, compared to placebo, to existing ADHD pharmacotherapy with psychostimulants as measured by the ADHD-RS-IV Total Score. The effect was seen in children (6-12 years) as well as in adolescents (13-17 years). This is an important finding since efficacy of Intuniv in adolescents with ADHD was not thoroughly determined in the Intuniv monotherapy trials.

7 Review of Safety

Safety Summary

No deaths occurred during the studies 313, 114 and 115. Five subjects reported SAEs (two cases of syncope, self-injurious behavior, poison ivy, and accidental ingestion by the sibling of a study subject). There were no safety signals with regard to TEAEs leading to discontinuation.

Intuniv plus psychostimulant was well tolerated and reasonably safe in the study population. No new safety signals emerged from the administration of Intuniv as adjunctive therapy to psychostimulants (amphetamine or methylphenidate) compared with Intuniv or psychostimulants administered alone. Furthermore, data from Study 313 suggest that the effect of the adjunctive therapy on heart rate, blood pressure and sedative events could be less marked than that observed with Intuniv or psychostimulants administered alone.

The most frequently reported Treatment-Emergent Adverse Events (TEAEs) was headache, which occurred in a higher proportion of subjects receiving Intuniv plus psychostimulant (21.2%) compared with subjects receiving placebo plus psychostimulant (13.1%). Other TEAEs occurring in a significant larger proportion of subjects in the Intuniv group compared with the placebo group were somnolence, fatigue, insomnia, abdominal pain, and dizziness. These TEAEs are generally known to be reported with Intuniv or psychostimulant treatment.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety review is focused on the safety of Intuniv as adjunctive therapy in ADHD pediatric patients as derived from study 313, where 455 patients comprised the safety population defined as all subjects who received at least 1 dose of any study drug during the study. In addition, information regarding adverse events at the more serious end of

the spectrum (deaths, non-fatal serious adverse events, and adverse events that led to dropout) from two drug interaction studies that were completed after the original ADHD application (studies 114 and 115) was examined. This population was used to assess comparative safety information.

7.1.2 Categorization of Adverse Events

Studies 313, 114 and 115 utilized MedDRA coding for categorization of adverse events. The categorization of investigator-reported adverse events under MedDRA preferred terms in all 3 reviewed studies was audited by this reviewer, as described in section 3.1. The categorization was deemed to be acceptable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

There is only one trial of Intuniv as adjunctive treatment in ADHD. Therefore, the issue of study pooling is a moot point for this supplement.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As of the last safety update (7/28/2010), 1327 subjects have been exposed to Intuniv in completed monotherapy clinical studies, including 935 pediatric subjects with ADHD and 392 healthy volunteers. Regarding adjunctive therapy trials, 75 pediatric subjects with ADHD received Intuniv as adjunctive therapy to psychostimulants in an open-label study (SPD503-205). Fifty-four subjects from Study SPD503-205 entered an open-label, long-term extension study (SPD503-305), 42 of who were exposed to Intuniv for at least 6 months (183 days) across the 2 studies. Twenty-three of these subjects completed Study SPD503-305 through 2 years.

In addition, 382 subjects were exposed to Intuniv as adjunctive therapy to psychostimulants in Studies 313, 114 and 115, including 302 pediatric patients with ADHD and 80 healthy adult volunteers. There has been no further clinical trial with coadministration of Intuniv and psychostimulants since completion of Studies 114, 115, and 313.

In summary, as of 7/28/2010, 1784 subjects have been exposed to Intuniv in completed monotherapy and adjunctive therapy clinical studies, including 1312 pediatric subjects with ADHD and 472 healthy volunteers. The highest studied dose in clinical trials was 4 mg/day as monotherapy or as adjunctive therapy to psychostimulants. In conclusion,

the overall exposure to Intuniv is deemed to be acceptable to support the adjunctive ADHD indication.

7.2.2 Explorations for Dose Response

Study 313 was a flexible dose trial. Therefore, dose-response for adverse events could not be evaluated in this trial.

7.2.3 Special Animal and/or In Vitro Testing

Two additional nonclinical studies in the neonatal/juvenile rat have been conducted to support the use of guanfacine as adjunctive therapy to a stimulant (methylphenidate). The data from these co-administration studies do not alter the established risk:benefit profile for guanfacine, supporting its use as adjunctive therapy to stimulants in the treatment of ADHD in adolescents and children.

7.2.4 Routine Clinical Testing

Safety assessments included weekly vital signs, clinical monitoring of adverse events and concomitant medications; physical examination (Visits 1 and 10); pregnancy tests (Visits 1, 2, and 12); hematology, clinical chemistry, urinalysis, height, and weight (Visits 1, 2, and 10); and ECGs (Visits 2, 4, 6, and 8). Suicidal thoughts and behaviors (e.g., using the Columbia-Suicide Severity Rating Scale) were not systematically monitored during study 313, as is now required for all clinical trials of psychopharmacological agents. Otherwise, clinical safety monitoring was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolism, clearance, and drug-drug interactions for Intuniv have already been characterized and are described in Intuniv labeling. This submission includes two drug interaction studies: one with CONCERTA (Study 114), and the other with VYVANSE (Study 115). These studies concluded that there are no drug interactions between guanfacine and methylphenidate following co-administration of 4 mg of Intuniv and 36 mg of CONCERTA, and between guanfacine and lisdexamfetamine following co-administration of 4 mg of Intuniv and 50 mg of VYVANSE.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

In general, monitoring for important adverse events seen with other drugs in the class of selective α2-adrenergic receptor agonists, such as orthostasis, hypotension, bradycardia, and weight gain, was adequate.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during Studies 313, 114 or 115. Furthermore, there were no deaths in the two pivotal placebo-controlled studies (Studies 301 and 304), the long-term open-label studies (Studies 303 and 305), or the phase 1/2 studies submitted with the initial application for approval of Intuniv as monotherapy for ADHD.

7.3.2 Nonfatal Serious Adverse Events

For each of the 3 studies examined, a serious adverse event was defined as any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an Important Medical Event - defined as events that may not be immediately life threatening, result in death or hospitalization, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other serious outcomes

Four non-fatal serious adverse events were reported among the Intuniv-treated patients in Study 313:

1) A 9-year-old Hispanic boy, who was receiving Concerta 54 mg and Intuniv 3mg PM, had syncope preceded by nausea and vomiting. No dose adjustments were made and the subject completed the study.
2) A 12-year old Hispanic boy, who was receiving Adderall XR 20 mg and Intuniv 4 mg AM, had an episode of self-injurious behavior, worsening aggression, and homicidal ideation (the patient threatened his sister with a knife). The subject had a history of family dysfunction and similar behaviors prior to entering the study. The patient was hospitalized and discontinued from the study.
3) A 10-year-old Caucasian boy, who was receiving Vyvanse 40 mg and Intuniv 1 mg PM had poison ivy. The subject was discontinued from the study.
4) The 2-year-old brother of a study participant accidentally ingested eight 1mg tablets of Intuniv. The subject was taken to the emergency room and given activated charcoal. He was observed and released. No symptoms were reported.

In this reviewer's opinion, SAE # 3 and SAE # 4 could not be reasonably attributed to Intuniv therapy.

In Study 114, one subject had an SAE of orthostatic syncope: a 22-year-old Hispanic man with no relevant medical history received a single oral dose of Intuniv 4mg. Two hours later, the subject rose for a standing blood pressure reading, became lightheaded and fainted. He regained consciousness spontaneously and in less than 1 minute. His urine drug screen was negative, and he was not taking concomitant medications. A supine blood pressure of 101/59mmHg and pulse of 52bpm were obtained approximately 4 minutes after his recovery. The subject completed the study.

No serious adverse events were reported in Study 115 or among the placebo-treated patients in all 3 reviewed studies.

7.3.3 Dropouts and/or Discontinuations

A total of **461 subjects were randomized** into the study; 6 subjects did not receive study drug. The **safety population** then consisted of **455 patients** (153 placebo patients, 150 patients on Intuniv AM and 152 patients on Intuniv PM). A total of 378 (82.0%) subjects completed the study through Visit 12 (final follow-up visit). A total of **83 patients dropped out** of the study at any time point before visit 12 (Table 8).
For subjects who "refused further study participation," the sponsor did an assessment of the subject including adverse events and vital signs and additional clarifications were obtained from the sites. No identifiable safety reasons for them to leave the study were found. In addition, the sponsor assessed subjects terminating for “lost to follow-up” including a review for adverse events present near the time of last visit as well as vital sign measurements, failing to find any identifiable safety reasons for them to leave the study. Eleven (2.4%) subjects discontinued because of an adverse event. The adverse events leading to discontinuation included fatigue, pharyngitis, poison ivy, decreased weight, dizziness, somnolence, aggression and orthostatic hypotension.

More patients in the Intuniv AM (n = 4) and Intuniv PM (n = 6) groups dropped out due to an adverse event compared with the placebo group (n = 1). Also, non-adherence/non-compliance was a more frequent drop-out cause in the Intuniv AM (n = 8) and Intuniv PM (n = 6) groups compared with the placebo group (n = 3). Conversely, refusal to further participation was more common in the placebo group (n = 11) than in the Intuniv AM (n = 7) and Intuniv PM (n = 8) groups.

However, these differences are considered unlikely to affect the overall results of the study. No other clinically important differences in subject disposition across the treatment groups were detected.

I also examined reasons for early termination in studies 114 and 115 in order to identify any clinically significant, unexpected adverse events. No subject dropped out of these studies due to adverse events.

Table 8 Summary of Subject Disposition

	Placebo + Stimulant (N = 154)	SPD503 AM + Stimulant (N = 154)	SPD503 PM + Stimulant (N = 153)	Overall SPD503 + Stimulant (N = 307)	Total (N = 461)
Subjects					
Randomized	154 (100.0)	154 (100.0)	153 (100.0)	307 (100.0)	461 (100.0)
Safety Population[a]	153 (99.4)	150 (97.4)	152 (99.3)	302 (98.4)	455 (98.7)
Full Analysis Set[a]	153 (99.4)	150 (97.4)	152 (99.3)	302 (98.4)	455 (98.7)
Completed through Visit 10[b]	131 (85.1)	125 (81.2)	130 (85.0)	255 (83.1)	386 (83.7)
Study Completers[c]	129 (83.8)	121 (78.6)	128 (83.7)	249 (81.1)	378 (82.0)
Early Termination[d]	25 (16.2)	33 (21.4)	25 (16.3)	58 (18.9)	83 (18.0)
Reasons for Early Termination					
Adverse Event	1 (0.6)	4 (2.6)	6 (3.9)	10 (3.3)	11 (2.4)
Protocol non-adherence/ subject non-compliance	3 (1.9)	8 (5.2)	6 (3.9)	14 (4.6)	17 (3.7)
Refused further participation in the study	11 (7.1)	7 (4.5)	8 (5.2)	15 (4.9)	26 (5.6)
At or Before Visit 10	10 (6.4)	7 (4.5)	7 (4.5)	14 (4.6)	24 (5.2)
After Visit 10	1 (0.7)	0 (0.0)	1 (0.7)	1 (0.3)	2 (0.4)
Lost to follow-up	5 (3.2)	9 (5.8)	3 (2.0)	12 (3.9)	17 (3.7)
At or Before Visit 10	5 (3.2)	8 (5.1)	2 (1.3)	10 (3.3)	15 (3.3)
After Visit 10	0 (0.0)	1 (0.7)	1 (0.7)	2 (0.7)	2 (0.4)
Lack of efficacy	5 (3.2)	3 (1.9)	2 (1.3)	5 (1.6)	10 (2.2)
Other	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.7)	2 (0.4)

[a] Includes all subjects who received at least 1 dose of any study drug during this study.
[b] Visit 10 was the last visit before taper and is considered the Endpoint for statistical purposes, provided that subjects were still on study drug.
[c] Includes subjects who completed through Visit 12 (final follow-up visit).
[d] Early termination includes any subject who did not complete all visits through Visit 12.

Note: Corresponds to Table 2 in Study 313 report document

7.3.4 Significant Adverse Events

No other significant adverse events were identified in this review.

7.3.5 Submission Specific Primary Safety Concerns

No major submission specific safety concerns were found.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-Emergent Adverse Events are defined as adverse events which start or worsen during the period between the day of a subject's first dose of investigational product and the third day (inclusive) after their treatment is stopped. Treatment-emergent adverse events occurring in at least 2% of patients in study 313 (safety population) are displayed in Table 9 below.

Table 9: Percentage of Patients Experiencing Common (≥ 2%) Adverse Reactions in Study 313[4]

Adverse Reaction Term	Placebo (N=153)	All Doses of INTUNIV™ (N=302)[a]
Headache	13%	21%
Somnolence[b]	7%	18%
Insomnia[c]	6%	13%
Fatigue	3%	10%
Abdominal pain	3%	10%
Dizziness	4%	8%
Decreased appetite	4%	7%
Nausea	3%	5%
Diarrhea	1%	4%
Hypotension[d]	0%	3%
Affect lability	1%	2%
Bradycardia	0%	2%
Constipation	0%	2%
Dizziness postural	0%	2%
Dry mouth	0%	2%

a: The morning and evening dose groups of INTUNIV™ are combined.

b: The somnolence term includes somnolence, sedation, and hypersomnia.

c: The insomnia term includes insomnia, initial insomnia, and middle insomnia.

d: The Hypotension term includes hypotension and orthostatic hypotension

4 All percentages are rounded to the nearest whole number. Those events for which the placebo group reporting rate was equal to or greater than that in the Intuniv group are not included in this table. These events were: upper respiratory tract infection, nasopharyngitis, pharyngolaryngeal pain, pyrexia, irritability and cough.

The most frequently reported TEAE, headache, occurred in 21 % of subjects receiving Intuniv plus psychostimulant and 13 % of subjects receiving placebo plus psychostimulant. Other TEAEs reported more frequently in subjects receiving Intuniv plus psychostimulant compared with placebo plus psychostimulant were somnolence, insomnia, fatigue, abdominal pain, and dizziness.

There were no clinically meaningful differences between Intuniv administered in the morning and in the evening in the proportion of all TEAEs, serious TEAEs, TEAEs leading to discontinuation, or TEAEs leading to dose reduction. Severe TEAEs were reported in 6.6% of the Intuniv PM group compared with 2.0% of the Intuniv AM group. Fatigue was the only severe TEAE reported in more than 1 subject; both events were reported by subjects in the Intuniv PM group. Given the small number of subjects and adverse events involved, and the fact that no other differences were found between the Intuniv AM and PM groups, it is difficult to draw meaningful safety conclusions from this minor disparity.

There were no clear safety signals for TEAEs in subjects receiving Intuniv plus amphetamine compared with subjects receiving Intuniv plus methylphenidate. The differences were generally consistent with the known safety profile of either amphetamines or methylphenidate. TEAEs by age, sex and race are discussed in Section 7.5.3 below.

7.4.2 Laboratory Findings

In study 313, laboratory testing was done at study screening (Visit 1), at randomization (Visit 2), at endpoint (Visit 10) and at the final follow-up visit (Visit 12). There were no clinically important differences between the treatment groups regarding **clinical hematology and urinalysis** results in the mean changes from Baseline at Endpoint. In addition, there were no clinically meaningful differences between the Intuniv AM and PM groups with regard to clinical hematology and urinalysis results. Regarding the **clinical chemistry** results, there were significant changes from baseline at endpoint for the following parameters: albumin and aspartate aminotransferase (Table 10). Currently, the potential clinical significance of these mean changes is unclear.

Table 10 Clinical Chemistry Results for Which ≥5% Subjects in Any Group Had a Shift from Normal at Baseline to Low or High At Endpoint (Safety Population)

	Placebo	Intuniv AM	Intuniv PM
Parameter change	**N (%)**	**N (%)**	**N (%)**
Albumin (Normal to High)	14 (9.2)	19 (12.7)	26 (17.1)
Aspartate aminotransferase (Normal to Low)	4 (2.6)	10 (6.7)	9 (5.9)

There were no dropouts due to laboratory abnormalities among Intuniv-treated patients in this study.

7.4.3 Vital Signs

At Endpoint, subjects receiving Intuniv plus psychostimulant had a mean decrease from Baseline in supine **pulse, systolic and diastolic blood pressure** (-5.6 bpm, -2.2 mmHg, and -1.2 mmHg, respectively) compared with subjects receiving placebo plus psychostimulant (2.1 bpm, -0.6 mmHg, and -0.0 mmHg, respectively). Similar results were shown for standing pulse, systolic and diastolic blood pressure. There were no clinically meaningful differences between the Intuniv AM and PM groups regarding changes in pulse, systolic and diastolic blood pressure at Endpoint.

In the outlier analysis, subjects in the Intuniv group were more likely than subjects in the placebo group to have a supine pulse ≤50bpm at any time during the study (4 % and 0 %, respectively). There were fewer outliers of supine pulse ≥100bpm in those receiving Intuniv compared with subjects receiving placebo. Regarding postural orthostatic blood pressure, a decrease of ≥25mmHg in systolic blood pressure was reported by 4.7% of subjects in the Intuniv group and 0.7% of subjects in the placebo group throughout the study.

These changes in pulse and blood pressure are consistent with the known effects of Intuniv. Also, these results regarding changes in pulse and blood pressure when Intuniv is used concomitantly with a psychostimulant suggests a potential offsetting of the increase in pulse and blood pressure observed when psychostimulants are administered alone. However, no definite conclusions can be reached in that regard. It is of note that supine pulse, systolic and diastolic blood pressure in study 313 tended to reach their lowest point around end of dose optimization and then began to return to Baseline during maintenance.

There were no meaningful differences between subjects receiving Intuniv plus psychostimulant and subjects receiving placebo plus psychostimulant for **respiratory rate, temperature, or height**. At Endpoint, mean **weight** was higher for subjects receiving Intuniv plus psychostimulant compared with subjects receiving placebo plus psychostimulant (change from Baseline of 1.31 and 0.90 pounds, respectively). In the outlier analysis, throughout the study, 7.1% of subjects receiving Intuniv plus psychostimulant reported an increase in body weight from Baseline of ≥7% compared with 2.1% of subjects receiving placebo plus psychostimulant. There were no differences in mean weight change from Baseline at Endpoint between the Intuniv AM and PM groups.

Overall, these findings are consistent with data from the ADHD monotherapy trials and with the safety profile described in the Intuniv labeling.

7.4.4 Electrocardiograms (ECGs)

No subject in any of the treatment groups had an uncorrected QT interval ≥480msec, a QTcF ≥480msec, or a QTcB interval ≥500msec. No patient dropped out of study 313 due to an ECG abnormality. At Endpoint, subjects receiving Intuniv plus psychostimulant had a larger mean change from Baseline in heart rate, RR interval, and uncorrected QT interval (-9.8, 105.2, and 18.7, respectively) compared with subjects receiving placebo plus psychostimulant (-0.3, 4.9, and 2.4, respectively). However, there were no clinically significant differences for QTcF and QTcB between the Intuniv and placebo groups. Table 11 below displays the mean change from Baseline to Endpoint in the ECG parameters.

In the analysis by actual dose, there was a dose-related trend for mean change from Baseline in heart rate, RR interval, and uncorrected QT interval. No evidence of dose-related trends was found for other ECG parameters.
All these ECG findings are consistent with the known effects of Intuniv and with the current Intuniv labeling.

Table 11 Mean Change from Baseline to Endpoint in ECG Parameters (Safety Population)

	Placebo+ Stimulant (N=153)	SPD503 AM+ Stimulant (N=150)	SPD503 PM+ Stimulant (N=152)	All SPD503+ Stimulant (N=302)
PR Interval (msec)				
Mean change (SD)	-1.1 (10.91)	-0.6 (10.30)	0.7 (16.25)	0.1 (13.61)
Heart rate (bpm)				
Mean change (SD)	-0.3 (11.38)	-11.0 (13.26)	-8.7 (11.62)	-9.8 (12.50)
RR Interval (msec)				
Mean change (SD)	4.9 (103.25)	115.9 (141.49)	94.6 (131.08)	105.2 (136.56)
QRS Interval (msec)				
Mean change (SD)	-0.0 (5.39)	0.2 (4.87)	-0.0 (5.39)	0.1 (5.13)
QT Interval (msec)				
Mean change (SD)	2.4 (21.64)	20.2 (25.55)	17.2 (23.66)	18.7 (24.63)
QTcF (msec)				
Mean change (SD)	2.0 (13.52)	2.8 (14.81)	3.1 (14.09)	3.0 (14.43)
QTcB (msec)				
Mean change (SD)	1.7 (16.19)	-6.9 (18.87)	-4.7 (17.78)	-5.8 (18.34)

Note: Corresponds to Table 35 in Study 313 report document

7.4.5 Special Safety Studies/Clinical Trials

No special clinical safety studies were conducted to support this supplement.

7.4.6 Immunogenicity

No evaluations of immunogenicity were reported under this supplement.
Rash was reported by 7 (2.3 %) subjects receiving Intuniv plus psychostimulant and 1 (0.7%) subject receiving placebo plus psychostimulant. All cases of rash were mild to moderate in severity. Two of the 7 cases of rash that occurred in Intuniv-treated subjects had other specific causes (contact dermatitis from sunblock and rash from football helmet strap). These results do not suggest hypersensitivity reactions associated with the administration of Intuniv.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Study 313 utilized a flexible dosing regimen. Therefore, no conclusions regarding dose-response for adjunctive therapy can be drawn from this study. However, data suggest a possible dose-related trend for fatigue, decrease in pulse and mean change from baseline in heart rate, RR interval, and uncorrected QT interval. The remaining individual TEAE data suggest no consistent dose-related trends between the frequency of TEAEs and the actual dose received at the time of TEAE onset. These data are consistent with the known effects of Intuniv.

TEAEs requiring dose reductions occurred in 44 (14.6%) subjects receiving Intuniv plus psychostimulant and 13 (8.5%) subjects receiving placebo plus psychostimulant. . Similar proportions of subjects had a TEAE requiring a dose reduction in the Intuniv dose groups (15.3% in AM and 13.8% in PM). TEAEs requiring dose reductions more frequently in the Intuniv-treated patients than in the placebo-treated patients were somnolence, fatigue, insomnia, irritability, dizziness, orthostatic hypotension, sedation, decreased appetite, abdominal pain, headache, and nightmare.

7.5.2 Time Dependency for Adverse Events

Time to event and duration of event analyses were conducted for the sedative adverse events (somnolence, sedation, and hypersomnia). This and other analyses regarding sedative events are described in Section 7.7.2 below

7.5.3 Drug-Demographic Interactions

Age

There were no clinically meaningful differences between children and adolescents regarding severe TEAEs, TEAEs leading to discontinuation, or TEAEs leading to dose reduction. Among children, TEAEs were reported in 79.0% of subjects receiving

Intuniv plus psychostimulant and in 61.0% of subjects receiving placebo plus psychostimulant. Among adolescents, TEAEs were reported in 68.8% of subjects in the Intuniv group and in 73.3% of subjects in the placebo group. In general, children reported a larger variety of events than adolescents. This difference could be related to the larger proportion of children compared with adolescents enrolled in the study.

In the outlier analysis of vital signs, children (6-12 years) in the Intuniv group were more likely than children in the placebo group to have low systolic (<90 mmHg) or diastolic (<50 mmHg) blood pressure (27.4 % and 17.9 % vs.8.9 % and 4.1 %, respectively). Among adolescents (13-17 years), more subjects receiving Intuniv had low systolic (<100 mmHg) or diastolic (<60 mmHg) blood pressure (44.4 % and 66.7 %, respectively) than subjects receiving placebo (26.7 % and 33.3 %, respectively). These data are consistent with known effects of Intuniv and do not reveal a clinically meaningful difference between age groups. In addition, assessment of the proportions of subjects reporting individual TEAEs suggests no clear safety signal for TEAEs in children compared with adolescents in the Intuniv group as a whole or for morning and evening doses.

Gender and Race

In general, boys and whites reported a larger variety of events than girls. Similar to the difference between age groups, this could be a factor of the larger proportion of boys and whites enrolled in the study. Assessment of the proportions of subjects reporting individual TEAEs suggest no clear safety signals for TEAEs in boys and whites compared with girls and non-white patients, respectively.

7.5.4 Drug-Disease Interactions

No studies examining drug-disease interactions were reported under this supplement.

7.5.5 Drug-Drug Interactions

This submission includes two drug interaction studies: one with CONCERTA (Study 114), and the other with VYVANSE (Study 115). The two drug interaction studies concluded that there are no drug interactions between guanfacine and methylphenidate following co-administration of 4 mg of Intuniv and 36 mg of CONCERTA, and between guanfacine and lisdexamfetamine following co-administration of 4 mg of Intuniv and 50 mg of VYVANSE. Refer to section 4.3.3.

7.6 Additional Safety Evaluations

7.6.1 Human Reproduction and Pregnancy Data

No adequate studies of the effect of Intuniv on pregnancy in humans are available.

7.6.2 Pediatrics and Assessment of Effects on Growth

No studies examining the effect of Intuniv on growth were reported under this supplement. However, analysis of vital signs data from Study 313 revealed no meaningful differences between subjects receiving Intuniv plus psychostimulant and subjects receiving placebo plus psychostimulant for height. At Endpoint, mean weight was higher for subjects in the Intuniv group compared with subjects in the placebo group (change from Baseline of 1.31 and 0.90 pounds, respectively). In the outlier analysis, throughout the study, 7.1% of subjects receiving Intuniv plus psychostimulant reported an increase in body weight from Baseline of ≥7% compared with 2.1% of subjects receiving placebo plus psychostimulant. There were no differences in mean weight change from Baseline at Endpoint between the Intuniv AM and PM groups. Overall, these findings are consistent with data from the ADHD monotherapy trials and with the safety profile described in the Intuniv labeling.

7.6.2 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No studies examining drug abuse potential were reported under this supplement. According to current labeling, Intuniv is not a controlled substance and has no known potential for abuse or dependence.

The highest dose studied in the Intuniv clinical development program was 4mg/day in monotherapy trials and in trials of Intuniv as adjunctive therapy to a psychostimulant. There was one case of accidental overdose reported in study 313. The 2-year-old brother of a study participant accidentally ingested eight 1mg tablets of Intuniv. The subject was taken to the emergency room and given activated charcoal. He was observed and released. No symptoms were reported.

7.7 Additional Submissions / Safety Issues

A 4-month Safety Update was submitted to this NDA on 8/27/10. This document summarizes additional safety information from clinical studies, marketed product experience, and published literature obtained between 28 Jul 2009 and 28 Jul 2010. Two completed bioequivalence studies (SPD503-119, SPD503-120) and 2 ongoing placebo-controlled efficacy studies (SPD503-314 and SPD503-315) were reported. The safety data of all four studies were examined with a focus on SAEs and discontinuations as the result of an adverse event.

Studies SPD503-119 and SPD503-120 were crossover bioequivalence studies in healthy volunteers comparing 2 oral formulations of Intuniv 2mg (Study 119) and 4 mg (Study 120) tablets manufactured at different facilities. Intuniv was well-tolerated in both studies. The most frequently reported TEAE was headache. There were no SAEs and no clinically significant changes in laboratory values or vital sign, physical examination, or ECG assessments. One subject in Study 120 experienced an AE leading to discontinuation (otitis media).

Study SPD503-314 is an ongoing randomized, placebo-controlled, dose optimization study designed to evaluate the efficacy and tolerability of Intuniv (1, 2, 3, and 4mg/day) administered either in the morning or evening in children aged 6-12 years with a diagnosis of ADHD. As of 28 Jul 2010, 340 subjects had been randomized in the study and had received blinded investigational product. No deaths have been reported. Three subjects have experienced SAEs (2 cases of syncope and 1 case of suicidal ideation and self-injurious behavior) which led to discontinuation from the study. As of the 28 Jul 2010 cut-off date, 16 subjects have experienced 1 or more AEs that led to early discontinuation from the study. These included sedation (4 reports), tiredness (2 reports), daytime drowsiness (1 report), somnolence (1 report), hypotension (1 report), weight gain (1 report), rash (1 report), syncope (2 reports, both SAEs), self-injurious behavior (1 report, SAE), suicidal ideation (1 report, SAE), and suicidal thoughts (1 non-serious report).

Study SPD503-315 is a placebo-controlled, randomized, withdrawal study designed to assess the long-term maintenance of efficacy and safety in children and adolescents aged 6-17 years with ADHD. As of 28 Jul 2010, 85 subjects had been enrolled into the open-label phase of the study and have received Intuniv. No subjects have been randomized into the placebo-controlled, randomized-withdrawal phase of the study yet. No deaths or SAEs have been reported during the study. As of the cut-off date, 1 subject has discontinued as the result of a TEAE (headache). No other TEAEs leading to early discontinuation have been reported.

The analysis of safety data from the four studies contained in this safety update did not reveal any new safety signals for Intuniv. The overall benefit-risk assessment of Intuniv remains unchanged from the original NDA and current efficacy supplement.

7.7.1 Suicidality and Other Psychiatric Adverse Events

Suicidal thoughts and behaviors (e.g., using the Columbia-Suicide Severity Rating Scale) were not systematically monitored during study 313, as is now required for all clinical trials of psychopharmacological agents. An assessment of events of suicidality was made by searching the clinical database for the following items: "accident, asphyxiation, attempt, burn, cut, drown, firearm, gas, gun, hang, hung, immolate, injur, jump, monoxide, mutilate, overdos, poison, self damage, self harm, self inflict, self injur,

shoot, slash, suffocation, suic." One event was assessed as a possible suicidal event: self-injurious behavior reported by 1 (0.3%) subject in the Intuniv AM group and no subjects in the placebo group. The case of self-injurious behavior was considered a SAE and is described in Section 7.3.2 above (SAE # 2).

Psychiatric adverse events were reported in 7 (2.3%) subjects receiving Intuniv plus psychostimulant and 5 (3.3%) subjects receiving placebo plus psychostimulant, with no differences between the Intuniv AM (2.0%) and PM (2.6%) groups. No safety signals for psychiatric TEAEs were detected. A summary of psychiatric TEAEs are presented in table 12 below.

Table 12 Summary of Psychiatric Treatment-emergent Adverse Events by System Organ Class and Preferred Term and by Randomized Treatment Group (Safety Population)

System-organ Class Preferred Term	Placebo+ Stimulant (N=153)	SPD503 AM+ Stimulant (N=150)	SPD503 PM+ Stimulant (N=152)	All SPD503+ Stimulant (N=302)
Total Psychiatric Adverse Events	5 (3.3)	3 (2.0)	4 (2.6)	7 (2.3)
Aggression and violent behavior	5 (3.3)	3 (2.0)	3 (2.0)	6 (2.0)
Aggression	3 (2.0)	3 (2.0)	2 (1.3)	5 (1.7)
Anger	1 (0.7)	0	0	0
Negativism	2 (1.3)	0	1 (0.7)	1 (0.3)
Psychosis/Mania	0	0	1 (0.7)	1 (0.3)
Psychotic Disorder	0	0	1 (0.7)	1 (0.3)
Suicidal ideation and behavior	0	1 (0.7)	0	1 (0.3)
Self injurious behaviour	0	1 (0.7)	0	1 (0.3)

Note: Corresponds to Table 26 in Study 313 report document

7.7.2 Sedative events

The analysis of sedative events included the following preferred terms: somnolence, sedation, and hypersomnia. Sedative events were reported in 18.2% of subjects in the Intuniv group and in 6.5% of subjects in the placebo group. In the monotherapy trials, sedative events were reported by 38 % of Intuniv-treated patients and in 12 % of placebo-treated patients. Therefore, these new data seem to indicate a lower frequency of sedative adverse events when Intuniv is administered as adjunctive therapy to psychostimulants than when it is used alone.

One subject receiving Intuniv plus psychostimulant discontinued the study due to a treatment-emergent sedative event and 13 (4.3%) subjects receiving Intuniv plus psychostimulant had a dose reduction because of a treatment-emergent sedative event. Nine of these patients were receiving Intuniv 3 or 4 mg/day. Dose reduction because of a sedative event occurred in 25.8% of subjects in the Intuniv AM group and 15.2% of subjects in the Intuniv PM group. No subject receiving placebo plus psychostimulant

discontinued because of a sedative event or had a dose reduction because of a sedative event. The majority of sedative events occurred during titration and resolved during the dose maintenance phase. There were no new reports of sedative events at Weeks 8 or 9 (Visits 9 or 10).

Sedation and somnolence are already discussed under WARNINGS AND PRECAUTIONS in the current Intuniv labeling. No new safety signal regarding sedative events was found.

8 Postmarket Experience

Intuniv was approved for the treatment of ADHD in children and adolescents aged 6 -17 years on September 2, 2009. Intuniv is currently only marketed in the US.
According to Dr. Mehta's review from the Office of Surveillance and Epidemiology (OSE) on use data, 265,214 patients aged 6-12 years and 113,825 patients aged 13-17 years received a prescription for a guanfacine product (Intuniv, generic guanfacine HCL, or Tenex) in the outpatient setting in the 13-month period between September 2009 and September 2010. Intuniv accounted for 49 % of these prescriptions[5].

Dr. Salaam from OSE conducted a review of post-marketing adverse event reports associated with the use of Intuniv in children (age 0-16 years) and adults (17 years and greater) in the AERS database from September 2, 2009 to September 30, 2010. That review identified 47 cases of SAEs in pediatric patients, including two fatal cases: sudden unexpected death in epilepsy (1) and "poly-drug toxicity" (1). Both fatal cases were confounded and neither case was attributable to guanfacine XR based on the medical examiner's reports. Based on the OSE review of the 45 non-fatal cases, the pediatric safety profile is consistent with the present guanfacine XR label. Syncope was the most frequently reported adverse event among the non-fatal serious pediatric cases.

The cardiovascular and gastrointestinal events were consistent with the present guanfacine XR label. The neurological events were either labeled or confounded unlabeled events. The psychiatric events included two cases of suicidal ideation. In one case, the event resolved and guanfacine XR was continuing; in the second case, external stressors may have contributed to the adverse events. Other psychiatric reports included two cases of intentional overdose confounded by inappropriate medication administration, two cases of aggression confounded by concomitant medications also labeled for aggression, and one case of mania with a positive dechallenge.[6]

5 See Dr. Mehta's review from the Office of Surveillance and Epidemiology dated 12/17/2010
6 See Dr. Salaam's review from the Office of Surveillance and Epidemiology dated 12/22/2010

9 Appendices

9.1 Literature Review/References

The sponsor conducted a literature search covering the period from 22 Jul 2009 to 15 Jul 2010. The strategy used the term “guanfacine” in the title, abstract, or descriptor in the MEDLINE and EMBASE databases. Physician review of the abstracts of clinical articles from the resulting list identified 9 relevant publications in the various searches. The full text of these articles underwent physician review. Of these, 5 articles were publications of studies submitted in the original NDA or in the resubmission. The 4 remaining articles were found to provide no new safety information relating to the use of guanfacine.

9.2 Labeling Recommendations

I will provide my complete labeling recommendations to the Review Team in a separate Word document using track changes. A summary of major labeling recommendations is presented below. In general, other labeling changes proposed by the sponsor are deemed acceptable.

HIGHLIGHTS

Section INDICATIONS AND USAGE should include the indication of Intuniv for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as adjunctive therapy to stimulant medications.

FULL PRESCRIBING INFORMATION

- The reference to the use of Intuniv “in combination with psychostimulants” and the Intuniv “combination trial” should be replaced throughout the label with the reference to Intuniv “as adjunctive therapy to psychostimulants” and the Intuniv “adjunctive trial”.

- Section 1, INDICATIONS AND USAGE, should include the indication of Intuniv for the treatment of ADHD as adjunctive therapy to stimulant medications.

- In section 6, ADVERSE REACTIONS, Table 3 should be modified to include the combined frequency of related adverse reactions (e.g. hypotension and orthostatic hypotension should be combined under the single term hypotension).

- In section 14, CLINICAL STUDIES, the description of the adjunctive trial should be modified to reflect the study design including a 5-week dose-optimization period and

a 3-week maintenance period, and the study primary endpoint as mean change from baseline to endpoint at the end of week 8 in ADHD-RS-IV total scores. In addition, references to the use of the Connor's Global Index-Parent (CGI-P) scale in the adjunctive trial should be removed.

Despite the addition of aggressive behavioral changes and mania to the guanfacine immediate-release label (PRECAUTIONS/Pediatric Use section), Dr. Salaam from OSE does not think that the data supports the addition of these adverse events to the guanfacine XR label at this time.

9.3 Advisory Committee Meeting

It was decided that this supplement would not be presented to the Psychopharmacologic Drugs Advisory Committee.

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

/s/

SILVANA BORGES
01/19/2011

NI A KHIN
01/19/2011
See also CDTL memo for additional comments.