Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Guanfacine hydrochloride

Proprietary Product Name: Intuniv

Sponsor: Shire Australia Pty Limited

Date of first round report: 30 August 2016
Date of second round report: 6 March 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS-IV	Attention Deficit Hyperactivity Disorder – Rating Scale, Version IV
AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BP	Blood pressure
bpm	Beats per minute
BPRS-C	Brief Psychiatric Rating Scale for Children
BRIEF	Behavior Rating Inventory of Executive Function
BSFQ	Before-school Functioning Questionnaire (Wil-Hammer)
CANTAB	Cambridge Neuropsychological Test Automated Battery
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression – Improvement
CGI-P	Connor's Global Index - Parent
CGI-S	Clinical Global Impression – Severity of illness
CHQ	Child Health Questionnaire
CHQ-PF50	Child Health Questionnaire – Parent Form
CHQ-CF87	Child Health Questionnaire – Child Form
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CPRS-R	Connors' Parent Rating Scale – Revised: Short Form

Abbreviation	Meaning
CPRS-R:L	Conners' Parent Rating Scale – Revised: Long Form
CRT	Choice Reaction Time in the Cambridge Neuropsychological Test Automated Battery
CSHQ	Children's Sleep Habits Questionnaire
C-SSRS	Columbia-Suicide Severity Rating Scale
CTRS-R	Connors' Teacher Rating Scale – Revised: Short Form
DAE	Discontinuation due to Adverse Event
DBP	Diastolic Blood Pressure
DSM-IV-TR®	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – Text Revision
DSST	Digit Symbol Substitution Task
ECG	Electrocardiogram
FAS	Full Analysis Set
FOCP	Females of Childbearing Potential
GGT	Gamma-glutamyl transferase
HAM-A	Hamilton Anxiety Scale
HAM-D	Hamilton Depression Scale
HCG	Human Chorionic Gonadotropin
HR	Heart rate
HUI2/3	Health Utilities Index – Mark 2 and Mark 3
ICH	International Conference on Harmonisation
ITT	Intention to Treat
IVRS	Interactive Voice Response System
KBIT	Kaufman Brief Intelligence Test
K-SADS-PL	Kiddie-Sads-Present and Lifetime – Diagnostic Interview
LOCF	Last observation carried forward

Abbreviation	Meaning
LS	Least squares
MedDRA®	Medical Dictionary for Regulatory Activities
MSS	Medication Satisfaction Survey
NDTI	National Disease Therapeutic Index™
NOS	Not otherwise specified
NYPRS-S	New York Parent's Rating Scale – School-aged
ODD	Oppositional Defiant Disorder
PDSS	Pediatric Daytime Sleepiness Scale
PERMP	Permanent Product Measure of Performance
PGA	Parent Global Assessment
PSERS	Pittsburgh Side Effect Rating Scale
PSI/SF	Parent Stress Index – Short Form
PSQ	Post-sleep Questionnaire
PSS	Pictorial Sleepiness Scale
QoL	Quality of Life
QT	QT Interval
QTc	QT Interval Corrected for HR
QTcF	QT Corrected For Heart Rate Using the Fridericia Method
QTcNi	QT Corrected For Heart Rate Using a Subject-Specific Correction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SGOT	Serum Glutamic Oxaloacetic Transaminase

Abbreviation	Meaning
SGPT	Serum Glutamic Pyruvic Transaminase
SPD503	Intuniv (guanfacine hydrochloride)
SSEQ	Structured Side-Effect Questionnaire
SWM	Spatial Working Memory
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
WFIRS-P	Weiss Functional Impairment Rating Scale - Parent
WBC	White Blood Cell Count

1. Submission details

1.1. Identifying information

Submission number	PM-2016-00711-1-1
Sponsor	Shire Australia Pty Limited
Trade name	Intuniv
Active substance	Guanfacine hydrochloride

1.2. Submission type

This is a Category 1, Type A (New Chemical Entity) application to register Intuniv (guanfacine hydrochloride) 1 mg, 2 mg, 3 mg and 4 mg modified release tablets.

1.3. Drug class and therapeutic indication

Guanfacine is a selective alpha$_{2A}$-adrenergic receptor agonist. It has 15 to 20 times the affinity for the apha$_{2A}$ subtype than for the alpha$_{2B}$ or alpha$_{2C}$ subtypes. It has actions as an antihypertensive agent, through decreasing sympathetic efferent impulses from the CNS to the heart and blood vessels. The mode of action in ADHD has not been fully established, but it is proposed modulation of signalling in the prefrontal cortex and basal ganglia through direct modification of synaptic norepinephrine transmission at the alpha$_2$-adrenergic receptors.

The proposed indication is:

Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive).

1.4. Dosage forms and strengths

The following dose forms and strengths are proposed:

- Intuniv (guanfacine hydrochloride) 1 mg modified release tablets
- Intuniv (guanfacine hydrochloride) 2 mg modified release tablets
- Intuniv (guanfacine hydrochloride) 3 mg modified release tablets
- Intuniv (guanfacine hydrochloride) 4 mg modified release tablets

1.5. Dosage and administration

The following dosage recommendations are proposed in the Product Information:

'Dosage in Paediatric Patients (Children and Adolescents)
The recommended starting dose for Intuniv is 1 mg, taken orally once a day, for both monotherapy and when co-administered with psychostimulants.
The dose is adjusted in increments of no more than 1 mg/week for both monotherapy and when co-administered with psychostimulants.
In monotherapy clinical trials, there was dose- and exposure-related clinical improvement as well as risks for several clinically significant adverse reactions (hypotension, bradycardia,

sedative events). To balance the exposure-related potential benefits and risks, the recommended maintenance dose range depending on clinical response and tolerability for Intuniv is 0.05-0.12 mg/kg/day (total daily dose between 1-7 mg. See Table 3).

Table 3: Recommended target dose range for maintenance therapy with Intuniv

Weight	Target dose range (0.05 - 0.12 mg/kg/day)
25.0-33.9 kg	2-3 mg/day
34.0-41.4 kg	2-4 mg/day
41.5-49.4 kg	3-5 mg/day
49.5-58.4 kg	3-6 mg/day
58.5-91.0 kg	4-7 mg/day
≥91.0 kg	5-7 mg/day
Doses above 4 mg/day have not been evaluated in children (ages 6-12 years) and doses above 7 mg/day have not been evaluated in adolescents (ages 13-17 years)	

In the co-administration trial which evaluated Intuniv treatment with psychostimulants, the majority of subjects reached optimal doses in the 0.05-0.12 mg/kg/day range. Doses above 4 mg/day have not been studied in co-administration trials.

The dosing information also gives advice on withdrawing treatment slowly to avoid rebound hypertension.

2. Background

2.1. Information on the condition being treated

The following background information comes from The Mental Health of Children and Adolescents Report on the second Australian Child and Adolescent Survey of Mental Health and Wellbeing (Lawrence et. al. 2015).

ADHD is a persistent pattern of inattention and/ or hyperactivity-impulsivity more frequent and severe than in other individuals at a similar developmental stage. There are three subtypes of ADHD based on the most common symptoms. Those with mostly inattentive symptoms are diagnosed with ADHD, predominantly inattentive type and individuals with primarily hyperactivity-impulsivity symptoms are diagnosed with ADHD, predominantly hyperactive-impulsive type. Those children and adolescence with symptoms of both inattentiveness and hyperactivity are diagnosed with ADHD, combined type. The DSM-IV criteria require at least six symptoms of either inattention or hyperactivity-impulsivity to have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level. Symptoms must be present in at least two settings (for example, at school and at home), and some symptoms causing impairment must have been present before the age of 7 years.

The prevalence of ADHD in Australian children and adolescents is 7.4%, equivalent to an estimated 298,000 children and adolescents. Of the three sub-types of ADHD, inattentive type was the most common, with 3.4% of children and adolescents having inattentive type, 1.2% hyperactive type and 2.8% combined type. The prevalence of ADHD was higher in males than females, with more than twice as many males as females having had ADHD in the previous 12 months (10.4% compared with 4.3%).

The severity of impact of ADHD on children and adolescents in four different domains (school or work, friends and social actives, family and impact on self) and overall is reported in Table 1. Overall one in ten (10.5%) children and adolescents with ADHD had severe impact on

functioning in at least one of these domains. Severe impact on functioning was reported most commonly in the domain of family (17.3%), and then school or work (12.8%). Only 3.7% of children and adolescents with ADHD had a severe level of impact on functioning in the self domain (that is, where the young person experienced a high level of distress due to their symptoms). Two fifths (40.9%) of children and adolescents with ADHD had no impact in the friends domain, while only 13.3% of children with ADHD had no impact in the school or work domain.

Table 1: Severity of impact in different life domains among 4-17 year-olds with ADHD (copied from Table 5-8, Lawrence et al 2015)

Severity	School/work (%)	Friends (%)	Family (%)	Self (%)	Overall severity (%)
None	13.3	40.9	18.1	29.3	
Mild	40.0	24.9	35.8	45.7	65.7
Moderate	31.1	23.6	28.8	21.3	23.8
Severe	12.8	10.6	17.3	3.7	10.5
Does not go to school or work	2.8				

2.2. Current treatment options

Pharmacological approaches are usually used in managing ADHD in Australia. Current pharmacological treatment options available in Australia include:

- CNS stimulants
  - Methylphenidate
  - Dexamfetamine
  - Lisdexamfetamine
- Atomoxetine (selective inhibitor of norepinephrine reuptake)

Non-pharmacological interventions include general behavioural approaches and cognitive behavioural therapy.

2.3. Clinical rationale

The sponsor has identified the following situations where an alternative to psychostimulants would be desirable:

- A subset of ADHD patients will fail to respond to stimulant monotherapy.
- A subset of ADHD patients will have side effects that preclude stimulant use, for example insomnia and anorexia with stimulants.
- In some children treated with psychostimulants, ADHD symptoms may not be adequately controlled in the hours before school or in the evening. In addition, some stimulants have a short duration of action, requiring multiple doses per day, which can result in compliance problems, especially in children.
- Psychostimulants may also have limitations in the treatment of some patients with comorbid symptoms (for example, oppositional defiant disorder, anxiety disorder, substance abuse, tics, and Tourette's syndrome).

- Patients in whom stimulants or other non-stimulants (that is, atomoxetine) are contraindicated.
- In addition, physicians and/or parents may prefer a treatment option which is not a controlled substance due to the potential for abuse or dependence.

The sponsor gives the following rational for developing guanfacine:

'*Several studies published in peer reviewed journals have documented the beneficial effects of guanfacine and other alpha-2-adrenergic agonists (such as clonidine) for treatment of the symptoms of ADHD. Shire has developed a modified-release version of guanfacine HCl (SPD503) as an additional alternative non-stimulant option for the treatment of ADHD*.' The studies referred to were not cited by the sponsor.

2.4. Guidance

The following guidance applies to the present application:

- EMA/CHMP/185423/2010 Rev 2. Guideline on clinical investigation of medicinal products in the treatment of Attention Deficit Hyperactivity Disorder (ADHD).
- CHMP/ICH/2/04. ICH Topic E 14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

2.5. Evaluator's commentary on the background information

The rationale for developing guanfacine is not clear. The sponsor mentions published data in the statement: '*Several studies published in peer reviewed journals have documented the beneficial effects of guanfacine and other alpha-2-adrenergic agonists (such as clonidine) for treatment of the symptoms of ADHD*.' However, the sponsor does not provide references for these data.

The indication sought by the sponsor is similar to that which is approved in the US, but the EU indication is much more restrictive. The EU indication requires prior treatment with CNS stimulants to be '*not suitable, not tolerated or have been shown to be ineffective.*'

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The dossier represented a development program for guanfacine extended release (SPD503) in children and adolescents with ADHD.

- There were 15 studies with pharmacokinetic data.
- There were two studies with pharmacodynamic data
- There was one population pharmacokinetic-pharmacodynamic study
- There were eight pivotal studies conducted in children and adolescents with ADHD
- There were three long-term follow-on studies.
- There were three other efficacy and safety studies.
- There were two other safety studies.

3.2. Paediatric data

Data relating to children and adolescents aged 6 to 17 years is included in the dossier.

3.3. Good clinical practice

The clinical studies presented in the dossier are stated to have adhered to GCP and appear to have adhered to GCP.

3.4. Evaluator's commentary on the clinical dossier

The clinical dossier represents a complete clinical development program in a specific population (that is, children and adolescents with ADHD).

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

Table 2: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
General Pharmacokinetics	General PK - Multi-dose	Study SPD503-113	*
		Study 1209A3111	*
		Study SPD503-206	*
	Bioequivalence † - Single dose	Study SPD503-101	*
		Study SPD503-103	*
		Study SPD503-110,	*
		Study SPD503-119	*
		Study SPD503-120	*
	Food effect	Study SPD503-104	*
PK in special populations	Target population § - Multi dose	Study SPD503-107	*

PK topic	Subtopic	Study ID	*
PK interactions	Ketoconazole	Study SPD503-106	*
	Rifampicin	Study SPD503-108	*
	Methylphenidate	Study SPD503-114	*
	Lisdexamphetamine (*d*-amphetamine)	Study SPD503-115	*
Population PK analyses	Target population §	Study SPD503-312	*

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

From the Product Information: Guanfacine hydrochloride is a white to off-white crystalline powder that is sparingly soluble in water. Guanfacine exhibits only a single polymorphic form and does not exhibit optical rotation. Guanfacine hydrochloride has a 2-octanol/water partition coefficient (logP) of 0.10; a dissociation constant of 7.69; and pH of ~4 when dissolved in water.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

Sites and mechanism of absorption

Guanfacine is absorbed from the gastrointestinal tract.

4.2.2.2. Bioavailability

Absolute bioavailability

The absolute bioavailability of guanfacine is 81% (Carchman et al, 1987).

Bioavailability relative to an oral solution or micronised suspension

No new data were presented.

Bioequivalence of clinical trial and market formulations

The sponsor had some difficulties in replicating manufacture at different sites for the 4 mg formulation (Study SPD503-103). However, the sponsor did demonstrate bioequivalence between guanfacine extended release 2 mg tablet manufactured by Shire US Manufacturing Incorporated (SUMI) and those manufactured by Pharmaceutics International Incorporated (PII) (Study SPD503-109). Guanfacine extended release 4 mg tablet manufactured by SUMI were bioequivalent to those manufactured by PII.

Bioequivalence of different dosage forms and strengths

Guanfacine 1 mg and 4 mg tablets were demonstrated to be bioequivalent (Study SPD503-104). Although not intended for marketing in Australia, guanfacine extended release 2.5 mg tablets

manufactured at SUMI and PII were bioequivalent (when dose normalised) to guanfacine extended release 2 mg tablets (Study SPD503-110).

The sponsor demonstrated bioequivalence for two different manufacturing sites for Guanfacine extended release 2 mg tablets: Owings Mills and DSM Pharmaceutical Products (Study SPD503-119). The sponsor demonstrated bioequivalence for two different manufacturing sites for Guanfacine extended release 4 mg tablets: Owings Mills and DSM Pharmaceutical Products (Study SPD503-120).

Bioequivalence to relevant registered products

Modified release formulations provided a more satisfactory plasma concentration time profile for the management of patients with ADHD (Study SPD503-101).

Influence of food

Food increased the AUC_{0-t} of a 4mg dose by 39% and C_{max} by 75% (Study SPD503-104).

Dose proportionality

There was dose proportionality for AUC_{0-t} but not for C_{max} in the dose range 1 mg to 4 mg. C_{max} increased to a lesser than expected extent from 1 mg to 2 mg (Study SPD503-109). For tablets manufactured by PII, mean (SD) AUC_{0-t} was 29.3 (8.84) h•ng/mL for 1 mg, 55.0 (18.0) h•ng/mL for 2 mg and 120 (41.5) h•ng/mL for 4 mg. Mean (SD) C_{max} was 0.98 (0.26) ng/mL for 1 mg, 1.59 (0.49) ng/mL for 2 mg and 3.58 (1.39) h•ng/mL for 4 mg.

In Japanese and Non-Hispanic Caucasian subjects the PK of guanfacine was linear in the dose range 1 to 4 mg, with multiple dosing (Study 1209A3111).

In Study SPD503-206, guanfacine 1 mg, 2 mg and 3 mg were dose proportional at steady state (Table 3).

Table 3: Arithmetic Mean (CV%) of Select Pharmacokinetic Parameters

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

Values are expressed as Mean (CV%)

* T_{max} is expressed as Median (Range)

† N=57

Bioavailability during multiple-dosing

No relative bioavailability data were presented.

Effect of administration timing

Other than with regard to food, no data on the effect of administration time were presented.

4.2.2.3. Distribution

Volume of distribution

Volume of distribution was in the range of 823 to 894 L (Study SPD503-109).

Plasma protein binding

The mean plasma protein binding is 71.6%, and is not influenced by plasma concentration or route of administration (Carchman *et al* 1987).

Erythrocyte distribution

There were no data on erythrocyte distribution.

Tissue distribution

The volume of distribution is 6 L/kg which implies extensive tissue distribution (Carchman *et. al.* 1987).

4.2.2.4. Metabolism

Interconversion between enantiomers

Guanfacine does not have enantiomers.

Sites of metabolism and mechanisms / enzyme systems involved

Guanfacine is metabolised via CYP3A4/5 mediated oxidation, with subsequent phase II reactions of sulfation and glucuronidation. The major circulating metabolite is 3-OH-guanfacine sulphate. Guanfacine is primarily metabolised by the CYP3A4 isoenzyme. In vitro studies with human liver microsomes and recombinant CYP's demonstrated that guanfacine was primarily metabolized by CYP3A4.

Non-renal clearance

Non-renal clearance is hepatic.

Metabolites identified in humans: active and other

The major circulating metabolite is 3-OH-guanfacine sulphate.

Pharmacokinetics of metabolites

The metabolites are excreted renally.

Consequences of genetic polymorphism

No data were presented on genetic polymorphism.

4.2.2.5. Excretion

Routes and mechanisms of excretion

The fraction excreted unchanged in the urine is approximately 36% of the ingested dose (Study 1209A3111). Urine recovery after intravenous dosing was 50% (Carchman *et. al.* 1987)

Mass balance studies

Mass balance studies were not included in the dossier.

Renal clearance

Renal clearance was 0.12 L/kg/hour (Study 1209A3111). Renal clearance of guanfacine was 50% of total body clearance and appeared to be due to a net renal tubular secretory process (Carchman *et.al.* 1987). This secretory process appears to be mediated by OCT2.

4.2.2.6. Intra and inter individual variability of pharmacokinetics

The main covariates contributing to variability in CL were weight and age (Study SPD503-312). Race and sex were statistically significant but not clinically significant.

4.2.3. Pharmacokinetics in the target population

Study SPD503-107 demonstrated linear kinetics at steady state in the dose range 2 mg to 4 mg, and also between single dose and steady state for the 2 mg dose level. Age and gender differences in PK were attributed to differences in body weight. The study was conducted in children and adolescents with ADHD aged 7 to 16 years.

4.2.4. Pharmacokinetics in special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

No data were included in the dossier.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

No data were included in the dossier.

4.2.4.3. Pharmacokinetics according to age

In Study SPD503-113 clearance, scaled to body weight, decreased with increasing, but usually parameters such as CL would be related to allometric scaling for body weight (for example, weight$^{0.75}$). Exposure, corresponding, increased with increasing weight, reflecting the decreased CL.

4.2.4.4. Pharmacokinetics related to genetic factors

No data were included in the dossier.

4.2.4.5. Pharmacokinetics in other special population / with other population characteristic

The PK of guanfacine was similar in Japanese and Non-Hispanic Caucasian subjects (Study 1209A3111).

4.2.5. Population pharmacokinetics

4.2.5.1. PopPK Study SPD503-312

In Study SPD503-312 weight was the main predictor for guanfacine exposure, when scaled allometrically. Race and gender did not significantly affect guanfacine exposure.

4.2.6. Pharmacokinetic interactions

4.2.6.1. Ketoconazole

Exposure to guanfacine was significantly increased by ketoconazole (Study SPD503-106). At a 4 mg dose, the ratio (90% CI) exposed / unexposed for AUC_{0-t} was 278.59 (227.53 to 341.11) and for C_{max} was 174.54 (145.65 to 209.17).

4.2.6.2. Rifampicin

Co-administration with rifampicin significantly decreased guanfacine AUC_{0-t} by 69% and C_{max} by 54% (Study SPD503-108). At a 4 mg dose, the ratio (90% CI) exposed / unexposed for AUC_{0-t} was 30.92 (25.22 to 37.92) and for C_{max} was 45.64 (38.75 to 53.75).

4.2.6.3. Methylphenidate

There was also no effect of methylphenidate on guanfacine bioavailability (Study SPD503-114). The geometric mean ratio (90% CI) guanfacine/methylphenidate + guanfacine for AUC_{0-t} was 1.08 (0.974 to 1.198) and for C_{max} was 1.065 (0.945 to 1.2).

There was also no effect of guanfacine on *d*-methylphenidate bioavailability. The geometric mean ratio (90% CI) methylphenidate/methylphenidate + guanfacine for AUC_{0-t} was 1.043 (0.977 to 1.114) and for C_{max} was 0.957 (0.907 to 1.01).

There was also no effect of guanfacine on *l*-methylphenidate bioavailability. The geometric mean ratio (90% CI) methylphenidate/methylphenidate + guanfacine for AUC_{0-t} was 1.08 (0.974 to 1.198) and for C_{max} was 1.065 (0.945 to 1.2).

4.2.6.4. Lisdexamphetamine (d-amphetamine)

Guanfacine and lisdexamphetamine did not have any clinically significant effects upon the PK of the other (Study SPD503-115). The geometric mean ratio (90% CI) for guanfacine (guanfacine/lisdexamphetamine + guanfacine) for AUC_{0-t} was 1.092 (1.020 to 1.169) and for C_{max} was 1.187 (1.066 to 1.321). The geometric mean ratio (90% CI) for d-amphetamine (guanfacine/lisdexamphetamine + guanfacine) for AUC_{0-t} was 1.007 (0.968 to 1.048) and for C_{max} was 0.993 (0.967 to 1.019).

4.2.7. Clinical implications of *in vitro* findings

The in vitro data support CYP3A4 as being the enzyme responsible for the oxidative metabolism of guanfacine.

4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics of guanfacine has been adequately characterised. Guanfacine in the extended release formulation (SPD503) has a favourable PK profile for use in children and adolescents with ADHD.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

There were no new data in the dossier examining primary pharmacology.

Table 4: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Secondary Pharmacology	Effect on PD parameter: blood pressure	Study SPD503-102	
	Effect on PD parameter: QTc prolongation	Study SPD503-112	
Population PD and PK-PD analyses	Target population	Study SPD503-312,	

* Indicates the primary PD aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

There were no new data on mechanism of action.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

The population PKPD study (Study SPD503-312) indicated that the guanfacine exposure response time course of ADHD-RS-IV scores was best describe by a linear drug effect proportional to the placebo response trajectory. The typical (95% CI) decrease in ADHD-RS-IV score, compared to placebo, was 37.1% (32.2% to 42.0%) per 0.1 mg of guanfacine exposure.

5.2.2.2. Secondary pharmacodynamic effects

Following up-titration of guanfacine dose to 4 mg daily, abrupt cessation did not result in rebound hypertension or other clinically significant adverse effects in comparison with tapered cessation (Study SPD503-102).

At doses titrated up to 8 mg, there was prolongation of QTcF to the threshold of regulatory concern, but there was no prolongation when QTc was calculated by QTcNi (Study SPD503-112). The mean (90% CI) for difference guanfacine-placebo, change for baseline in QTcF was 3.54 (0.78 to 6.29) at 6 hours post dose, and 7.61 (4.87 to 10.34) at 12 hours post dose. However, heart rate decreased by a mean of 20 bpm in the guanfacine group.

5.2.3. Time course of pharmacodynamic effects

There were no new data on time course of pharmacodynamic effects.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

The population PKPD data indicated that the guanfacine exposure response time course of ADHD-RS-IV scores was best describe by a linear drug effect proportional to the placebo response trajectory (Study SPD503-312).

5.2.5. Genetic, gender and age related differences in pharmacodynamic response

The efficacy data did not indicate any gender or age related differences in PD response.

5.2.6. Pharmacodynamic interactions

There were no new data on PD interactions.

5.3. Evaluator's overall conclusions on pharmacodynamics

In the dose range studied, the plasma concentration effect relationship was linear. There were no rebound effects on blood pressure with the extended release formulation.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

The PK and PD studies investigated the dose range from 1 mg to 8mg per day in adults.

6.2. Phase II dose finding studies

The Phase II studies examined the dose range 1 mg/day to 4 mg/day in the age range 6 to 17 years.

6.3. Phase III pivotal studies investigating more than one dose regimen

The Phase III pivotal studies investigated the dose range up to 4 mg/day in children aged 6 to 12 years and up to 7 mg/day in adolescents aged 13 to 17 years.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

The sponsor has investigated tolerability, safety and efficacy in the dose range 1 mg to 7 mg per day. The final dosing used in the clinical trials was a weight-based dosing regimen that reflected the findings of the dose-finding studies. This weight-based dosing regimen supports the dosing recommendations in the Product Information document.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

There were eight pivotal efficacy studies conducted in children and adolescents with ADHD. Studies were performed as monotherapy and as co-medication with psychostimulants. A study was also conducted in children and adolescents with ADHD and oppositional features. There were five supportive efficacy studies including two long-term follow-on studies.

7.2. Pivotal or main efficacy studies

7.2.1. Study SPD503-301

7.2.1.1. Study design, objectives, locations and dates

Study SPD503-301 was a randomised, double blind, parallel group, placebo controlled, forced dose escalation, efficacy and safety study. The study was conducted at 48 centres in the US from January 2003 to August 2003.

7.2.1.2. Inclusion and exclusion criteria

The study included subjects with ADHD. The inclusion criteria included:

- Male or female subjects aged 6 to 17 inclusive.
- Females of childbearing potential must have negative pregnancy tests and must have abstained from sexual activity that could have resulted in pregnancy, or used acceptable contraceptives throughout the period of study drug exposure and for 30 days after the last dose of study drug.
- Subject met DSM-IV-TR criteria for a primary diagnosis of ADHD (diagnostic code 314.01) combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype based on a detailed psychiatric evaluation.
- Subject was intellectually functioning at age-appropriate levels, as deemed by the Investigator.
- Subject had no concomitant illnesses that could affect efficacy, safety, or tolerability or in any way interfere with the subject's participation in the study.
- Subject had blood pressure (BP) measurements within the 95th percentile for his/her age, gender, and height.

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

The exclusion criteria included:

- Subject had a current, uncontrolled, comorbid psychiatric diagnosis (except oppositional defiant disorder) with significant symptoms such as any severe comorbid Axis II disorders or severe Axis I disorders, or other symptomatic manifestations that, in the opinion of the examining physician, contraindicated SPD503 treatment or confounded efficacy or safety assessments. Comorbid psychiatric diagnosis was established with select modules of the K-SADS-PL.
- Subject weighed less than 55lb (25kg).
- Subject, in the opinion of the Investigator, was morbidly overweight or obese.
- Subject had a QTc interval greater than 440 milliseconds at the Screening Visit.
- Subject had, in the opinion of the Investigator, any specific cardiac condition or family history, which required exclusion.
- Subject was hypertensive.
- Subject was taking medications that affected BP or heart rate (with the exception of subject's current ADHD therapy).
- Subject had a history of seizure during the last 2 years (exclusive of febrile seizures), a tic disorder, or a family history of Tourette's disorder. Medication induced tics were not exclusionary.
- Subject was taking any medication that was excluded.
- Subject was taking other medications that have central nervous system (CNS) effects or affected performance, such as sedating antihistamines and decongestant sympathomimetics. Bronchodilators were not exclusionary.
- Subject had any abnormal thyroid function that was not adequately treated in the opinion of the Investigator.
- Subject had any clinically significant laboratory abnormalities at Screening, in the opinion of the Investigator.
- Subject had a concurrent chronic or acute illness (such as allergic rhinitis or severe cold), disability, or other condition that could confound the results of safety assessments administered in the study or that could increase risk to the subject.
- Any additional condition(s) that, in the Investigator's opinion, could prohibit the subject from completing the study or would not be in the best interest of the subject. This included any significant illness or unstable medical condition that could have led to difficulty in complying with the protocol. Mild, stable asthma was not exclusionary.
- Female subject was pregnant or lactating.

7.2.1.3. Study treatments

The study treatments were:

1. Guanfacine extended release 2 mg daily
2. Guanfacine extended release 3 mg daily
3. Guanfacine extended release 4 mg daily
4. Placebo

There was a washout period from all psychoactive medication lasting 1 week. The treatments were up-titrated over a 3 week period. The maintenance phase was 2 weeks in duration. There was a 3 week taper of treatment for those subjects who did not continue into the open label extension (Study SPD503 302).

7.2.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the change from baseline in ADHD Rating Scale-IV (ADHD-RS-IV) total score at endpoint. The secondary efficacy outcome measures were:

- Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) total score
- Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R) total score
- Clinical Global Impression-Improvement (CGI-I)
- Parent Global Assessment (PGA)
- Child Health Questionnaire-Parent Form (CHQ-PF50)
- Child Health Questionnaire-Child Form (CHQ-CF87)

The safety outcome measures were: AEs, vital signs, physical examinations, height, weight, 12 lead ECGs, clinical laboratory tests and concomitant medications.

7.2.1.5. Randomisation and blinding methods

Subjects were randomised to treatment in the ratio 1:1:1:1.

7.2.1.6. Analysis populations

The ITT population included all randomised subjects who had a baseline and at least one post-baseline measure for ADHD-RS-IV. The safety population included all subjects who participated or enrolled in the study.

7.2.1.7. Sample size

The sample size calculation was based on the primary efficacy outcome measure. An effect size of 0.50 was observed in a Phase2 study, and at an alpha of 0.05 (2-tailed), 70 subjects in each group would provide a power >80% for comparisons between individual treatment groups and placebo.

7.2.1.8. Statistical methods

Hypothesis tests were performed using ANOVA and ANCOVA models.

7.2.1.9. Participant flow

A total of 345 subjects enrolled in the study: 87 in the 2 mg group, 86 in the 3 mg, 86 in the 4 mg and 86 in the placebo (Table 5). A total of 215 subjects completed the study: 58 (66.7%) in the 2 mg group, 55 (64.0%) in the 3 mg, 49 (57.0%) in the 4 mg and 53 (61.6%) in the placebo. A greater proportion of subjects in the placebo group discontinued because of lack of efficacy, and dose-related greater proportions discontinued in the guanfacine groups because of AE.

Table 5: Distribution and Disposition by Randomized Dose (All Subjects) (copied from Table 7, Study SPD503-301 CSR)

	Placebo N=86	SPD503 2mg N=87	SPD503 3mg N=86	SPD503 4mg N=86	Total N=345
Subject Disposition, n (%)					
Enrolled (Safety)	86 (100.0%)	87 (100.0%)	86 (100.0%)	86 (100.0%)	345 (100.0%)
Randomized	86 (100.0%)	87 (100.0%)	86 (100.0%)	86 (100.0%)	345 (100.0%)
Completed	53 (61.6%)	58 (66.7%)	55 (64.0%)	49 (57.0%)	215 (62.3%)
Early termination	33 (38.4%)	29 (33.3%)	31 (36.0%)	37 (43.0%)	130 (37.7%)
Intent-to-treat	78 (90.7%)	84 (96.6%)	82 (95.3%)	81 (94.2%)	325 (94.2%)
Per-protocol	61 (70.9%)	63 (72.4%)	62 (72.1%)	54 (62.8%)	240 (69.6%)
Reason for early termination, n (%)					
Adverse event	1 (1.2%)	9 (10.3%)	13 (15.1%)	20 (23.3%)	43 (12.5%)
Protocol violation	1 (1.2%)	3 (3.4%)	0	0	4 (1.2%)
Subject choice	9 (10.5%)	2 (2.3%)	3 (3.5%)	4 (4.7%)	18 (5.2%)
Lost to follow-up	3 (3.5%)	2 (2.3%)	4 (4.7%)	3 (3.5%)	12 (3.5%)
Lack of efficacy	15 (17.4%)	8 (9.2%)	6 (7.0%)	7 (8.1%)	36 (10.4%)
Other	4 (4.7%)	5 (5.7%)	5 (5.8%)	3 (3.5%)	17 (4.9%)

7.2.1.10. Major protocol violations/deviations

Withdrawal due to protocol violation was recorded for three (3.4%) subjects in the guanfacine 2 mg group and one (1.2%) in the placebo.

7.2.1.11. Baseline data

There were 257 (74.5%) males, 88 (25.5%) females and the age range was 6 to 17 years. There were 91 (26.4%) subjects aged 6 to 8 years, 174 (50.4%) aged 9 to 12 years and 80 (23.2%) aged 13 to 17 years. There were 248 (71.9%) subjects with combined ADHD subtype, 90 (26.1%) with inattentive and seven with hyperactive-impulsive. Prior treatment with methylphenidate was recorded for 54 (15.7%) subjects and with amphetamine for 30 (8.7%). The most commonly used concomitant medications were paracetamol in 58 (16.8%) subjects and ibuprofen in 44 (12.8%). Compliance for the ITT population was reported as 97.6%. Baseline efficacy scores were similar for the four treatment groups (Table 6).

Table 6: Baseline efficacy outcome measure scores (copied from Tables 12 and 12, Study SPD503-301 CSR)

ADHD-RS-IV

	Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
Baseline, N	78	84	82	81
Mean (SD)	38.14 (9.34)	36.10 (9.99)	36.77 (8.72)	38.40 (9.21)
Median	39.00	36.00	37.50	37.00
Min, Max	13, 54	11, 54	17, 54	15, 54

Secondary Efficacy Measures

Baseline	Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
CPRS-R				
Day Total, N	77	84	81	80
Mean (SD)	44.98 (17.77)	42.92 (18.48)	42.32 (18.29)	43.71 (16.41)
Morning Total (0600 hours), N	74	82	80	79
Mean (SD)	40.53 (20.89)	37.65 (21.84)	40.45 (19.94)	40.65 (18.84)
Afternoon Total (1800 hours), N	74	84	81	78
Mean (SD)	49.34 (18.95)	46.99 (19.55)	45.59 (19.01)	46.94 (16.27)
Evening Total (2000 hours), N	74	83	80	77
Mean (SD)	45.08 (20.30)	43.75 (20.80)	40.59 (22.20)	43.68 (18.89)
CTRS-R				
Day Total, N	77	83	81	81
Mean (SD)	33.86 (19.40)	34.23 (20.11)	33.19 (17.34)	38.11 (17.10)
Morning Total (1000 hours), N	75	82	78	76
Mean (SD)	33.51 (20.30)	32.52 (20.35)	32.56 (18.25)	39.88 (16.30)
Afternoon Total (1400 hours), N	74	80	76	78
Mean (SD)	34.47 (19.49)	36.43 (21.46)	34.95 (19.88)	36.92 (19.29)
CGI-S, N	78	84	82	81
Mean (SD)	4.65 (0.79)	4.61 (0.74)	4.61 (0.66)	4.68 (0.67)

7.2.1.12. Results for the primary efficacy outcome

ADHD-RS-IV improved in a dose-related manner for all guanfacine groups compared to placebo. Mean (SD) change from baseline in ADHD-RS-IV was -15.40 (12.82) for guanfacine 2 mg, -15.79 (13.00) for 3 mg, -18.96 (13.71) for 4 mg and -8.86 (12.90) for placebo (p values all <0.001). When analysed by weight adjusted dose, there was a more obvious dose-dependency in the change from baseline in ADHD-RS-IV total score. Efficacy was significantly greater than placebo in the younger age groups but not in the 13 to 17 years age group (Table 7). Efficacy was demonstrated separately for ADHD-RS-IV total score for the combined type, but not for the inattentive type (Table 8). However, efficacy was demonstrated for both inattentive and hyperactive/impulsivity subscales (Table 9).

Table 7: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and by Age Groups (ITT Population) (copied from Table 18, Study SPD503-301 CSR)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
Age 6-8 years					
Endpoint[1]	N	22	16	20	27
	Mean (SD)	36.59 (9.86)	21.00 (13.58)	19.15 (13.83)	16.11 (9.81)
Change from Baseline	Mean (SD)	-3.82 (10.00)	-16.88 (12.99)	-17.85 (14.41)	-25.85 (11.73)
Placebo-adjusted difference[3]	LS mean	NA	-14.57	-16.06	-21.11
	(95% CI)	NA	(-23.38, -5.75)	(-24.39, -7.73)	(-28.80, -13.42)
	P-Value (Dunnett)[2]	NA	0.0005	<0.0001	<0.0001
Age 9-12 years					
Endpoint[1]	N	37	51	37	39
	Mean (SD)	27.95 (15.77)	20.25 (13.95)	21.32 (14.85)	21.62 (12.81)
Change from Baseline	Mean (SD)	-9.49 (12.73)	-16.57 (12.96)	-16.92 (13.32)	-15.36 (12.36)
Placebo-adjusted difference[3]	LS mean	NA	-7.26	-7.20	-6.00
	(95% CI)	NA	(-13.69, -0.83)	(-14.12, -0.28)	(-12.83, 0.83)
	P-Value (Dunnett)[2]	NA	0.0225	0.0393	0.0979
Age 13-17 years					
Endpoint[1]	N	19	17	25	15
	Mean (SD)	23.42 (15.48)	21.71 (12.46)	21.92 (12.77)	19.73 (12.32)
Change from Baseline	Mean (SD)	-13.47 (14.72)	-10.53 (11.76)	-12.48 (11.09)	-15.93 (16.31)
Placebo-adjusted difference[3]	LS mean	NA	0.63	-0.24	-3.07
	(95% CI)	NA	(-9.76, 11.03)	(-9.61, 9.12)	(-13.64, 7.51)
	P-Value (Dunnett)[2]	NA	0.9978	0.9998	0.8273

Source: Section 12.1 Tables 2.12.1, 2.12.2, and 2.12.3

1 Endpoint is the last valid measurement after randomization (last observation carried forward) and prior to dose tapering.

2 P-value and 95% CI from Dunnett's adjustment for multiple means comparisons.

3 Placebo-adjusted difference in change from Baseline.

Table 8: ADHD-RS-IV Total Score at Endpoint for Inattentive and Combined ADHD Subtypes by Randomized Dose (ITT Population) (copied from Table 21, Study SPD503-301 CSR)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
Inattentive Type					
Endpoint[1]	N	16	28	17	23
	Mean (SD)	19.25 (13.32)	16.64 (10.96)	11.71 (7.62)	17.83 (11.57)
Change from Baseline	Mean (SD)	-10.44 (13.85)	-11.64 (9.99)	-17.59 (11.15)	-13.30 (13.39)
Placebo-adjusted difference[3]	LS mean	NA	-2.12	-7.41	-1.93
	(95% CI)	NA	(-10.13, 5.89)	(-16.29, 1.48)	(-10.25, 6.39)
	P-Value (Dunnett)[2]	NA	0.8517	0.1212	0.8930
Combined Type					
Endpoint[1]	N	62	53	64	56
	Mean (SD)	31.87 (14.32)	22.58 (14.42)	23.53 (14.22)	20.29 (11.99)
Change from Baseline	Mean (SD)	-8.45 (12.73)	-17.57 (13.40)	-15.38 (13.58)	-21.41 (13.33)
Placebo-adjusted difference[3]	LS mean	NA	-9.18	-7.47	-12.43
	(95% CI)	NA	(-14.91, -3.45)	(-12.94, -2.00)	(-18.08, -6.78)
	P-Value (Dunnett)[2]	NA	0.0006	0.0040	<0.0001

Source: Section 12.1 Tables 2.11.1 and 2.11.2
1 Endpoint is the last valid measurement after randomization and prior to dose tapering.
2 P-value and 95% CI from Dunnett's adjustment for multiple means comparisons.
3 Placebo-adjusted difference in change from Baseline.

Table 9: ADHD-RS-IV Inattentiveness and Hyperactivity/Impulsivity Subscale Scores at Endpoint by Randomized Dose (ITT Population) (copied from Table 22, Study SPD503-301 CSR)

		Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
Inattentiveness					
Endpoint[1]	N	78	84	82	81
	Mean (SD)	16.08 (7.90)	12.30 (7.28)	12.13 (7.06)	12.16 (7.21)
Change from Baseline	Mean (SD)	-4.78 (7.84)	-8.46 (7.49)	-8.71 (7.27)	-9.51 (7.64)
Placebo-adjusted difference[3]	LS mean	NA	-3.74	-3.94	-4.26
	(95% CI)	NA	(-6.37, -1.10)	(-6.59, -1.28)	(-6.93, -1.60)
	P-Value (Dunnett)[2]	NA	0.0027	0.0015	0.0006
Hyperactivity/Impulsivity					
Endpoint[1]	N	78	84	82	81
	Mean (SD)	13.22 (8.34)	8.39 (7.13)	8.84 (7.56)	7.27 (5.80)
Change from Baseline	Mean (SD)	-4.06 (6.15)	-6.94 (6.46)	-7.09 (6.96)	-9.46 (7.16)
Placebo-adjusted difference[3]	LS mean	NA	-3.68	-3.58	-5.62
	(95% CI)	NA	(-5.96, -1.41)	(-5.87, -1.30)	(-7.91, -3.34)
	P-Value (Dunnett)[2]	NA	0.0005	0.0007	<0.0001

Source: Section 12.1 Tables 2.2.1 and 2.3.1
1 Endpoint is the last valid measurement after randomization and prior to dose tapering.
2 P-value and 95% CI from Dunnett's adjustment for multiple means comparisons.
3 Placebo-adjusted difference in change from Baseline.

7.2.1.13. Results for other efficacy outcomes

- There was a significant improvement in CPRS-R total score overall and at all time points during the day
- There was a significant improvement in CTRS-R total score overall and at all time points during the school day
- A greater proportion of subjects treated with guanfacine had improvement in CGI-I: 47 (55.95%) subjects in the 2 mg group, 41 (50.0%) in the 3 mg, 45 (55.56%) in the 4 mg and 20 (25.64%) in the placebo (Table 10)
- A greater proportion of subjects treated with guanfacine had improvement PGA: 41 (62.12%) subjects in the 2 mg group, 31 (50.82%) in the 3 mg, 39 (66.10%) in the 4 mg and 15 (23.08%) in the placebo (Table 10)
- Consistent improvement in CHQ-PF50 was only seen at the 4 mg dose level
- There was a significant improvement in CHQ-CF87 only at the 4 mg dose level, and only for Family Activities: LS mean placebo adjusted difference (95% CI) 14.93 (2.89 to 26.98) p = 0.0108; and for Bodily Pain: -9.41 (-17.81 to 0.0236).

Table 10: Summary and Analysis of CGI-I and PGA Scores by Randomized Dose (ITT Population) (copied from Table 28, Study SPD503-301 CSR)

	Placebo	SPD503 2mg	SPD503 3mg	SPD503 4mg
CGI-I score at Endpoint[1], N	78	84	82	81
Improvement[2], n (%)	20 (25.64)	47 (55.95)	41 (50.00)	45 (55.56)
No Improvement, n (%)	58 (74.36)	37 (44.05)	41 (50.00)	36 (44.44)
Improved difference vs. placebo, %	NA	30.31	24.36	29.92
p-value[3]	NA	<0.0001	0.0016	0.0001
PGA score at Endpoint[1], N	65	66	61	59
Improvement[2], n (%)	15 (23.08)	41 (62.12)	31 (50.82)	39 (66.10)
No Improvement, n (%)	50 (76.92)	25 (37.88)	30 (49.18)	20 (33.90)
Improved difference vs. placebo, %	NA	39.04	27.74	43.02
p-value[3]	NA	<0.0001	0.0013	<0.0001

Source: Section 12.1 Tables 2.9.1 and 2.10.1

1 Endpoint is the last valid measurement after randomization (last observation carried forward) and prior to dose tapering

2 CGI-I and PGA response scales were dichotomized into two categories: "very much improved" and "much improved" in one category and the remaining items in the second category.

3 P-value (CMH general association test) for pairwise comparison of each active dose versus placebo.

7.2.1.14. Evaluator commentary

Study SPD503-301 demonstrated the dose range on a mg/kg basis that could be expected to have efficacy (linear response up to 0.17 mg/kg/day). The study maintenance phase was of too short a duration to establish efficacy (two weeks). Efficacy was not demonstrated for the inattentive subtype of ADHD.

7.2.2. Study SPD503-304

7.2.2.1. Study design, objectives, locations and dates

Study SPD503-304 was a randomised, double blind, parallel group, placebo controlled, forced dose escalation, efficacy and safety study. The study was conducted at 51 centres in the US from March 2004 to October 2004.

7.2.2.2. Inclusion and exclusion criteria

The study included male or female subjects with ADHD aged 6 to 17 years inclusive. The inclusion and exclusion criteria were essentially the same as for Study SPD503-301 (see above).

7.2.2.3. Study treatments

The study treatments were:

5. Guanfacine extended release 1 mg/day (only for subjects weighing <110 lb [approximately 50 kg])
6. Guanfacine extended release 2 mg/day
7. Guanfacine extended release 3 mg/day
8. Guanfacine extended release 4 mg/day
9. Placebo

There was a 3 week forced titration to the randomised dose, a 3 week maintenance phase and a 3 week taper of dose. Each active strength had a matching placebo and each subject took four tablets each morning: no more than one active and no less than three placebo.

There was a washout period of 7 days for psychostimulants. Psychostimulants and other psychoactive drugs were prohibited during the study: for example, tricyclic antidepressants, sedating antihistamines, Strattera®, clonidine, benzodiazepines, neuroleptics, anticonvulsants. Cardiac and vascular (antihypertensive medications) were also prohibited.

7.2.2.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the change from baseline in ADHD Rating Scale-IV (ADHD-RS-IV) total score at endpoint. The secondary efficacy outcome measures were:

- CPRS-R total score
- Clinical Global Impression-Severity (CGI-S)
- CGI-I
- PGA
- CHQ-PF50

The safety outcome measures were: AEs, vital signs, physical examinations, height, weight, 12 lead ECGs, clinical laboratory tests and Pediatric Daytime Sleepiness Scale (PDSS).

The schedule of study visits was similar to that for Study SPD503-301.

7.2.2.5. Randomisation and blinding methods

Randomisation was by IVRS, and stratified by weight (<75 lb, 75 to <110 lb and ≥ 110 lb). Blinding was maintained by matching placebo for each dose level.

7.2.2.6. Analysis populations

The ITT population included all randomised subjects who had a baseline and at least one post-baseline measure for ADHD-RS-IV. The safety population included all subjects who received at least one dose of study drug.

7.2.2.7. Sample size

The sample size calculation was based on the primary efficacy outcome measure, assumed an effect size of 0.6 in the active treatment groups, and calculated a sample size of 60 subjects in each group to provide 90% power at a 2-sided alpha of 0.05 (for tests between active and placebo groups).

7.2.2.8. Statistical methods

Hypothesis tests were performed using ANOVA and ANCOVA models.

7.2.2.9. Participant flow

A total of 329 subjects were enrolled and 324 were randomised to treatment: 62 to 1 mg, 65 to 2 mg, 65 to 3 mg, 66 to 4 mg and 66 to placebo (Table 11). A total of 211 (65.1%) subjects completed the study: 17 (27.4%) subjects in the 1 mg group, 18 (27.7%) in the 2 mg, 27 (41.5%) in the 3 mg, 26 (39.4%) in the 4 mg and 25 (37.9%) in the placebo discontinued. There were 306 (94.4%) subjects included in the ITT population and 322 (99.4%) in the safety population.

Table 11: Distribution and Disposition by Randomized Dose (All Enrolled Subjects) (copied from Table 8, Study SPD503-304 CSR)

	Placebo N=66	SPD503 1mg N=62	SPD503 2mg N=65	SPD503 3mg N=65	SPD503 4mg N=66	Total N=324
Study Subjects, n (%)						
Randomized	66 (100%)	62 (100%)	65 (100%)	65 (100%)	66 (100%)	324 (100%)
Completed	41 (62.1%)	45 (72.6%)	47 (72.3%)	38 (58.5%)	40 (60.6%)	211 (65.1%)
Early termination	25 (37.9%)	17 (27.4%)	18 (27.7%)	27 (41.5%)	26 (39.4%)	113 (34.9%)
Intent-to-treat	63 (95.5%)	57 (91.9%)	63 (96.9%)	60 (92.3%)	63 (95.5%)	306 (94.4%)
Per protocol	41 (62.1%)	45 (72.6%)	48 (73.8%)	37 (56.9%)	41 (62.1%)	212 (65.4%)
Safety	66 (100%)	61 (98.4%)	65 (100%)	65 (100%)	65 (98.5%)	322 (99.4%)
Reason for Early Termination, n (%)						
AE	5 (7.6%)	2 (3.2%)	2 (3.1%)	6 (9.2%)	9 (13.6%)	24 (7.4%)
Protocol violation	1 (1.5%)	1 (1.6%)	0	0	0	2 (0.6%)
Withdrew consent	5 (7.6%)	6 (9.7%)	8 (12.3%)	8 (12.3%)	4 (6.1%)	31 (9.6%)
Lost to follow-up	4 (6.1%)	4 (6.5%)	1 (1.5%)	5 (7.7%)	8 (12.1%)	22 (6.8%)
Other	10 (15.2%)	4 (6.5%)	7 (10.8%)	8 (12.3%)	5 (7.6%)	34 (10.5%)

7.2.2.10. Major protocol violations/deviations

Two (0.6%) subjects terminated the study because of protocol violations.

7.2.2.11. Baseline data

There were 233 (72.4%) males, 89 (27.6%) females and the age range was 5 to 17 years. There were 241 (74.8%) subjects aged 6 to 12 years and 80 (24.8%) aged 13 to 17 years. The treatment groups were similar in demographic and physical characteristics. However, there were a higher proportion of subjects with inattentive type ADHD in the placebo group: 34.8% compared with 25.5% for the total study population. ADHD-RS-IV total score at baseline was slightly higher in the 1 mg dose group (Table 12). The baseline scores for the secondary efficacy outcome measures were similar for the five treatment groups.

Table 12: ADHD-RS-IV Total Score at Baseline by Randomized Dose (ITT Population) (copied from Table 13, Study SPD503-304 CSR)

Baseline	Placebo N=63	SPD503 1mg N=57	SPD503 2mg N=63	SPD503 3mg N=60	SPD503 4mg N=63
Mean (SD)	39.3 (8.85)	41.7 (7.81)	39.9 (8.74)	39.1 (9.22)	40.6 (8.57)
Median	40.0	42.0	40.0	40.5	41.0
Min, Max	24, 54	24, 54	21, 54	18, 52	25, 54

7.2.2.12. Results for the primary efficacy outcome

All the active treatment groups were superior to placebo in the reduction in ADHD-RS-IV score from baseline. The LS mean (95%) placebo adjusted difference was -6.75 (-11.3 to -2.2) for 1 mg, -5.41 (-9.9 to -0.9) for 2 mg, -7.31 (-11.8 to -2.8) for 3 mg and -7.88 (-12.3 to -3.4) for 4 mg. When analysed by weight adjusted dose, there was a clear dose effect relationship with greatest effect at the highest dose: 0.13 to 0.16 mg/kg/day (Table 13). Efficacy was demonstrated in the 6 to 12 years age group but not in the 13 to 17 years age group (Table 14). Efficacy was demonstrated by inattentive subscale scores (Table 15). Efficacy was demonstrated by hyperactivity/impulsivity subscale scores (Table 16). A subgroup analysis by ADHD type was not presented.

Table 13: ADHD-RS-IV Total Score by Weight-adjusted Actual Dose at Endpoint (ITT Population) (copied from Table 17, Study SPD503-304 CSR)

		Placebo	SPD503 0.01-0.04 mg/kg	SPD503 0.05-0.08 mg/kg	SPD503 0.09-0.12 mg/kg	SPD503 0.13-0.16 mg/kg
Endpoint[1]	N	63	112	84	33	14
	Mean (SD)	27.1 (15.02)	22.1 (13.17)	19.7 (12.44)	19.8 (11.55)	16.8 (10.47)
Change from Baseline	Mean (SD)	-12.2 (12.96)	-17.6 (14.05)	-20.0 (13.82)	-23.5 (13.35)	-24.8 (11.05)
Placebo-adjusted difference[2]	Difference in LS mean[3]	NA	-5.13	-7.56	-8.98	-11.24
	(95% CI)	NA	(-9.0, -1.2)	(-11.7, -3.4)	(-14.4, -3.6)	(-18.6, -3.9)
	p-value	NA	0.0104	0.0004	0.0012	0.0028

Source: Section 12.1, Table 2.1.4.1.

Note: Weight-adjusted actual dose is defined as the actual dose received at each visit divided by the weight at Baseline. For subjects not dispensed a dose at a visit, the assessment is presented under the last reported dose.

1. Endpoint was obtained from the last post-randomization treatment week of the dose titration and dose maintenance phases for which a valid ADHD-RS-IV score was obtained.
2. Placebo-adjusted difference in change from Baseline.
3. Differences in LS mean compared to placebo. A negative difference indicates a positive effect of the active treatment over placebo.

Table 14: ADHD-RS-IV Total Score at Endpoint by Randomized Dose and Age Subgroups (ITT Population) (copied from Table 18, Study SPD503-304 CSR)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Age 6-12 years						
Endpoint[1]	N	45	50	46	41	48
	Mean (SD)	29.9 (14.88)	21.1 (12.87)	24.1 (14.71)	19.7 (13.22)	19.2 (10.35)
Change from Baseline	Mean (SD)	-11.5 (13.74)	-21.0 (14.45)	-16.4 (14.93)	-21.9 (13.97)	-22.3 (11.59)
Placebo-adjusted difference[2]	Difference in LS mean[3]	NA	-9.08	-5.44	-10.29	-10.77
	(95% CI)	NA	-14.3, -3.9	-10.8, -0.1	-15.8, -4.8	-16.0, -5.5
	p-value	NA	0.0007	0.0448	0.0003	<0.0001
Age 13-17 years						
Endpoint[1]	N	18	7	17	19	15
	Mean (SD)	20.1 (13.29)	22.6 (13.05)	16.0 (10.40)	19.7 (10.97)	21.5 (13.15)
Change from Baseline	Mean (SD)	-14.0 (10.95)	-15.9 (9.89)	-22.2 (14.32)	-14.0 (14.90)	-16.2 (12.01)
Placebo-adjusted difference[2]	Difference in LS mean[3]	NA	1.06	-5.43	-0.24	0.26
	(95% CI)	NA	-9.6, 11.7	-13.5, 2.7	-8.0, 7.5	-8.1, 8.6
	p-value	NA	0.8426	0.1867	0.9503	0.9516

Source: Section 12.1, Table 2.1.3.

1. Endpoint was obtained from the last post-randomization treatment week of the dose titration and dose maintenance phases for which a valid ADHD-RS-IV score was obtained.
2. Placebo-adjusted difference in change from Baseline.
3. Differences in LS mean compared to placebo. A negative difference indicates a positive effect of the active treatment over placebo.

Table 15: ADHD-RS-IV Inattentive Subscale Scores by Randomized Dose at Endpoint (ITT Population) (copied from Table 19, Study SPD503-304 CSR).

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Endpoint[1]	N	63	57	63	60	63
	Mean (SD)	15.8 (7.86)	11.6 (6.68)	13.0 (7.74)	12.6 (7.84)	12.0 (6.35)
Change from Baseline	Mean (SD)	-6.4 (7.09)	-10.5 (7.02)	-9.5 (8.36)	-10.1 (7.75)	-10.6 (6.42)
Placebo-adjusted difference[2]	Difference in LS mean[3]	NA	-4.16	-2.96	-3.47	-3.99
	(95% CI)	NA	-6.7, -1.6	-5.5, -0.5	-6.0, -1.0	-6.5, -1.5
	p-value	NA	0.0015	0.0197	0.0070	0.0017

Source: Section 12.1, Table 2.2.1.

1. Endpoint was obtained from the last post-randomization treatment week of the dose titration and dose maintenance phases for which a valid ADHD-RS-IV score was obtained.
2. Placebo-adjusted difference in change from Baseline.
3. Differences in LS mean compared to placebo. A negative difference indicates a positive effect of the active treatment over placebo.

Table 16: ADHD-RS-IV Hyperactivity/Impulsivity by Randomized Dose at Endpoint (ITT Population) (copied from Table 21, Study SPD503-304 CSR)

		Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg	SPD503 4mg
Endpoint[1]	N	63	57	63	60	63
	Mean (SD)	11.3 (8.35)	9.7 (6.87)	8.9 (8.05)	7.1 (5.76)	7.7 (5.96)
Change from Baseline	Mean (SD)	-5.8 (7.09)	-9.9 (7.67)	-8.5 (7.88)	-9.3 (8.07)	-10.3 (6.72)
Placebo-adjusted difference[2]	Difference in LS mean[3]	NA	-2.65	-2.48	-3.85	-3.94
	(95% CI)	NA	-5.0, -0.3	-4.8, -0.2	-6.2, -1.5	-6.2, -1.7
	p-value	NA	0.0280	0.0340	0.0012	0.0008

Source: Section 12.1, Table 2.3.1.

1. Endpoint was obtained from the last post-randomization treatment week of the dose titration and dose maintenance phases for which a valid ADHD-RS-IV score was obtained.
2. Placebo-adjusted difference in change from Baseline.
3. Differences in LS mean compared to placebo. A negative difference indicates a positive effect of the active treatment over placebo.

7.2.2.13. Results for other efficacy outcomes

- In comparison with placebo there was a greater improvement in CPRS-R total score overall for all treatment groups. However, in the 2 mg group there were several time points when efficacy was not demonstrated: 4 hours, 12 hours and 14 hours post-dose.
- Clinical Global Impression-Severity (CGI-S) was not reported as an efficacy outcome.
- There was a significant improvement in CGI-I compared to placebo for the 1 mg, 3 mg and 4 mg dose groups but not for the 2 mg. Improvement in CGI was reported for 31 (54.4%) subjects in the 1 mg group, 27 (42.9%) in the 2 mg, 33 (55.0%) in the 3 mg, 35 (55.6%) in the 4 mg and 19 (30.2%) in the placebo.
- There was a significant improvement in PGA compared to placebo for the 1 mg, 3 mg and 4 mg dose groups but not for the 2 mg. Improvement in PGA was reported for 27 (50.9%) subjects in the 1 mg group, 20 (36.4%) in the 2 mg, 29 (61.7%) in the 3 mg, 30 (56.6%) in the 4 mg and 16 (30.2%) in the placebo.
- In comparison with placebo there was no consistent improvement in CHQ-PF50 scores for any active treatment group.

7.2.2.14. Evaluator commentary

Study SPD503-304 confirmed the findings of Study SPD503-301. There was a clear linear relationship between dose and efficacy up to 0.16 mg/kg/day. The study maintenance phase was of too short a duration to demonstrate efficacy.

7.2.3. Study SPD503-307

7.2.3.1. Study design, objectives, locations and dates

Study SPD503-307 was a randomised, double blind, placebo controlled dose optimisation study conducted in subjects with ADHD and oppositional symptoms. The study was conducted at 33 centres in the US from December 2006 to January 2008.

7.2.3.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female, aged 6-12 years
- DSM-IV-TR™ criteria for a primary diagnosis of ADHD, any sub-type, based on a detailed psychiatric evaluation using the K-SADS-PL

- A minimum Oppositional subscale of the CPRS-R:L score of 14 for males and 12 for females at the Baseline Visit
- A minimum ADHD-RS-IV score of 24 at the Baseline Visit
- A CGI-S score ≥ 4 at the Baseline Visit
- Normal or clinically insignificant Screening ECG findings
- Intellectual function at age-appropriate levels as deemed by the investigator
- Blood pressure measurements within the 95th percentile for age, gender, and height
- Able to swallow intact tablets
- Females of child-bearing potential (FOCP) were to have a negative serum beta human chorionic gonadotropin (HCG) pregnancy test at Screening, a negative urine pregnancy test at Baseline and were to use or agree to use acceptable methods of contraception.

The exclusion criteria included:

- Any current, controlled (requiring a prohibited medication) or uncontrolled, comorbid psychiatric diagnosis (except ODD), including all anxiety disorders (except simple phobias), all major depressive disorders (dysthymia allowed unless medication required), and any severe comorbid Axis II disorders or severe Axis I disorders such as post-traumatic stress disorder, bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder, substance abuse disorder, or other symptomatic manifestations that, in the opinion of the investigator, would contraindicate guanfacine treatment or confound efficacy or safety assessments
- History or presence of planned predatory aggression as indicated by DSM-IV symptoms of conduct disorder
- Baseline (Visit 2) rating of pretty much or very much for Questions 8, 18-22, 25, 29, 31, 33, or 35 on the 40-item Conduct Problem Scale of the New York Parent's Rating Scale – School-aged (NYPRS-S)
- Any condition or illness (including clinically significant abnormal laboratory values) which, in the opinion of the investigator, represented an inappropriate risk to the subject and/or could confound the interpretation of the study
- History or presence of known structural cardiac abnormalities, syncope, cardiac conduction problems, exercise-related cardiac events, or bradycardia (resting heart rate ≤ 50bpm)
- A decrease of >20mmHg in systolic and/or >10mmHg diastolic blood pressure between supine and standing blood pressure measurements at Screening or Baseline
- History of controlled or uncontrolled hypertension
- Current use of any prohibited medication or other medications, including herbal supplements, that had central nervous system (CNS) effects or affected cognitive performance, such as sedating antihistamines and decongestant sympathomimetics (bronchodilators were permitted)
- Current use of any medication, including herbal supplements, that affects blood pressure or heart rate (excluding the subject's current ADHD medication)
- Body mass index (BMI) for age >90th percentile per Center for Disease Control
- Body weight of less than 55 lbs (25kg)
- Known or suspected allergy, hypersensitivity, or clinically significant intolerance to guanfacine or any components found in SPD503

- Clinically important abnormality on urine drug and alcohol screen (with the exception of the subject's current ADHD stimulant, if applicable) at Screening
- Pregnant or currently lactating
- History of alcohol or other substance abuse or dependence, as defined by DSM-IV-TR (with the exceptions of caffeine or nicotine) within the last year.

7.2.3.3. Study treatments

The study treatments were:

- Guanfacine extended release 1 mg to 4 mg
- Placebo

Subjects were titrated in 1mg weekly increments to their optimal dose based upon tolerance and response. Subjects who achieved a CGI-S score ≤ 2 at a given tolerated dose were considered to be at an optimal dose. Subjects with a CGI-S score of 2 at a given tolerated dose could be titrated to a higher dose based on the investigator's discretion. The dose optimisation period was for 5 weeks, subjects were maintained at optimal dose for 3 weeks and there was a 1 week tapering period. There was a washout period for previous psychoactive medications. Tricyclic antidepressants, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors including atomoxetine (Strattera®), antipsychotics, neuroleptics, anxiolytics, benzodiazepines or benzodiazepine derivatives, psychostimulants, methylphenidate, amphetamines (including sympathomimetics, appetite suppressants, modafinil, and pemoline), cough/cold preparations containing stimulants, other medications containing amphetamine or pemoline, clonidine and guanfacine, monoamine oxidase inhibitors, anticonvulsant medications, sedatives, sedative-hypnotics such as zopiclone, sedating antihistamines (as a single preparation or in combination), all investigational medications, any herbal preparations that have CNS effect, affect cognitive performance, and/or affect BP or heart rate, and antihypertensives were prohibited.

7.2.3.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the Oppositional Subscale of the Conners' Parent Rating Scale-Revised: Long Form (CPRS-R:L). The secondary efficacy outcome measures were:

- ADHD-RS-IV
- CGI-I
- 40-item Conduct Problem Scale of the New York Parent's Rating Scale – School- Aged (NYPRS-S)
- Parent Stress Index – Short Form (PSI/SF)
- Medication Satisfaction Survey (MSS)

The safety outcome measures were AEs, clinical laboratory tests, vital signs, physical examination and ECGs.

7.2.3.5. Randomisation and blinding methods

Subjects were randomised to treatment using IVRS. Randomisation was in the ratio 2:1 for gaunfacine: placebo. There were matching placebos for the 1 mg, 2 mg, 3 mg and 4 mg tablets.

7.2.3.6. Analysis populations

The full analysis set (FAS) and the safety population included all randomised subjects who received at least one dose of study treatment.

7.2.3.7. Sample size

The sample size calculation was based on the primary efficacy outcome measure, an effect size of 0.5 (a difference between active and placebo group of 3.5 points, and a SD of 7 points), power of 90% and an alpha of 0.05. This resulted in 128 subjects in the guanfacine group and 64 in the placebo. To account for dropouts, a total of 210 subjects were required.

7.2.3.8. Statistical methods

Hypothesis tests were performed using ANCOVA and expressed as LS means and 95% CI. Imputation was performed using LOCF.

7.2.3.9. Participant flow

There were 217 subjects randomised to treatment: 138 to guanfacine and 79 to placebo. A total of 157 subjects completed the study: 109 (79.0%) in the guanfacine group and 48 (60.8%) in the placebo (Table 17). There were 14 (10.1%) subjects in the guanfacine group who terminated because of AE and one (1.3%) in the placebo. There were three (2.2%) subjects in the guanfacine group who terminated because of lack of efficacy and twelve (15.2%) in the placebo.

Table 17: Summary of Subject Disposition (All Subjects) (copied from Table 6, Study SPD503-307 CSR)

	SPD503 (N=138) # (%) Subjects	Placebo (N=79) # (%) Subjects	Total (N=217) # (%) Subjects
Subjects Who Were			
Enrolled	138 (100.0)	79 (100.0)	217 (100.0)
Randomized	138 (100.0)	79 (100.0)	217 (100.0)
Safety Population*	136 (98.6)	78 (98.7)	214 (98.6)
Full Analysis Set†	136 (98.6)	78 (98.7)	214 (98.6)
Modified Full Analysis Set‡	123 (89.1)	77 (97.5)	200 (92.2)
Study Completers	109 (79.0)	48 (60.8)	157 (72.4)
Early Termination	29 (21.0)	31 (39.2)	60 (27.6)
Subjects Who Ended Study Due To			
Adverse Event(s)	14 (10.1)	1 (1.3)	15 (6.9)
Protocol Violation	1 (0.7)	7 (8.9)	8 (3.7)
Consent Withdrawn	7 (5.1)	6 (7.6)	13 (6.0)
Lost to Follow-up	1 (0.7)	4 (5.1)	5 (2.3)
Lack of Efficacy	3 (2.2)	12 (15.2)	15 (6.9)
Other§	3 (2.2)	1 (1.3)	4 (1.8)

* Safety population includes all subjects who received one dose of investigational product during this study.

† Full Analysis Set includes all subjects who received one dose of investigational product during this study.

‡ The Modified Full Analysis Set (Modified FAS) includes all subjects in the FAS with the exception of those who had major violations of the entry criteria.

§ In the SPD503 group, the other reasons for early termination were: subject was in juvenile detention center, subject refused Baseline blood collection, and subject did not respond to calls or letters. In the placebo group, the other reason for early termination was subject had history of lead poisoning, low WBC count, and neutropenia.

Note: Subjects enrolled include all subjects who are not considered screening failures.

Note: Percentages are based on the number of enrolled subjects in each treatment group.

7.2.3.10. Major protocol violations/deviations

There was one (0.7%) subjects in the guanfacine group who terminated because of protocol violation and seven (8.9%) in the placebo.

7.2.3.11. Baseline data

There were 147 (68.7%) males, 67 (31.3%) females and the age range was 6 to 13 years. There was a higher proportion of females in the guanfacine group, 36.0%, compared to the placebo, 23.1%. Otherwise the treatment groups were similar in demographic characteristics. The treatment groups were similar in disease characteristics. Overall, there were 180 (84.1%) subjects with combined type ADHD, 27 (12.6%) with inattentive, seven with hyperactive/impulsive and 143 (66.8%) with a diagnosis of Oppositional Defiant Disorder (ODD). A total of 145 (67.8%) subjects had received prior psychoactive medication,

predominantly with psychostimulants. Three subjects used prohibited medication during the study. Mean treatment compliance rates were 97.2% for guanfacine and 96.7% for placebo.

7.2.3.12. Results for the primary efficacy outcome

There was a significant improvement in the oppositional subscale of CPRS-R:L in the guanfacine group compared to placebo. The LS mean change from baseline was -10.9 in the guanfacine group and -6.8 in the placebo, LS mean difference (95% CI) -4.1 (-6.1 to -2.1) p <0.001. At endpoint there was a mean reduction of 56.2% in the guanfacine group and 33.7% in the placebo. At endpoint, there were 86 (67.2%) responders in the guanfacine group and 21 (28.4%) in the placebo, p <0.001. In females, at endpoint the LS mean change from baseline was -12.4 in the guanfacine group and -5.1 in the placebo, p <0.001. There was no difference in efficacy by race. A subgroup analysis was not presented by ADHD type.

7.2.3.13. Results for other efficacy outcomes

There was improvement in the guanfacine group compared to placebo for all secondary endpoints.

- For ADHD-RS-IV, at endpoint the LS mean change from baseline was -23.8 in the guanfacine group and -11.5 in the placebo, LS mean difference (95% CI) -12.3 (-16.1 to -8.5) p <0.001. There was a 56.7% reduction in ADHD-RS-IV score in the guanfacine group and 26.5% reduction in the placebo.
- For CGI-I, at endpoint there was improvement in 93 (71.5%) subjects in the guanfacine group and 24 (32.0%) in the placebo, p <0.001.
- For NYPRS-S, at endpoint the LS mean change from baseline was -16.0 in the guanfacine group and -9.6 in the placebo, LS mean difference (95% CI) -6.5 (-9.6 to -3.3) p <0.001.
- For PSI/SF, at endpoint the LS mean change from baseline was 17.0 in the guanfacine group and 7.7 in the placebo, LS mean difference (95% CI) 9.2 (3.4 to 15.1) p <0.001.
- For MSS a higher proportion of parents in the guanfacine group were satisfied with their child's behaviour, social interactions and attention while they were taking the medication; were happy with duration of effect but felt their child was sleepier during the day p<0.001. Overall satisfaction was higher with guanfacine than placebo.

7.2.3.14. Evaluator commentary

Study SPD503-307 demonstrated clinically and statistically significant improvement in oppositional features in children and adolescents aged 6 to 17 years with ADHD. The maintenance phase was of too short a duration to establish efficacy (3 weeks).

7.2.4. **Study SPD503-312**

7.2.4.1. Study design, objectives, locations and dates

Study SPD503-312 was a randomised, double blind, placebo controlled, dose optimisation study of the efficacy and safety of guanfacine in adolescents aged 13 to 17 years with ADHD. The study was conducted at 48 centres in the US from September 2011 to May 2013.

7.2.4.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female, aged 13-17 years.
- Subject met DSM-IV-TR criteria for a primary diagnosis of ADHD, combined subtype, hyperactive/impulsive subtype, or inattentive subtype, based on a detailed psychiatric evaluation using the K-SADS-PL.
- Minimum ADHD-RS-IV total score of 32.

- Minimum CGI-S score of 4.
- Functioning at an age-appropriate level intellectually, as deemed by the Investigator.
- All female subjects had to have a negative β-hCG and a negative urine pregnancy test and agree to abstain from sexual activity or comply with any applicable contraceptive requirements of the protocol.
- Supine and standing blood pressure measurement within the 95th percentile for age, sex, and height.

The exclusion criteria included:

- Current, controlled (requiring a prohibited medication or behavioural modification program) or uncontrolled, comorbid psychiatric diagnosis (except ODD), including any severe comorbid Axis II disorders or severe Axis I disorders such as post-traumatic stress disorder, bipolar illness, psychosis, pervasive developmental disorder, obsessive compulsive disorder, substance abuse disorder, or other symptomatic manifestations or lifetime history of bipolar illness, psychosis, or conduct disorder that, in the opinion of the investigator, would contraindicate SPD503 treatment or confound efficacy or safety assessments.
- Any condition or illness including clinically significant abnormal Screening Visit (Visit 1) laboratory values which, in the opinion of the investigator, represented an inappropriate risk to the subject and/or could have confounded the interpretation of the study.
- Known history or presence of structural cardiac abnormalities, serious heart rhythm abnormalities, syncope, cardiac conduction problems (for example, clinically significant heart block), exercise-related cardiac events including syncope and pre-syncope, or clinically significant bradycardia.
- Orthostatic hypotension or a known history of controlled or uncontrolled hypertension.
- Clinically significant ECG findings as judged by the investigator with consideration of the central ECG interpretation.
- Subject used any prohibited medication or other medications, including herbal supplements, that affect blood pressure, heart rate, have central nervous system effects, or affect cognitive performance, such as sedating antihistamines and decongestant sympathomimetics (inhaled bronchodilators were permitted) or a history of chronic use of sedating medications (that is, antihistamines) at the Baseline Visit (Visit 2).
- History of alcohol or other substance abuse or dependence, as defined by DSM-IV-TR (with the exception of nicotine), within the last 6 months.
- Subject was significantly overweight based on Centers for Disease Control and Prevention BMI-for-age sex-specific charts at the Screening Visit (Visit 1). Significantly overweight was defined as a BMI >95th percentile for this study.
- Body weight of <34.0kg or >91.0kg at the Screening Visit (Visit 1).
- Known or suspected allergy, hypersensitivity, or clinically significant intolerance to guanfacine hydrochloride or any components found in SPD503.
- Clinically important abnormality on the urine drug and/or alcohol screen (excluding the subject's current ADHD stimulant if applicable).
- Subject was female and was pregnant or currently lactating.
- Subject was considered a suicide risk in the opinion of the investigator, had previously made a suicide attempt, or had a prior history of, or was demonstrating active suicide ideation.

Subjects with intermittent passive suicidal ideation were not necessarily excluded based on the assessment of the investigator.

- History of failure to respond to an adequate trial (consisting of an appropriate dose and adequate duration of therapy), in the opinion of the investigator, of an α2-agonist for the treatment of ADHD.
- History of a seizure disorder (other than a single childhood febrile seizure occurring before the age of 3 years) or the presence of a serious tic disorder (including Tourette's Syndrome).

7.2.4.3. Study treatments

The Study treatments were:

1. Guanfacine 1 to 7 mg daily
2. Placebo

There was a 7 week optimisation phase, a 6 week maintenance phase and a 2 week taper. The dose was considered optimal if a subject achieved at least a 30% reduction from Baseline in ADHD-RS-IV total score and a CGI-S score of 1 or 2 with tolerable side effects. Maximum dose was based on weight, and subjects in the 58.5 to 91.0 kg group could be titrated up to 7 mg/day. The prohibited medications were the same as for Study SPD503-307.

7.2.4.4. Efficacy variables and outcomes

The primary efficacy outcome measure was ADHD-RS-IV. The secondary efficacy outcome measures were:

- CGI-S
- CGI-I
- WFIRS-P
- BRIEF-Parent Form

The safety outcome measures were: AEs, clinical laboratory tests, vital signs, physical examinations, ECGs, BPRS-C, SSEQ, C-SSRS, and PDSS.

7.2.4.5. Randomisation and blinding methods

Subjects were randomised 1:1 to treatment group by interactive response technology. Randomisation was stratified by weight groupings. Blinding was maintained by using corresponding placebo for each tablet strength.

7.2.4.6. Analysis populations

The FAS and safety populations included all randomised subjects who took at least one dose of study treatment.

7.2.4.7. Sample size

The sample size calculation was based on the primary efficacy outcome measure. In order to detect a 4 point difference, assuming a SD of 10 points, for 90% power at an alpha of 0.05, and a 5% drop-out rate, 140 subjects were required in each treatment group.

7.2.4.8. Statistical methods

Hypothesis tests were performed using ANCOVA. Missing data were imputed using multiple imputations based on the placebo data.

7.2.4.9. Participant flow

A total of 314 subjects were enrolled and randomised, 157 to guanfacine and 157 to placebo. A total of 207 (65.9%) subjects completed: 105 (66.9%) in the guanfacine group and 102 (65.0%)

in the placebo. The commonest reason for withdrawal was lack of efficacy: nine (5.7%) subjects in the guanfacine group and 25 (15.9%) in the placebo.

7.2.4.10. Major protocol violations/deviations

There was one (0.6%) subject in the guanfacine group and three (1.9%) in the placebo who were withdrawn because of protocol violation.

7.2.4.11. Baseline data

There were 202 (64.7%) males, 110 (35.3%) males and the age range was 13 to 17 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in ADHD characteristics (Table 18). There was prior psychostimulant use by 110 (70.1%) subjects in the guanfacine group and 120 (77.4%) in the placebo. Mean compliance was 98.86% in the guanfacine group and 99.19% in the placebo.

Table 18: Summary of Disease Characteristics (Safety Population) (copied from Table 9, Study SPD503-312 CSR)

	Placebo (N = 155)	SPD503 (N = 157)	Total (N = 312)
ADHD subtype, n (%)			
Predominately inattentive	45 (29.0)	46 (29.3)	91 (29.2)
Predominately hyperactive-impulsive	4 (2.6)	5 (3.2)	9 (2.9)
Combined subtype	106 (68.4)	106 (67.5)	212 (67.9)
Time since ADHD diagnosis (yrs)			
Mean (SD)	5.4 (3.83)	4.8 (3.92)	5.1 (3.88)
Median	6.0	5.0	6.0
Min, Max	0, 15	0, 14	0, 15
Baseline ADHD-RS-IV total score			
Mean (SD)	40.0 (6.11)	39.9 (5.57)	39.9 (5.83)
Median	38.0	39.0	39.0
Min, Max	32, 54	32, 53	32, 54
Baseline CGI-S, n (%)			
Normal, not at all ill	0	0	0
Borderline mentally ill	0	0	0
Mildly ill	0	0	0
Moderately ill	83 (53.5)	87 (55.4)	170 (54.5)
Markedly ill	67 (43.2)	67 (42.7)	134 (42.9)
Severely ill	5 (3.2)	3 (1.9)	8 (2.6)
Among the most extremely ill subjects	0	0	0
Current psychiatric comorbidities, n (%)			
None	136 (87.7)	133 (84.7)	269 (86.2)
Diagnosis of ODD [a]	16 (10.3)	20 (12.7)	36 (11.5)
Other	5 (3.2)	6 (3.8)	11 (3.5)
Significant oppositional symptoms[b], n (%)			
Yes	69 (44.5)	79 (50.3)	148 (47.4)
No	86 (55.5)	78 (49.7)	164 (52.6)

[a] Diagnosis of ODD per psychiatric history electronic case report form comes from the diagnosis of ODD in the current psychiatric comorbidities section.

[b] Defined as a CPRS-R:L oppositional subscale score at the Baseline Visit (Visit 2) of □9 for males and □8 for females.

Note: Percentages are based on the number of subjects with data in each treatment group and total. Subjects may have more than 1 other psychiatric comorbidity.

ADHD=attention-deficit/hyperactivity disorder; CPRS-R:L=Conners' Parent Rating Scale-Revised: Long Form
CGI-S=Clinical Global Impressions–Severity; ODD=oppositional defiant disorder; SD=standard deviation

7.2.4.12. Results for the primary efficacy outcome

There was a significant improvement in the primary efficacy outcome measure, ADHD-RS-IV, in the guanfacine group compared to placebo (Table 19). The mean (SD) change (improvement) from baseline in the guanfacine group was -25.7 (10.09) and in the placebo was -19.5 (12.63),

LS mean difference (95% CI) was -6.026 (-8.865 to -3.187) p <0.001. Efficacy was not influenced by weight adjusted dose, sex or race.

Table 19: Summary of MMRM Analysis of ADHD-RS-IV Total Score and Change from Baseline in ADHD-RS-IV Total Score at Week 13 – (FAS) (copied from Table 11, Study SPD503-312 CSR)

	Placebo (N=155)	SPD503 (N=157)
Baseline		
N	155	157
Mean (SD)	40.0 (6.11)	39.9 (5.57)
Visit 13		
N	106	109
Mean (SD)	20.3 (13.35)	14.1 (9.38)
Change from baseline		
Mean (SD)	-19.5 (12.63)	-25.7 (10.09)
Comparison to placebo [a]		
LS mean	-18.527	-24.552
Difference in LS means	NA	-6.026
(95% CI)	NA	-8.865, -3.187
Effect Size	NA	0.52
p-value		<0.001

[a] LS Mean, standard error (SE), effect size, and p-value are based on repeated measures analysis for the change from baseline scores at Visits 3-13 (Weeks 1-13), with an unstructured covariance structure, random subject effect, treatment (2 levels), time (11 levels), treatment group-by-time, and weight group (4 levels) as fixed effects and including baseline and baseline-by-time as covariates. Note: A negative difference in LS Mean (SPD503 - placebo) indicates a positive effect of the active treatment over the placebo.

ADHD-RS-IV=Attention deficit/Hyperactivity Disorder Rating Scale-IV; CI=confidence interval; FAS=Full Analysis Set; LS=least squares; MMRM=mixed model repeated measures; NA=not applicable; SD=standard deviation.

7.2.4.13. Results for other efficacy outcomes

- For CGI-S, there were 78 (50.6%) subjects in the guanfacine group and 56 (36.1%) in the placebo who were normal or borderline mentally ill, p = 0.010
- CGI-I improved in 104 (67.5%) subjects in the guanfacine group and 71 (45.8%) in the placebo, p <0.001.
- There was no significant difference between the treatment groups in WFIRS-P learning and school domain, family domain or global scores.
- There was no significant difference between the treatment groups in BRIEF-Parent Form, change from baseline.

7.2.4.14. Evaluator Commentary

Study SPD503-312 demonstrated efficacy in the 13 to 17 years age group. The primary efficacy outcome measure was ADHD-RS-IV which was also used in the inclusion criteria, was measured at baseline and the change from baseline to endpoint was analysed. Response by ADHD-RS-IV was not used as an outcome measure. The maintenance phase was of 6 weeks duration.

7.2.5. **Study SPD503-313**

7.2.5.1. Study design, objectives, locations and dates

Study SPD503-313 was a double blind, randomised, placebo controlled trial of guanfacine extended release in subjects with ADHD on psychostimulant treatment. The study was conducted at 59 centres in the US from September 2008 to December 2009.

7.2.5.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female, aged 6-17 years.

- DSM-IV-TR criteria for a primary diagnosis of ADHD, any sub-type, based on a detailed psychiatric evaluation using the K-SADS-PL.
- A minimum ADHD-RS-IV score of 24.
- A CGI-S score ≥ 3.
- Receiving a stable, once-daily dose, consistent with the package insert, of one of the following long-acting psychostimulants, approved for the treatment of ADHD, for at least 4 weeks prior to Screening:
  - Subjects aged 6-17 years receiving Adderall XR® (mixed salts of a single-entity amphetamine product).
  - Subjects aged 6-12 years only receiving Vyvanse™ (lisdexamfetamine dimesylate)
  - Subjects aged 6-17 years receiving Concerta® (methylphenidate HCl)
  - Subjects aged 6-17 years receiving Focalin XR® (dexmethylphenidate hydrochloride)
  - Subjects aged 6-12 years only receiving Ritalin LA® (methylphenidate hydrochloride extended-release)
  - Subjects aged 6-15 years only receiving Metadate CD™ (methylphenidate hydrochloride, USP)
  - FDA-approved generic equivalents of the above psychostimulants with the same dose and age ranges.
- Demonstrated a partial but sub-optimal response to subject's current stimulant medication; in the Investigator's opinion, need for additional treatment.
- Normal or clinically insignificant Screening ECG findings
- Intellectual function at age-appropriate levels as deemed by the Investigator.
- Blood pressure measurements within the 95th percentile for age, gender, and height.
- FOCP must have a negative serum beta Human Chorionic Gonadotropin (HCG) pregnancy test at Screening, a negative urine pregnancy test at Baseline and must use or agree to use acceptable methods of contraception.

The exclusion criteria included:

- Any current, controlled (requiring a prohibited medication or behavioural modification program) or uncontrolled, co-morbid psychiatric diagnosis (except ODD), including any severe co-morbid Axis II disorders or severe Axis I disorders such as Post Traumatic Stress Disorder (PTSD), bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder (OCD), substance abuse disorder, or other symptomatic manifestations or lifetime history of bipolar illness, psychosis or conduct disorder that, in the opinion of the Investigator, contraindicate SPD503 treatment or confound efficacy or safety assessments.
- Subjects who are at suicide risk, any subject who has previously made a suicide attempt or those who are currently demonstrating active suicide ideation.
- Any condition or illness (including clinically significant abnormal Screening laboratory values) which, in the opinion of the Investigator, represents an inappropriate risk to the subject and/or could confound the interpretation of the study.
- Subject has a history of seizure disorder (other than a single childhood febrile seizure occurring before the age of 3 years).
- History or presence of known structural cardiac abnormalities, symptomatic cardiovascular disease, advanced arteriosclerosis, cardiomyopathy, serious heart rhythm abnormalities,

coronary artery disease, syncope, cardiac conduction problems (for example, clinically significant heart block or clinically significant abnormality in QT or QTc interval, etc.), exercise-related cardiac events including syncope and pre-syncope, clinically significant bradycardia or any other serious cardiac problem that may place a subject at increased vulnerability to the effects of a stimulant and/or α2-agonist medication.

- Subject has a family history of sudden cardiac death or ventricular arrhythmia.
- Subject has symptomatic or clinically meaningful orthostatic hypotension based on clinical judgment.
- History of controlled or uncontrolled hypertension.
- Current use of any prohibited medication or other medications, including herbal supplements, that have central nervous system (CNS) effects or affect cognitive performance, such as sedating antihistamines and decongestant sympathomimetics (bronchodilators are permitted).
- Current use of any medication including herbal supplements that affects BP or HR or are known to prolong the QT/QTc interval (excluding the subject's current ADHD medication).
- Morbidly overweight or obese, as defined by a BMI >95th percentile.
- Weight less than 55 lbs (25kg).
- Weight greater than 176 lbs (80kg).
- Clinically important abnormality on urine drug and alcohol screen (UDS) (excluding the subject's current ADHD stimulant) at Screening
- Pregnancy or currently lactating.
- History of alcohol or other substance abuse or dependence, as defined by DSM-IV (with the exceptions of caffeine or nicotine) within the last year.

7.2.5.3. Study treatments

The study treatment were:

1. Guanfacine extended release 1 to 4 mg in the morning
2. Guanfacine extended release 1 to 4 mg in the evening
3. Placebo

There was a five week dose optimisation phase, a three week maintenance phase and a 9 day taper.

Subjects continued to take their usual dose of psychostimulant. The following medications were prohibited: any antihypertensives, tricyclic antidepressants, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors including Strattera®, antipsychotics, neuroleptics, anxiolytics, benzodiazepines or benzodiazepine derivatives, psychostimulants (other than entry defined use of certain pre-specified long acting oral psychostimulants), including sympathomimetics, appetite suppressants, modafinil, and pemoline, cough/cold preparations containing stimulants, other medications containing amphetamine or pemoline, clonidine and guanfacine, monoamine oxidase inhibitors, anticonvulsant medications, sedatives, sedative hypnotics such as zopiclone, sedating antihistamines (as a single preparation or in combination), and melatonin.

7.2.5.4. Efficacy variables and outcomes

The primary efficacy outcome variable was ADHD-RS-IV. The secondary efficacy outcome variables were:

- CGI-I
- Connor's Global Index – Parent (CGI-P)
- Before-school Functioning Questionnaire (Wil-Hammer) (BSFQ)
- CPRS-R:L
- Post-Sleep Questionnaire

The safety outcome measures were: AEs clinical laboratory tests, vital signs, height, weight, ECGs and physical examination findings.

7.2.5.5. Randomisation and blinding methods

Randomisation was by IVRS in the ratio 1:1:1. There were matching placebo tablets that were used for the evening or morning dose and in the placebo group.

7.2.5.6. Analysis populations

The FAS and safety populations included all subjects who received at least one dose of study treatment.

7.2.5.7. Sample size

The sample size was based on the primary efficacy outcome measure and comparisons with placebo. To detect an effect size of 0.4, equivalent to a 4 point difference, assuming a SD of 10, at a power of 90% and alpha of 0.05 a samples size of 133 per treatment group was required. To account for dropouts a sample size of 147 subjects per group was required.

7.2.5.8. Statistical methods

Hypothesis tests were performed using ANCOVA and CMH. Missing data were imputed using LOCF. Dunnett's adjustment for multiplicity was used.

7.2.5.9. Participant flow

There were 461 subjects randomised to treatment: 154 in the guanfacine morning (AM) group, 153 in the guanfacine evening (PM) group and 154 in the placebo (Table 20). Six subjects did not receive study treatment. The FAS and safety analysis included 150 (97.4%) subjects in the AM group, 152 (99.3%) in the PM and 153 (99.4%) in the placebo. There were 121(78.6%) subjects in the AM group, 128 (83.7%) in the PM and 129 (83.8%) in the placebo who completed the study.

Table 20: Summary of Subject Disposition (copied from Table 2, Study SPD503-313 CSR)

	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.

7.2.5.10. Major protocol violations/deviations

A total of 17 (3.7%) subjects were withdrawn because of protocol violation: eight (5.2%) in the AM group, six (3.9%) in the PM and three (1.9%) in the placebo.

7.2.5.11. Baseline data

There were 326 (71.6%) males, 129 (28.4%) females and the age range was 6 to 17 years. The treatment groups were similar in demographic characteristics and psychostimulant treatment, but the PM group had a lower mean weight: mean (SD) weight 90.76 (29.7) lb in the AM group, 85.40 (26.5) lb in the PM and 89.14 (27.9) lb in the placebo. The treatment groups were similar in disease characteristics (Table 21). Compliance was 98.8% for the AM dose and 96.65 for the PM.

Table 21: Summary of Disease Characteristics (copied from Table 4, Study SPD503-313 CSR)

	Placebo + Stimulant (N = 153)	SPD503 AM + Stimulant (N = 150)	SPD503 PM + Stimulant (N = 152)	Overall SPD503 + Stimulant (N = 302)	Total (N = 455)
ADHD Subtype, n (%)					
Predominately Inattentive	26 (17.0)	31 (20.7)	24 (15.8)	55 (18.2)	81 (17.8)
Predominately Hyperactive-impulsive	1 (0.7)	3 (2.0)	2 (1.3)	5 (1.7)	6 (1.3)
Combined subtype	126 (82.4)	116 (77.3)	126 (82.9)	242 (80.1)	368 (80.9)
Time Since ADHD Diagnosis (yrs)					
Mean (SD)	3.9 (2.99)	3.9 (2.80)	3.8 (2.87)	3.9 (2.83)	3.9 (2.88)
Median	4.0	4.0	4.0	4.0	4.0
Min, Max	0, 15	0, 11	0, 13	0, 13	0, 15
Baseline ADHD-RS-IV					
Mean (SD)	37.7 (7.75)	37.6 (8.13)	37.0 (7.65)	37.3 (7.89)	NA
Median	37.0	38.0	37.0	37.0	NA
Min, Max	24, 52	16, 54[a]	16, 54[a]	16, 54[a]	NA
Current Psychiatric Comorbidities, n (%)					
None	119 (77.8)	114 (76.0)	123 (80.9)	237 (78.5)	356 (78.2)
Diagnosis of ODD[a]	31 (20.3)	33 (22.0)	26 (17.1)	59 (19.5)	90 (19.8)
Other	7 (4.6)	9 (6.0)	7 (4.6)	16 (5.3)	23 (5.1)
Current diagnosis of ODD[b] (per CRF), n (%)					
Yes	31 (20.3)	33 (22.0)	26 (17.1)	59 (19.5)	90 (19.8)
No	122 (79.7)	117 (78.0)	126 (82.9)	243 (80.5)	365 (80.2)
Significant oppositional symptoms[c], n (%)					
Yes	95 (62.1)	86 (57.3)	93 (61.2)	179 (59.3)	274 (60.2)
No	58 (37.9)	64 (42.7)	59 (38.8)	123 (40.7)	181 (39.8)
Prior Psychostimulant Use[d], n (%)					
Any	153 (100.0)	149 (99.3)	152 (100.0)	301 (99.7)	454 (99.8)
1	95 (62.1)	94 (62.7)	92 (60.5)	186 (61.6)	281 (61.8)
2	28 (18.3)	25 (16.7)	31 (20.4)	56 (18.5)	84 (18.5)
3	17 (11.1)	24 (16.0)	24 (15.8)	48 (15.9)	65 (14.3)
4	9 (5.9)	5 (3.3)	3 (2.0)	8 (2.6)	17 (3.7)
5	3 (2.0)	1 (0.7)	1 (0.7)	2 (0.7)	5 (1.1)
>5	1 (0.7)	0 (0.0)	1 (0.7)	1 (0.3)	2 (0.4)
Prior Antipsychotic Use, n (%)					
Any	6 (3.9)	6 (4.0)	7 (4.6)	13 (4.3)	19 (4.2)

[a] There were 2 subjects (52-011 in the SPD503 AM and 56-001 in the SPD503 PM group) who had ADHD-RS-IV Total scores below the protocol requirement of 24.

[b] Diagnosis of ODD per psychiatric history CRF comes from the diagnosis of ODD in the current psychiatric comorbidities section.

[c] Significant oppositional symptoms was defined as a score of ≥14 for boys and ≥12 for girls on the oppositional subscale of the CPRS-R:L.

[d] This denotes all prior psychostimulant use, including the concomitant psychostimulant. In the SPD503 AM group, a data error was found on the eCRF regarding the start date for Subject 54-003. This subject had the first dose of psychostimulant recorded as 22 Jun 2009 in the eCRF instead of 22 Jun 2007 as noted in the source docs; therefore, the psychostimulant was not identified as starting before the first dose of study drug.

7.2.5.12. Results for the primary efficacy outcome

Both guanfacine treatment groups had a greater improvement in ADHD-RS-IV score than placebo, but there was a slightly greater improvement in the PM group (Table 22). The LS mean (95%) difference from placebo was -4.5 (-7.5 to -1.4) p = 0.002 in the AM group and -5.3 (-8.3 to -2.3) p <0.001 in the PM group. There were 118 (79.2%) subjects coded as responders in the AM group, 123 (83.1%) in the PM group and 106 (69.7%) in the placebo. The effect size was similar for the subgroups of males and females and by race. The effect size was also similar for inattentiveness and hyperactivity/impulsiveness subscales.

Table 22: Summary of Change from Baseline in ADHD-RS-IV Total Score at Endpoint - LOCF (FAS) (copied from Table 5, Study SPD503-313 CSR)

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]

[a] Endpoint is the last valid ADHD-RS-IV Total score obtained post Baseline, before tapering.
[b] LS mean, effect size, and p-value were based on type III sum of squares from an ANCOVA model for the change from Baseline, including treatment group and psychostimulant type as fixed effects, and Baseline value as a covariate.
[c] p-value for SPD503 AM and PM groups based on Dunnett's multiple comparison procedure.
[d] p-value for All SPD503 was a t-test. This was a secondary efficacy analysis.

7.2.5.13. Results for other efficacy outcomes

- For CGI-I there was improvement compared to placebo in both guanfacine groups: 105 (70.5%) subjects in the AM group, p = 0.024, 110 (74.2%) in the PM, p = 0.003, and 88 (57.9%) in the placebo.
- For CGI-S there was significantly less severity in the guanfacine groups at endpoint (Table 23).

Table 23: Summary and Analysis of CGI-S (FAS) (copied from Table 10, Study SPD503-313 CSR)

	Placebo+ Stimulant (N=153)	SPD503 AM+ Stimulant (N=150)	SPD503 PM+ Stimulant (N=152)	All SPD503+ Stimulant (N=302)
Baseline				
Normal, not at all ill	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Borderline mentally ill	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mildly ill	4 (2.6)	5 (3.3)	7 (4.6)	12 (4.0)
Moderately ill	80 (52.3)	89 (59.3)	81 (53.3)	170 (56.3)
Markedly ill	59 (38.6)	46 (30.7)	57 (37.5)	103 (34.1)
Severely ill	10 (6.5)	10 (6.7)	7 (4.6)	17 (5.6)
Amongst the most extremely ill subjects	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CGI-S = 1 or 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CGI-S > 2	153 (100.0)	150 (100.0)	152 (100.0)	302 (100.0)
Endpoint				
Normal, not at all ill	23 (15.1)	34 (22.8)	37 (25.0)	71 (23.9)
Borderline mentally ill	27 (17.8)	29 (19.5)	39 (26.4)	68 (22.9)
Mildly ill	44 (28.9)	51 (34.2)	39 (26.4)	90 (30.3)
Moderately ill	41 (27.0)	24 (16.1)	24 (16.2)	48 (16.2)
Markedly ill	14 (9.2)	9 (6.0)	8 (5.4)	17 (5.7)
Severely ill	3 (2.0)	2 (1.3)	1 (0.7)	3 (1.0)
Amongst the most extremely ill subjects	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
p-value[a]		0.013	<0.001	<0.001
CGI-S = 1 or 2	50 (32.9)	63 (42.3)	76 (51.4)	139 (46.8)
CGI-S > 2	102 (67.1)	86 (57.7)	72 (48.6)	158 (53.2)
p-value[a]		0.093	0.001	0.005

[a] p-value is based on Cochran-Mantel-Haenszel statistic stratifying by psychostimulant type comparing the treatment groups.
Note: Endpoint is the last non-missing assessment obtained post-Baseline and before first dose of taper medication.

- For Connor's Global Index – Parent (CGI-P), both guanfacine treatment groups had a greater improvement than placebo, but there was a slightly greater improvement in the PM group. The LS mean (95%) difference from placebo was -1.7 (-3.2 to –0.3) p = 0.019 in the AM group and -2.6 (-4.0 to -1.1) p <0.001 in the PM group.
- For the Before-school Functioning Questionnaire (Wil-Hammer) (BSFQ) there was similar benefit compared to placebo for both active treatment groups. The LS mean (95%) difference from placebo was -5.1 (-8.0 to –2.2) p <0.001 in the AM group and -4.7 (-7.6 to -1.7) p = 0.002 in the PM group.
- For PGA there was improvement compared to placebo in both guanfacine groups: 90 (69.8%) subjects in the AM group, p <0.001, 90 (67.7%) in the PM, p <0.001, and 67 (47.5%) in the placebo.
- For CPRS-R:L both guanfacine treatment groups had a greater improvement than placebo, but there was a slightly greater improvement in the PM group. The LS mean (95%) difference from placebo was -2.4 (-3.9 to –0.9) p = 0.001 in the AM group and -2.2 (-3.6 to -0.7) p = 0.003 in the PM group.
- Post-Sleep Questionnaire there was no significant difference in quality of sleep between the treatment groups: mean (SD) change from baseline -6.6 (6.7) for AM, -6.3 (7.05) for PM and -4.2 (6.79) for placebo.

7.2.5.14. Evaluator Commentary

Study SPD503-313 indicates efficacy guanfacine in subjects aged 6 to 17 years with ADHD and co-medicated with psychostimulants. The study maintenance phase was not of sufficient duration to demonstrate efficacy (3 weeks). The primary efficacy outcome measure was ADHD-RS-IV, which was used in the inclusion criteria and measured at baseline and endpoint. The study did not examine doses higher than 4 mg/day in subjects co-medicated with psychostimulants. There was no clinically significant difference between morning and evening dosing.

7.2.6. **Study SPD503-314**

7.2.6.1. Study design, objectives, locations and dates

Study SPD503-314 was a double blind, randomised, placebo controlled dose optimisation study of guanfacine in children with ADHD aged 6 to 12 years, comparing morning dosing with evening dosing and with placebo. The study was conducted at 47 centres in the US and Canada from November 2009 to September 2010.

7.2.6.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female, aged 6-12 years.
- DSM-IV-TR criteria for a primary diagnosis of ADHD, combined sub-type or hyperactive/ impulsive sub-type, based on a detailed psychiatric evaluation K-SADS-PL.
- Minimum ADHD-RS-IV total score of 28.
- CGI-S score ≥ 4.
- Normal or clinically insignificant screening ECG findings as judged by the Investigator with consideration of the central ECG laboratory's interpretation.
- Functioning at an age-appropriate level intellectually, as deemed by the Investigator.
- Supine and standing BP measurement within the 95th percentile for age, gender, and height.

- FOCP must have a negative serum beta Human Chorionic Gonadotropin (HCG) pregnancy test at screening (Visit 1), a negative urine pregnancy test at baseline (Visit 2) and must abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

The exclusion criteria were similar to those for Study SPD503-313.

7.2.6.3. Study treatments

The study treatments were:

1. Guanfacine extended release 1 to 4 mg in the morning (AM)
2. Guanfacine extended release 1 to 4 mg in the evening (PM)
3. Placebo

There was a three week dose titration, 5 weeks of maintenance and two weeks for tapering.

7.2.6.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the change in ADHD-RS-IV from baseline. Secondary efficacy outcome measures were:

- CGI-I
- CGI-S
- CPRS-R:S
- HUI2/3
- WFIRS-P
- Bedtime Resistance subscale of the CSHQ
- PSQ

The safety outcome measures were: AEs, clinical laboratory tests, vital signs, clinical examination, ECGs, PDSS and C-SSRS.

7.2.6.5. Randomisation and blinding methods

Subjects were randomised to treatment using IVRS/IWRS. Subjects were randomised in the ratio 1:1:1. Blinding was maintained by using identical placebos for each dose level.

7.2.6.6. Analysis populations

The FAS and safety populations included all subjects randomised and who took at least one dose of study treatment.

7.2.6.7. Sample size

The sample size calculation was based on the primary efficacy outcome measure. To detect an effect size of 0.4, with 90% power at an alpha of 0.05, 105 subjects would be required for each treatment group. To allow for dropouts, 111 subjects would be required in each treatment group.

7.2.6.8. Statistical methods

Hypothesis tests were performed using ANCOVA and CMH. Imputation was performed using LOCF. A sequential process for hypothesis testing was used to account for multiplicity.

7.2.6.9. Participant flow

A total of 340 subjects were randomised to treatment: 113 to AM, 114 to PM and 113 to placebo. Seven subjects did not receive treatment and there were 107 (94.7%) subjects in the AM

FAS/safety populations, 114 (100%) in the PM and 112 (99.1%) in the placebo. There were 243 (71.5%) subjects who completed the study: 79 (69.6%) in the AM group, 88 (77.2%) in the PM and 76 (67.3%) in the placebo. Adverse event was a commoner reason for termination in the guanfacine group, and lack of efficacy in the placebo.

7.2.6.10. Major protocol violations/deviations

Three (1.3%) subjects in the guanfacine group and one (0.9%) in the placebo discontinued due to protocol violation.

7.2.6.11. Baseline data

There were 235 (70.6%) males, 98 (29.4%) females and the age range was 6 to 12 years. There were fewer females in the placebo group than the guanfacine groups. Otherwise the treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline disease characteristics. Prior psychoactive use was recorded for 50 (46.7%) subjects in the AM group, 66 (57.9%) in the PM and 51 (45.5%) in the placebo. Compliance was 99.2% in the AM group and 99.3% in the PM.

7.2.6.12. Results for the primary efficacy outcome

Both guanfacine groups were superior to placebo, with a similar effect size in the two guanfacine groups. The LS mean (95%) difference from placebo was -9.4 (-12.8 to -6.0) p <0.001 in the AM group and -9.8 (-13.1 to -6.4) p <0.001 in the PM group. There was a similar effect size for the subgroups of sex, race and presence of ODD. Improvement was demonstrated for guanfacine relative to placebo for both hyperactivity/impulsivity and inattentive subscores. There were 65 (62.5%) subjects coded as responders in the AM group, 67 (60.4%) in the PM group and 34 (30.9%) in the placebo.

7.2.6.13. Results for other efficacy outcomes

- For CGI-I, there was improvement in 69 (66.3%) subjects in the AM group, p <0.001, 75 (67.0%) in the PM, p <0.001, and 35 (31.8%) in the placebo.
- For CGI-S, there was lesser severity at endpoint in both of the guanfacine groups (Table 24). CGI-S category 1 or 2 was recorded for 33 (31.7%) subjects in the AM group, 41 (36.6%) in the PM and 14 (12.7%) in the placebo.

Table 24: Summary and Analysis of CGI-S at Endpoint (FAS) (copied from Table 11, Study SPD503-314 CSR)

	Placebo (N=112)	SPD503 AM (N=107)	SPD503 PM (N=114)	All-Active (N=221)
Endpoint[b]	n (%)	n (%)	n (%)	n (%)
Normal, not at all ill	5 (4.5)	12 (11.5)	18 (16.1)	30 (13.9)
Borderline mentally ill	9 (8.2)	21 (20.2)	23 (20.5)	44 (20.4)
Mildly ill	17 (15.5)	34 (32.7)	31 (27.7)	65 (30.1)
Moderately ill	38 (34.5)	23 (22.1)	25 (22.3)	48 (22.2)
Markedly ill	33 (30.0)	12 (11.5)	12 (10.7)	24 (11.1)
Severely ill	8 (7.3)	1 (1.0)	3 (2.7)	4 (1.9)
Amongst the most extremely ill subjects	0	1 (1.0)	0	1 (0.5)
p-value[a]		<0.001	<0.001	<0.001
CGI-S = 1 or 2	14 (12.7)	33 (31.7)	41 (36.6)	74 (34.3)
CGI-S > 2	96 (87.3)	71 (68.3)	71 (63.4)	142 (65.7)
p-value[a]		<0.001	<0.001	<0.001

[a] p-value is based on Cochran-Mantel-Haenszel comparing the treatment groups
[b] Endpoint is the last valid GCI-S score obtained post-Baseline before tapering. Endpoint is equivalent to Visit 10 LOCF

- For CPRS-R:S there was significant improvement in both guanfacine groups relative to placebo. The LS mean (95%) difference from placebo was -12.5 (-17.8 to -7.3) p <0.001 in the AM group and -10.8 (-16.0 to -5.6) p <0.001 in the PM group. There was a similar effect

size for both morning and evening assessments. There was improvement in the CPRS-R:S cognitive problems subscale: the LS mean (95%) difference from placebo was -2.7 (-4.2 to -1.2) p <0.001 in the AM group and -2.7 (-4.1 to -1.2) p <0.001 in the PM group.

- There was no significant difference between the treatment groups in HUI2/3.
- For WFIRS-P there was significant improvement in both guanfacine groups relative to placebo. The LS mean (95%) difference from placebo was -0.15 (-0.26 to -0.05) p = 0.004 in the AM group and -0.18 (-0.28 to -0.07) p = 0.001 in the PM group.
- There was no significant difference between guanfacine and placebo for Bedtime Resistance subscale of the CSHQ.
- At endpoint, there was no significant difference between guanfacine and placebo for PSQ.

7.2.6.14. Evaluator Commentary

In Study SPD503-314 there was no clinically significant difference in efficacy between morning and evening doses. The maintenance phase was of too short a duration to establish efficacy (5 weeks). The primary efficacy outcome measure was ADHD-RS-IV, which was used in the inclusion criteria and measured at baseline and endpoint.

7.2.7. **Study SPD503-315**

7.2.7.1. Study design, objectives, locations and dates

Study SPD503-315 was a randomised, placebo controlled, long-term, responder trial of guanfacine in children and adolescents aged 6 to 17 years with ADHD. The study comprised a 7 week dose optimisation phase, a six week maintenance open label phase and a 26 week placebo controlled, randomised withdrawal phase. The study was conducted at 67 centres in the US, Canada and the EU from May 2010 to June 2013.

7.2.7.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female aged 6-17 years
- DSM-IV-TR criteria for a primary diagnosis of ADHD, combined subtype, hyperactive/impulsive subtype, or inattentive subtype based on a detailed psychiatric evaluation using the K-SADS-PL.
- Minimum ADHD-RS-IV total score of 32.
- Minimum CGI-S score of 4.
- Functioning at an age-appropriate level intellectually, as deemed by the investigator.
- FOCP had a negative serum β-hCG pregnancy test and a negative urine pregnancy test and agreed to comply with any applicable contraceptive requirements of the protocol.
- Supine and standing blood pressure measurement within the 95th percentile for age, sex, and height.

The exclusion criteria included:

- Current, controlled (requiring a prohibited medication or behavioural modification program) or uncontrolled, comorbid psychiatric diagnosis except ODD, including any severe comorbid Axis II disorders or severe Axis I disorders such as post-traumatic stress disorder, bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder, substance abuse disorder, or other symptomatic manifestations or lifetime history of bipolar illness, psychosis, or conduct disorder that, in the opinion of the investigator, contraindicated SPD503 treatment or confounded efficacy or safety assessments.

- Subject was well controlled on their current ADHD medication with acceptable tolerability and the parent/caregiver did not object to the current ADHD medication.
- Any condition or illness including clinically significant abnormal laboratory values.
- Known history or presence of structural cardiac abnormalities, serious heart rhythm abnormalities, syncope, cardiac conduction problems (for example, clinically significant heart block), exercise-related cardiac events including syncope and pre-syncope, or clinically significant bradycardia.
- Subject had orthostatic hypotension or a known history of controlled or uncontrolled hypertension.
- Clinically significant ECG findings as judged by the investigator with consideration of the central ECG laboratory's interpretation.
- Subject used any prohibited medication or other medications, including herbal supplements, that affect blood pressure or heart rate or that have CNS effects or affect cognitive performance, such as sedating antihistamines and decongestant sympathomimetics (inhaled bronchodilators were permitted) or had a history of chronic use of sedating medications [that is, antihistamines]) in violation of the protocol-specified washout criteria at the Enrolment Visit (Visit 2/Week 0).
- Subject was significantly overweight based on Centers for Disease Control and Prevention BMI-for-age sex specific charts. Significantly overweight was defined as a BMI >95th percentile.
- Children aged 6-12 years who had a body weight of <25.0kg or adolescents aged 13-17 years who had a body weight of <34.0kg or >91.0kg.
- Subject had a clinically important abnormality on the urine drug and alcohol screen (excluding the subject's current ADHD stimulant if applicable) at the Screening Visit (Visit 1).
- History of alcohol or other substance abuse or dependence, as defined by DSM-IV-TR (with the exception of nicotine), within the last 6 months.
- Subject was female and pregnant or currently lactating.
- Subject was currently considered a suicide risk, in the opinion of the investigator, had previously made a suicide attempt, or had a prior history of, or was currently demonstrating active suicidal ideation.
- History of failure to respond to an adequate study of an α_2-agonist for the treatment of ADHD.
- History of a seizure disorder (other than a single childhood febrile seizure occurring before the age of 3 years) or the presence of a serious tic disorder (including Tourette's syndrome).

7.2.7.3. Study treatments

The study treatments were:

1. Guanfacine 1 mg to 4 mg daily for children 6 to 12 years age and 4 to 7 mg for adolescents aged 13 to 17 years
2. Placebo

All subjects were commenced on guanfacine and were titrated to optimal dose over 7 weeks. This was followed by a 6 week open label maintenance phase. Subjects who met response criteria ($\geq$ 30% reduction in ADHD-RS-IV and a CGI-S score of 1 or 2 with tolerable side effects)

were randomised to ongoing treatment or to placebo. The study phase lasted for 26 weeks. There was a 2 week taper at end of treatment.

7.2.7.4. Efficacy variables and outcomes

The primary efficacy outcome measure was treatment failure, defined as ≥ 50% increase in ADHD-RS-IV and a ≥ 2 point increase in CGI-S score. The secondary efficacy outcome measures were:

- ADHD-RS-IV score
- CGI-S
- WFIRS-P
- HUI-2/3

The safety outcome measures were: AEs, clinical laboratory tests, vital signs, ECGs and C-SSRS.

7.2.7.5. Randomisation and blinding methods

Randomisation was performed using IRT at the double-blind baseline visit. Randomisation was in the ratio 1:1. Identical placebo tablets were used to maintain blinding.

7.2.7.6. Analysis populations

The open-label safety population included all subjects who took at least one dose of investigational product. The randomised FAS and safety populations included all subjects who were randomised and who took at least one dose of study treatment during the double blind randomised withdrawal phase.

7.2.7.7. Sample size

The sample size calculation was based on the primary efficacy outcome measure and assumed failure rates of 40% and 60% in the guanfacine and placebo group respectively. For 90% power at an alpha of 0.05 140 subjects would be required in each treatment group. To achieve this at the end of the maintenance phase, to enter into the randomisation phase, a sample size of 510 subjects was required.

7.2.7.8. Statistical methods

Hypothesis tests were performed using CMH, ANCOVA and Kaplan-Meier plots. Missing responses were imputed by averaging out the remaining scores. LOCF was used for missing observations.

7.2.7.9. Participant flow

There were 528 subjects enrolled: 393 in the 6 to 12 years group and 135 in the 13 to 17 year group. There were 316 subjects who went on to be entered into the double blind phase: 157 in the guanfacine group and 159 in the placebo. A total of 121 (38.3%) subjects completed the randomised phase: 72 (45.9%) in the guanfacine and 49 (30.8%) in the placebo. The main reason for withdrawal was treatment failure.

7.2.7.10. Major protocol violations/deviations

Only one subject was withdrawn from the double blind phase because of a protocol violation.

7.2.7.11. Baseline data

In the randomised population, there were 234 (74.3%) males, 81 (25.7%) females and the age range was 6 to 17 years. There were 235 (74.6%) subjects aged 6 to 12 years and 80 (25.4%) aged 13 to 17 years. The treatment groups were similar in demographic characteristics and baseline efficacy scores.

7.2.7.12. Results for the primary efficacy outcome

There were 74 (49.3%) treatment failures in the guanfacine group and 98 (64.9%) in the placebo: difference (95% CI) -15.6 (-26.6 to -4.5) p = 0.006. Median time to treatment failure was 218 days in the guanfacine group and 56 in the placebo, logrank p = 0.003. The subgroup analyses were not sufficiently powered to demonstrate treatment differences.

7.2.7.13. Results for other efficacy outcomes

- The ADHD-RS-IV score decreased to a lesser extent in the guanfacine group compared to placebo: LS mean difference (95% CI) -6.24 (-9.01 to -3.48) p <0.001. Efficacy was demonstrated for both the hyperactivity/impulsivity and inattentiveness subscores.
- For CGI-S, 75 (50.0%) subjects in the guanfacine group and 49 (32.5%) in the placebo were normal/borderline mentally ill, p = 0.001.
- At end of study, there was no significant difference between the treatment groups in WFIRS-P, except for the learning and school domain score which was superior for the guanfacine group: LS mean (SE) 0.37 (0.056) for guanfacine and 0.23 (0.078) for placebo, p = 0.030.
- There was no significant difference between the treatment groups in HUI-2/3.

7.2.7.14. Evaluator Commentary

Study SPD503-315 demonstrated efficacy for guanfacine in children and adolescents aged 6 to 17 years with ADHD. The maintenance phase was of sufficient duration (6 weeks). The study demonstrated maintenance of efficacy for 26 weeks. The primary efficacy outcome measure was ADHD-RS-IV, which was used in the inclusion criteria and measured at baseline and endpoint. The benefits were primarily for symptomatic scores (ADHD-RS-IV) but benefit was also demonstrated for some functioning scores (WFIRS-P learning and school domain score). There was no significant difference in quality of life scores (HUI-2/3).

7.2.8. **Study SPD503-316**

7.2.8.1. Study design, objectives, locations and dates

Study SPD503-316 was a randomised, double blind, placebo and active (atomoxetine) controlled, dose optimisation study of guanfacine in children and adolescents aged 6 to 17 years with ADHD. The study was conducted at 58 centres in the US, Canada and the EU from January 2011 to May 2013.

7.2.8.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria were the same as for Study SPD503-315, with the additional exclusion criteria of a history of failure to respond to atomoxetine for the treatment of ADHD.

7.2.8.1. Study treatments

The study treatments were:

1. Guanfacine 1 mg to 4 mg daily for children 6 to 12 years age and 4 to 7 mg for adolescents aged 13 to 17 years
2. Placebo
3. Atomoxetine (Strattera®)

For children aged 6 to 12 years dose optimisation was performed over 4 weeks and for adolescents aged 13 to 17 years it was performed over 7 weeks. Dose optimisation of atomoxetine was in the range 25 mg to 100 mg based on weight. There was a 6 week maintenance phase followed by a 2 week taper.

7.2.8.2. Efficacy variables and outcomes

The primary efficacy outcome measure was the change from baseline in ADHD-RS-IV. The secondary efficacy outcome measures were:

- CGI-S
- CGI-I
- WFIRS-P
- HUI-2/3

The safety outcome measures were: AEs, clinical laboratory tests, vital signs, ECGs, BPRS-C, C-SSRS and SSEQ.

7.2.8.3. Randomisation and blinding methods

Randomisation was by IRT, in the ratio 1:1:1 and stratified by age range: 6 to 12 years and 13 to 17 years. Blinding was maintained by using placebos for both guanfacine and atomoxetine.

7.2.8.4. Analysis populations

The FAS and safety populations included all subjects who were randomised and took at least one dose of study treatment.

7.2.8.5. Sample size

The sample size calculation was based on a comparison between guanfacine and placebo for the primary efficacy outcome measure. The samples size calculation was based on an effect size of 0.45 (equivalent to a difference between treatment of 4.5 points and a SD of 10 points), power of 90% and an alpha of 0.05. This would require 105 subjects in each group, and to account for dropouts 111 subjects would be required in each group. A further 111 subjects were included in the atomoxetine group to provide 'reference data'.

7.2.8.6. Statistical methods

Hypothesis tests were performed using ANCOVA and CMH. LOCF was used to impute missing data. A hierarchical approach to hypothesis tests was used to account for multiplicity.

7.2.8.7. Participant flow

A total of 338 subjects were randomised to treatment: 115 to guanfacine, 111 to placebo and 112 to atomoxetine. A total of 269 (79.6%) subjects completed the study: 90 (78.3%) in the guanfacine group, 92 (82.9%) in the placebo and 87 (77.7%) in the atomoxetine. Twenty four (7.1%) subjects withdrew because of lack of efficacy: five (4.3%) in the guanfacine group, 14 (12.6%) in the placebo and five (4.5%) in the atomoxetine.

7.2.8.8. Major protocol violations/deviations

No subject was withdrawn because of protocol violation. One site was excluded from a sensitivity analysis because of concerns regarding data quality.

7.2.8.9. Baseline data

There were 249 (73.9%) males, 88 (26.1%) females and the age range was 6 to 17 years. There were 242 (71.8%) subjects aged 6 to 12 years and 95 (28.2%) aged 13 to 17 years. There was a higher proportion of females in the guanfacine group. Otherwise, the groups were similar in demographic characteristics. The treatment groups were similar in disease characteristics (Table 25). Prior stimulant medication had been used by 54 (47.4%) subjects in the guanfacine group, 57 (50.9%) in the atomoxetine and 56 (50.5%) in the placebo. Prior stimulants had been ceased because of lack of efficacy in 95 (55.9%) subjects with prior stimulant use and because of side effects in 63 (37.1%). Compliance was 99.0% for guanfacine, 99.6% for placebo and 98.9% for atomoxetine.

Table 25: Summary of Disease Characteristics (FAS/Safety Population) (copied from Table 13, Study SPD503-316 CSR)

	Placebo (N = 111)	SPD503 (N = 114)	STRATTERA (N = 112)	Total (N = 337)
ADHD subtype, n (%)				
Predominantly inattentive	11 (9.9)	15 (13.2)	10 (8.9)	36 (10.7)
Predominantly hyperactive-impulsive	5 (4.5)	6 (5.3)	3 (2.7)	14 (4.2)
Combined subtype	95 (85.6)	93 (81.6)	99 (88.4)	287 (85.2)
Time since ADHD diagnosis (yrs)				
Mean (SD)	2.1 (2.57)	2.3 (2.67)	2.0 (2.27)	2.2 (2.51)
Median	1.0	1.0	1.0	1.0
Min, Max	0, 12	0, 9	0, 10	0, 12
Baseline ADHD-RS-IV				
Mean (SD)	43.2 (5.60)	43.1 (5.47)	43.7 (5.86)	43.3 (5.63)
Median	44.0	43.0	45.0	44.0
Min, Max	32, 54	33, 54	30, 54	30, 54
Baseline CGI-S, n (%)				
Normal, not at all ill	0	0	0	0
Borderline mentally ill	0	0	0	0
Mildly ill	0	0	0	0
Moderately ill	33 (29.7)	21 (18.4)	23 (20.5)	77 (22.8)
Markedly ill	49 (44.1)	60 (52.6)	53 (47.3)	162 (48.1)
Severely ill	27 (24.3)	30 (26.3)	33 (29.5)	90 (26.7)
Among the most extremely ill subjects	2 (1.8)	3 (2.6)	3 (2.7)	8 (2.4)
Current psychiatric comorbidities, n (%)				
None	96 (86.5)	97 (85.1)	101 (90.2)	294 (87.2)
Diagnosis of ODD [a]	14 (12.6)	17 (14.9)	10 (8.9)	41 (12.2)
Other	1 (0.9)	1 (0.9)	1 (0.9)	3 (0.9)
n	111	113	110	334
Significant oppositional symptoms [b], n (%)				
Yes	60 (54.1)	60 (53.1)	68 (61.8)	188 (56.3)
No	51 (45.9)	53 (46.9)	42 (38.2)	146 (43.7)

Note: Percentages are based on the number of subjects with data in each treatment group and total.
[a] Diagnosis of ODD per psychiatric history case report form comes from the diagnosis of ODD in the current psychiatric comorbidities section.
[b] Defined as a CPRS-R:L oppositional subscale score at the Baseline Visit (Visit 2/Week 0) of ≥14 for males and ≥12 for females.
ADHD=attention-deficit/hyperactivity disorder; ADHD-RS-IV=ADHD Rating Scale-IV; CGI-S=Clinical Global Impression-Severity; CPRS-R:L= Conners' Parent Rating Scale-Revised: Long Form; FAS=Full Analysis Set; ODD=oppositional defiant disorder; SD=standard deviation.

7.2.8.10. Results for the primary efficacy outcome

Both guanfacine and atomoxetine were superior to placebo, with similar effect sizes. The mean (SD) change from baseline in ADHD-RS-IV was -23.9 (12.41) for guanfacine, -15.0 (13.07) for placebo and -18.6 (11.91) for atomoxetine. The LS mean difference (95% CI) to placebo was -8.9 (-11.9 to -5.8) p <0.001 for guanfacine and -3.8 (-6.8 to -0.7) p = 0.017 for atomoxetine. Similar efficacy was demonstrated for both the hyperactivity/impulsiveness and inattentive subscales. The sensitivity analysis did not have a significant effect on the results.

7.2.8.11. Results for other efficacy outcomes

- At endpoint CGI-S was normal/borderline mentally ill for 42 (37.5%) in the guanfacine group, 28 (25.2%) in the placebo and 29 (25.9%) in the atomoxetine.

- There was improvement in CGI-I for 76 (67.9%) subjects in the guanfacine group, 49 (44.1%) in the placebo and 63 (56.3%) in the atomoxetine. The difference (95% CI) for the % subjects with improvement from placebo was 23.7 (11.1 to 36.4) % p <0.001 for guanfacine and 12.1 (-0.9 to 25.1%Z) p = 0.024 for atomoxetine.
- The mean (SD) change from baseline in WFIRS-P Learning and School Domain scores was -0.610 (0.6695) for guanfacine, -0.378 (0.5489) for placebo and -0.571 (0.6367) for atomoxetine. The LS mean difference (95% CI) to placebo was -0.217 (-0.358 to -0.076) p = 0.003 for guanfacine and -0.162 (-0.305 to -0.019) p = 0.026 for atomoxetine.
- The mean (SD) change from baseline in WFIRS-P Family Domain scores was -0.596 (0.7706) for guanfacine, -0.507 (0.6893) for placebo and -0.571 (0.6367) for atomoxetine. The LS mean difference (95% CI) to placebo was -0.209 (-0.358 to -0.059) p = 0.006 for guanfacine and -0.090 (-0.241 to 0.061) p = 0.242 for atomoxetine.
- The mean (SD) change from baseline in WFIRS-P Global scores was -0.486 (0.5012) for guanfacine, -0.300 (0.3745) for placebo and -0.423 (0.4220) for atomoxetine. The LS mean difference (95% CI) to placebo was -0.165 (-0.266 to -0.064) p = 0.001 for guanfacine and -0.104 (-0.207 to -0.001) p = 0.048 for atomoxetine.
- There was no significant difference between the treatment groups in HUI-2/3 scores.

7.2.8.12. Evaluator commentary

Study SPD503-316 demonstrated efficacy for guanfacine in comparison with placebo in children and adolescents aged 6 to 17 years with ADHD. Efficacy was demonstrated for the symptomatic score of ADHD-RS-IV and the functional scores of WFIRS-P Global score, Learning and School Domain score and Family Domain score. No formal comparisons of either superiority or non-inferiority were performed in comparison with atomoxetine. Hence, no formal conclusions can be made with regard to efficacy in comparison with atomoxetine.

7.3. Other efficacy studies

7.3.1. Study SPD503-202

Study SPD503-202 was a randomised, double blind, placebo controlled, parallel group safety and efficacy study of immediate release guanfacine. The study was conducted in five centres in the USA and Canada from July to September 2001. The study included subjects with ADHD (by DSM-IV criteria) combined or hyperactive types, male or female, aged from 6 to 12 years. The study treatments were:

1. Guanfacine immediate release tablets, force titrated to 1.5 mg daily over 3 weeks, followed by a 2 week taper
2. Placebo

The efficacy outcome measures were the SKAMP Rating Scale, PERMP Derived Measures, and CGI. The safety outcome measures were: AEs, clinical laboratory evaluations, vital signs, physical examinations and ECGs. There were 55 subjects enrolled: 28 randomised to guanfacine and 27 to placebo. There were 53 subjects who completed the study: 27 in the guanfacine group and 26 in the placebo. One subject in each group discontinued because of AE. There were 45 males, ten females and the age range was 6 to 12 years. There were 53 subjects with combined type and two with hyperactive type ADHD. There were 54 subjects included in the ITT analysis, 27 from each group. Baseline ADHD scores were slightly higher in the guanfacine group (Table 26). There was improvement in SKAMP deportment scores relative to placebo in the guanfacine group but not in attention scores (Table 27). PERMP scores improved in the guanfacine group relative to placebo (Table 28). More subjects in the guanfacine group had improvement in CGI improvement scores but this was not statistically significant (Table 29).

Table 26: Baseline PERMP Level of Difficulty, CGI-S and SKAMP by treatment group for all randomised subjects (copied from Table 10, Study SPD503-202 CSR)

		Placebo N=27	SPD503 IR N= 27	Total N=54
PERMP level of difficulty, n (%)	Basic	7 (25.9)	12 (44.4)	19 (35.2)
	Easy	18 (66.7)	13 (48.1)	31 (57.4)
	Moderate	2 (7.4)	1 (3.7)	3 (5.6)
	Difficult	0 (0.0)	1 (3.7)	1 (1.9)
CGI-S, n (%)	Moderately ill	10 (37.0)	7 (25.9)	17 (31.5)
	Markedly ill	14 (51.9)	13 (48.1)	27(50.0)
	Severely ill	3 (11.1)	7 (25.9)	10 (18.5)
Average Baseline SKAMP Attention Rating*	Mean (SD)	0.98 (0.857)	1.20 (1.065)	1.09 (0.965)
	Median (Range)	0.75 (0.06 – 2.67)	0.92 (0.00 – 3.08)	0.90 (0.00 – 3.08)
Average Baseline SKAMP Deportment Rating*	Mean (SD)	1.38 (1.206)	1.75 (1.603)	1.57 (1.417)
	Median (Range)	1.31 (0.06 – 3.81)	1.08 (0.00 – 5.50)	1.17 (0.00 – 5.50)

*Averaged over Baseline Sessions 1 to 4

Table 27: SKAMP Ratings for Attention and Deportment for ITT Population (copied from Table 13, Study SPD503-202 CSR)

		Placebo N=27	SPD503 IR N=27	p-Value
Attention, Mean (SD)	Baseline	0.98 (0.857)	1.20 (1.065)	0.879
	Endpoint	1.82 (0.883)	1.92 (1.019)	
	Change	0.84	0.72	
Deportment, Mean (SD)	Baseline	1.38 (1.206)	1.75 (1.603)	0.001*
	Endpoint	2.08 (1.454)	1.64 (1.255)	
	Change	0.70	-0.11	

Source: Section 14 Tables 2.3.1, 2.3.2, 2.4.5 and 2.4.6.

*Statistically significant difference observed between SPD503 IR and placebo

Table 28: PERMP No. Attempted and No. Correct for ITT Population (copied from Table 16, Study SPD503-202 CSR)

		Placebo N=27 Mean (SD)	SPD503 IR N=27 Mean (SD)	p-Value
PERMP (No. Attempted), Mean score (SD)	Baseline	65.2 (31.91)	73.7 (36.14)	0.018*
	Endpoint	44.7 (28.44)	66.4 (51.52)	
	Change	-20.5	-7.3	
PERMP (No. Correct), Mean score (SD)	Baseline	61.2 (31.38)	70.0 (36.19)	0.009*
	Endpoint	40.4 (28.91)	64.7 (51.38)	
	Change	-20.8	-5.3	

Source: Section 14 Tables 2.4.7, 2.4.8, 2.4.9 and 2.4.10

*Statistically significant difference observed between SPD503 and placebo

Table 29: Results of Dichotomized CGI-I for ITT Population (copied from Table 19, Study SPD503-202 CSR)

Visit		Placebo	SPD503 IR	p-value (Unadjusted)	p-value (Adjusted)
Visit 3 (week 1)	Improvement, n (%)†	0 (0.0%)	3 (11.1%)	0.236‡	
	No improvement, n (%)†	27 (100.0%)	24 (88.9%)		
Visit 6 (week 2)	Improvement, n (%)†	5 (18.5%)	6 (22.2%)	0.738	0.740
	No improvement, n (%)†	22 (81.5%)	21 (77.8%)		
Visit 9 (week 3)	Improvement, n (%)†	4 (15.4%)	8 (32.0%)	0.166	0.137
	No improvement, n (%)†	22 (84.6%)	17 (68.0%)		
Endpoint Visit	Improvement, n (%)†	4 (14.8%)	8 (29.6%)	0.195	0.182
	No improvement, n (%)†	23 (85.2%)	19 (70.4%)		

Source Section 14 Table 2.4.12
†Improvement includes CGI-I categories 'very much improved' and 'much improved'. No improvement includes all other categories.
‡Fisher's Exact Test

7.3.2. Study SPD503-205

Study SPD503-205 was a multicentre (17 centres in the US), open label, single arm, dose escalation study to assess the efficacy, safety and tolerability of extended release guanfacine in subjects co-medicated with psychostimulants (amphetamine or methylphenidate). The study included males or females, aged 6 to 17 years, with ADHD (according to DSM-IV). The study treatments were guanfacine extended release tablets, force titrated from 1 mg to 4 mg daily over 3 weeks, followed by a 3 week taper. Study subjects also received concomitant psychostimulant medication. The efficacy outcome measures were: ADHD-RS-IV; GLI-S; CGI-I; PGA; CHQ-PF50 and CPRS-R. Safety outcome measures included AEs, clinical laboratory tests, PDSS and Pittsburgh Side Effect Rating Scale. The study included 75 subjects: 55 males, 20 females, age range 7 to 17 years, 42 subjects co-medicated with methylphenidate and 33 with amphetamine. A total of 63 subjects completed the study and twelve did not complete. Five (6.7%) subjects withdrew due to AE. The mean (SD) change from baseline in ADHD-RS-IV score was -17.8 (10.20), p <0.0001, in the methylphenidate group and -13.8 (11.19), p <0.0001, in the amphetamine. The mean (SD) change from baseline in CPRS-R score was -22.18 (15.47), p <0.0001, in the methylphenidate group and -16.28 (18.12), p = 0.0002, in the amphetamine. Improvement in CGI-I occurred for 28 (77.8%) subjects in the methylphenidate group and 18 (66.7%) in the amphetamine. Improvement in PGA score occurred for 32 (88.9%) subjects in the methylphenidate group and 21 (77.8%) in the amphetamine. There was no significant change in CHQ-PF-50 Physical Summary Score. The mean (SD) change from baseline in CHQ-PF-50 Psychosocial Summary Score was 8.98 (6.69), p <0.0001, in the methylphenidate group and 11.56 (10.00), p <0.0001, in the amphetamine.

7.3.3. Study SPD503-206

Study SPD503-206 was a multicentre (nine centres in the US), randomised, double blind, placebo-controlled, dose optimisation study conducted from May 2005 to October 2005. The study included males or females, aged 6 to 17 years with ADHD (according to DSM-IV-TR). The study treatments were:

1. Guanfacine extended release 1mg to 3 mg per day
2. Placebo

Dosing was flexible in the range 1 mg to 3 mg daily. Treatment duration was 7 weeks. The outcome measures were: cognitive assessments (CRT, SWM, DSST and PERMP); efficacy assessments (ADHD-RS-IV, CGI-S and CGI-I) and safety assessments (AEs, clinical laboratory tests, vital signs, physical examinations, assessments of sleepiness and sedation [PDSS and PSS]). The study included 178 subjects who were enrolled and received medication: 121 randomised to guanfacine and 57 to placebo. There were 114 (94.2%) subjects in the

guanfacine group and 54 (94.7%) in the placebo who completed the study. There were 124 males, 54 females and the age range was 6 to 17 years. For the cognitive outcome variables:

- There was no significant difference between the treatment groups in CRT: LS mean difference (95% CI), placebo – guanfacine, 2.2 (-16.3 to 20.7).
- There was no significant difference between the treatment groups in the change from baseline in reaction time for correct responses: mean change (SD) 20.2 (59.77) msec for guanfacine and 21.8 (58.09) msec for placebo.
- There was no significant difference between the treatment groups in the change from baseline in movement time: mean change (SD) 19.4 (74.27) msec for guanfacine and 8.8 (84.00) msec for placebo, p = 0.302.
- There was no significant difference between the treatment groups in the change from baseline in CRT total time: mean change (SD) 40.1 (114.34) msec for guanfacine and 30.7 (110.72) msec for placebo, p = 0.723.
- There was no significant difference between the treatment groups in the change from baseline in CRT accuracy: mean change (SD) 0.1 (1.22) for guanfacine and 0.1 (1.17) seconds for placebo, p = 0.980.
- There was no significant difference between the groups in SWM.
- There was no significant difference between the treatment groups in the change from baseline in DSST: mean change (SD) 18.3 (14.03) for guanfacine and 20.7 (17.18) seconds for placebo, p = 0.274.
- There was no significant difference between the treatment groups in the change from baseline in PERMP score: mean change (SD) 38.7 (74.80) for guanfacine and 17.2 (83.60) seconds for placebo, p = 0.151.

The results for the efficacy outcome measures were:

- There was a statistically significant improvement in ADHD-RS-IV in the guanfacine group compared with placebo: mean change (SD) -18.0 (10.72) for guanfacine and -11.9 (13.12) for placebo, p = 0.001.
- There was a statistically significant improvement in ADHD-RS-IV subscale score in the guanfacine group compared with placebo: mean change (SD) -8.8 (5.98) for guanfacine and -5.5 (7.23) for placebo, p = 0.001.
- There was a statistically significant improvement in ADHD-RS-IV hyperactivity / impulsivity subscale in the guanfacine group compared with placebo: mean change (SD) -9.2 (5.83) for guanfacine and -6.5 (6.68) for placebo, p = 0.002.
- A significantly greater proportion of subjects in the guanfacine group had improvement in CGI-I: 67(56.8%) in the guanfacine group and 20 (35.1%) in the placebo, p = 0.007.

7.3.4. **Study SPD503-303**

Study SPD503-303 was an open-label extension of study SPD503-301. The study was conducted at 45 centres in the US from March 2003 to July 2005. The treatment was guanfacine 2 mg to 4 mg daily, flexible dosing. Study duration was up to 24 months. Efficacy was assessed using ADHD-RS-IV, PGA, CHQ-PF50 and CHQ-CF87. Safety was assessed using AEs, clinical laboratory tests, vital signs, physical examinations, ECGs and HAM-A/HAM-D. There were 240 subjects enrolled and 42 completed. There were 184 males, 42 females and the age range was 6 to 17 years. For ADHD-RS-IV efficacy was maintained to endpoint for all three dose levels (prior to tapering): mean (SD) change from baseline -18.1 (13.38) for 2 mg, -17.6 (12.60) for 3 mg and -18.4 (13.13) for 4 mg (p <0.001). At endpoint, 95 (58.6%) subjects had demonstrated improvement in PGA. There was no significant change from baseline in CHQ-PF50 physical summary scores. There was a significant improvement from baseline in CHQ-PF50 psychosocial

summary score: mean (SD) change from baseline 12.3 (12.35) p <0.001. An analysis of CHQ-CF87 was not reported.

7.3.5. Study SPD503-305

Study SPD503-305 was an open label extension of Study SPD503-205 and Study SPD503-304. The study was conducted at 48 centres in the US from June 2004 to Jan 2007. The study treatment was guanfacine 1 mg to 4 mg once daily, flexible dose. Treatment duration was 24 months. The efficacy outcome measures were ADHD-RS-IV, CGI-I, PGA, CHQ-PF-50 and CPRS-R. The safety outcome measures were AEs, clinical laboratory tests, vital signs, physical examinations, ECGs, HAM-A/HAM-D and PDSS. The study included 262 subjects of whom 60 (22.9%) completed. Of the subjects who terminated early, 31 (11.8%) did so due to AE and 27 (10.3%) due to lack of efficacy. There were 188 males, 71 females and the age range was 6 to 17 years. There were 189 (73.0%) subjects with inattentive subtype, 62 (23.9%) with inattentive and eight (3.1%) with hyperactive. For ADHD-RS-IV efficacy was maintained to endpoint for all four dose levels (prior to tapering): mean (SD) change from baseline -23.8 (12.30) for 1 mg, -22.5 (12.25) for 2 mg, -20.0 (13.95) for 3 mg and -18.4 (13.73) for 4 mg (p <0.001). For CPRS-R efficacy was maintained to endpoint for all four dose levels (prior to tapering): mean (SD) change from baseline -17.4 (21.60) for 1 mg, -19.9 (17.53) for 2 mg, -20.3 (16.84) for 3 mg and -15.7 (21.79) for 4 mg (p <0.001). For CGI-I at endpoint, 63 (29.3%) subjects were very much improved, 62 (28.8%) were much improved and 48 (22.3%) were minimally improved. For PGA at endpoint, 32 (15.2%) subjects were very much improved, 94 (44.5%) were much improved and 52 (24.6%) were minimally improved. There was no significant change in CHQ-PF50 physical summary. CHQ-PF50 psychosocial summary improved by a mean (SD) of 9.2 (11.91) p <0.001.

7.3.6. Evaluator commentary: other efficacy studies

The long term follow-on studies, SPD503-303 and SPD503-305, supported maintenance of efficacy through to 24 months. Study SPD503-206 indicated that guanfacine did not have a significant effect on cognitive scores.

7.4. Analyses performed across trials: pooled and meta analyses

In a pooled analysis of Study SPD503-316 and Study SPD503-312, there was significant improvement in all the domains of the WFIRS-P with the exception of Child Self-concept and Risk (Table 30).

Table 30: Change from Baseline in WFIRS-P Domain and Subdomain Scores at FOTA, SPD503 versus Placebo – LOCF (Integrated Dose-optimization FAS) (copied from Table 25, Summary of Clinical Efficacy)

Domain/ Subdomain Score	LS Mean (SE)		Difference in LS Mean (SPD503 – placebo) (95% CI)	Effect Size (95% CI)	p-Value
	SPD503	Placebo			
Global	-0.39 (0.024)	-0.29 (0.024)	-0.11 (-0.17, -0.04)	0.29	0.0014
Learning and School	-0.56 (0.036)	-0.38 (0.036)	-0.18 (-0.28, -0.08)	0.33	0.0004
Academic Performance	-0.74 (0.055)	-0.50 (0.057)	-0.24 (-0.40, -0.09)	0.28	0.0024
Behavior in School	-0.49 (0.032)	-0.32 (0.033)	-0.17 (-0.26, -0.08)	0.33	0.0003
Family	-0.45 (0.035)	-0.32 (0.035)	-0.13 (-0.23, -0.03)	0.23	0.0099
Life Skills	-0.41 (0.027)	-0.33 (0.028)	-0.08 (-0.16, -0.01)	0.19	0.0309
Child Self-concept	-0.29 (0.039)	-0.32 (0.039)	0.02 (-0.08, 0.13)	0.04	0.6501
Social	-0.38 (0.032)	-0.27 (0.032)	-0.11 (-0.20, -0.03)	0.23	0.0113
Risk	-0.18 (0.017)	-0.16 (0.017)	-0.03 (-0.07, 0.02)	0.10	0.2696

Note: LS mean, effect size and p-value are based on type III sum of squares from an ANCOVA model for the change from Baseline (Visit 2/Week 0), including treatment group and study as fixed effects, and baseline value as a covariate. A negative difference in LS Mean (Treatment - Placebo) indicates a positive effect of the active treatment over the placebo. Day number shown in square parentheses represents the day relating to the visit schedule for the 13-17 years age group (if different from the 6-12 years age group).
CI=confidence interval; FAS=Full Analysis Set; LOCF=last observation carried forward; LS=least squares; FOTA=final on-treatment assessment; SE=standard error; WFIRS-P=Weiss Functional Impairment Rating Scale Parent

7.5. Evaluator's conclusions on clinical efficacy

The pivotal studies have demonstrated efficacy in comparison with placebo for guanfacine in comparison with placebo in subjects with ADHD aged 6 to 17 years. Study SPD503-312, Study SPD503-315 and Study SPD503-316 all had a maintenance phase ≥ 6 weeks in duration. The studies used outcome measures for both symptomatic and functional domains. The primary efficacy outcome measure was ADHD-RS-IV which was used for inclusion and for efficacy. SPD503-315 used a responder category that was based on ADHD-RS-IV and GCI-S. A pooled analysis of Study SPD503-316 and Study SPD503-312, there was significant improvement in all the domains of the functional score WFIRS-P with the exception of Child Self-concept and Risk.

Efficacy was demonstrated for oppositional symptoms in subjects with ADHD with oppositional symptoms in Study SPD503-307.

A linear dose-response up to 0.17 mg/kg/day was demonstrated in Study SPD503-301 and Study SPD503-304.

There is support for maintenance of efficacy for up to 24 months. Study SPD503-315 for 26 weeks. Study SPD503-303 and Study SPD503-305 were supportive of efficacy for up to 2 years.

There was no significant difference in efficacy between morning and evening dosing of guanfacine in Study SPD503-313 and Study SPD503-314.

Efficacy is supported in subjects with ADHD who are also taking psychostimulants. The dose of guanfacine tested in the study (Study SPD503-313) was up to 4 mg daily. This is less than the maximum dose in comparable age groups (that is, up to 7 mg/day in the 13 to 17 years age group).

Efficacy was not demonstrated separately for the inattentive subtype of ADHD. A subgroup analysis was performed in Study SPD503-301, but not in subsequent studies. This subgroup analysis did not show efficacy in the subgroup of subjects with inattentive type ADHD.

Improvement in quality of life scores (HUI-2/3) was not demonstrated in any of the clinical studies.

There were no comparator controlled studies. In Study SPD503-316 a group treated with atomoxetine was included to provide 'reference data' but no formal comparison of efficacy was either planned or conducted. However in that study the effect sizes of guanfacine and atomoxetine were comparable.

There is no evidence of efficacy in subjects with comorbid conditions including: any severe comorbid Axis II disorders or severe Axis I disorders such as post-traumatic stress disorder, bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder, substance abuse disorder, or other symptomatic manifestations or lifetime history of bipolar illness, psychosis, or conduct disorder. Subjects with these comorbid conditions were excluded from the pivotal studies.

The outcome measures used in the pivotal studies were a combination of symptomatic and functional scores. Symptomatic scores such as ADHD-RS-IV, CPRS-R, CTRS-R, CGI-I and PGA measured changes in ADHD symptomatology and indicated benefit for guanfacine. NYPRS-S and CPRS-R:L measured oppositional symptomatology and also indicted benefit. The results for the functional score WFIRS-P indicate benefit that became more apparent on the pooled analysis of Study SPD503-316 and Study SPD503-312. Quality of life outcome measures, such as CHQ-PF50, CHQ-CF87 and HUI-2/3 did not demonstrate benefit for guanfacine. All of these outcome measures have been appropriately validated and are acceptable outcome measures for children and adolescents with ADHD.

The pivotal studies were well designed. The outcome measures were appropriate. The inclusion criteria, whilst restrictive, still represent the general population of children and adolescents with ADHD in Australia. The studies were adequately powered. The statistical techniques were appropriate. There were adequate measures taken to account for multiplicity. There were few dropouts during the study and few subjects excluded from analysis.

The dosing regimen proposed by the sponsor in the Product Information document is supported by the pivotal studies. This is a weight based dosing regimen, which was used in the pivotal studies.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.1.2. Pivotal and/or main efficacy studies

The pivotal efficacy studies examined the following safety variables:

- Adverse Effects (AEs) including Treatment Emergent Adverse Effects (TEAEs), treatment related TEAEs, Serious Adverse Effects (SAEs), and discontinuations due to AEs (DAEs)
- Laboratory tests including clinical chemistry and full blood counts
- ECGs with particular attention to QTc prolongation
- Vital signs
- Sedative related events
- Treatment emergent psychiatric conditions, including suicidality

8.1.3. Other studies

8.1.3.1. Other efficacy studies

- Adverse Effects (AEs) including Treatment Emergent Adverse Effects (TEAEs), treatment related TEAEs, Serious Adverse Effects (SAEs), and discontinuations due to AEs (DAEs)
- Laboratory tests including clinical chemistry and full blood counts
- ECGs with particular attention to QTc prolongation
- Vital signs

In addition Study SPD503-202 examined psychiatric adverse effects and Study SPD503-206 examined cognitive adverse effects.

8.1.3.2. Studies with evaluable safety data: dose finding and pharmacology

- Adverse Effects (AEs) including Treatment Emergent Adverse Effects (TEAEs), treatment related TEAEs, Serious Adverse Effects (SAEs), and discontinuations due to AEs (DAEs)
- Laboratory tests including clinical chemistry and full blood counts
- ECGs with particular attention to QTc prolongation
- Vital signs

In addition, Study SPD503-102 examined for rebound hypertension and Study SPD503-112 was a thorough QT study.

8.1.3.3. Studies evaluable for safety only

Study SPD503-201

Study SPD503-201 was an open label, dose escalation, single centre, safety and tolerability study. The study recruited subjects with ADHD (according to DSM-IV), of the combined or hyperactive types, male or female, aged 6 to 12 years. The study treatment was: immediate release guanfacine, force titrated from 0.5 mg to 1.0 mg then to 1.5 mg over 3 weeks. Treatment was preceded by a one week washout period from all psychoactive medication. There was a one week taper at the end of the study. Treatments were administered once daily. The outcome measures were: AEs, clinical laboratory tests, vital signs, physical examinations and ECGs. Twenty subjects were enrolled and 19 completed. One subject was withdrawn because of hypertension with the 1 mg dose. There were 19 males, one female and the age range was 6 to 12 years.

Study SPD503-318

Study SPD503-318 was an open label long term safety and efficacy study conducted in children and adolescents with ADHD. The study was conducted at 51 sites in 11 countries in Europe. The study was commenced in March 2012 and is ongoing. Safety data were provided up to July 2013. The study included subjects who had participated in Study SPD503-315 or Study SPD503-316. The safety outcome measures were AEs, vital signs, ECGs, clinical laboratory tests, physical assessments and the C-SSRS.

Study SPD503-210

Study SPD503-210 was a randomised, double blind, placebo controlled study of guanfacine in children and adolescents aged 6 to 17 years with generalised anxiety disorder, separation anxiety disorder or social phobia. The study was conducted at 32 sites in the US from January 2012 to July 2013. Subjects were treated with up to 6 mg per day of guanfacine extended release. There was a 6 week dose optimisation period, 6 weeks maintenance and 2 weeks taper. A total of 83 subjects were included in the study: 62 in the guanfacine group and 21 in the placebo.

8.2. Studies that assessed safety as the sole primary outcome

There were no studies that assessed safety as the sole primary outcome.

8.3. Patient exposure

Overall exposure to guanfacine extended release (SPD503) was 2411 subjects, with 1718 aged 6 to 12 years and 693 aged 13 to 17 years at time of randomisation. There were 482 subjects exposed for ≥ 180 days, 235 subjects exposed for ≥ 360 days and 101 subjects exposed for >720 days. Subjects were exposed to up to 7 mg/day (Table 31) and up to 0.16 mg/kg/day (Table 32).

Table 31: Length of treatment exposure by actual dose – randomised pool (copied from Table 7, Summary of Clinical Safety)

		SPD503						
Parameter	Placebo (N=820)	1mg (N=1414)	2mg (N=1280)	3mg (N=965)	4mg (N=490)	5mg (N=116)	6mg (N=59)	7mg (N=16)
Length of exposure (days)								
n	820	1414	1280	965	490	116	59	16
Mean (SD)	71.2 (44.40)	14.5 (15.64)	20.0 (19.85)	25.4 (30.48)	31.7 (39.57)	31.7 (39.30)	34.4 (26.97)	36.4 (30.17)
Median	63.0	10.0	14.0	14.0	19.0	14.0	42.0	43.0
Min, Max	2, 274	1, 196	1, 192	1, 201	2, 199	1, 173	4, 166	6, 127
Total years exposed	159.9	56.3	70.1	67.0	42.5	10.1	5.5	1.6

Note: Percentages are based on the number of subjects who were dispensed the dosage of investigational product at least once.
Max=maximum; Min=minimum; SD=standard deviation.

Table 32: Length of treatment exposure by weight-adjusted dose – randomised pool (copied from Table 7, Summary of Clinical Safety)

		SPD503			
Parameter	Placebo (N=820)	0.01-0.04mg/kg (N=1418)	0.05-0.08mg/kg (N=1112)	0.09-0.12mg/kg (N=531)	0.13-0.16mg/kg (N=110)
Length of exposure (days)					
n	820	1418	1112	531	110
Mean (SD)	71.2 (44.40)	23.6 (23.60)	32.1 (31.07)	36.9 (39.95)	34.0 (40.15)
Median	63.0	15.0	23.0	27.0	21.0
Min, Max	2, 274	1, 212	2, 208	1, 197	2, 199
Total years exposed	159.9	91.6	97.7	53.6	10.2

Note: Percentages are based on the number of subjects who were dispensed the dosage of investigational product at least once.
Max=maximum; Min=minimum; SD=standard deviation.

Phase III studies:

In Study SPD503-301there were 87 subjects exposed to guanfacine extended dose up to 2 mg, 86 exposed to up to 3 mg and 86 exposed to up to 4 mg for up to 7 weeks.

In Study SPD503-304 there were 256 subjects exposed to guanfacine for up to 9 weeks: 61 exposed to 1 mg, 65 to 2 mg, 65 to 3 mg and 65 to 4 mg.

In Study SPD-503-307 there were 136 subjects aged 6 to 13 years with ADHD and oppositional features exposed to 1 mg to 4 mg guanfacine daily for a median of 9 weeks.

In Study SPD503-312 there were 157 subjects aged 13 to 17 years with ADHD, treated with up to 7 mg daily guanfacine extended release for a median of 105 days and a maximum of 132 days.

In Study SPD503-313 there were 302 subjects aged 6 to 17 years exposed to guanfacine in combination with psychostimulants. There were 150 dosed in the morning and 152 dosed in the

evening. Median duration of exposure was 9 weeks, with a maximum of 11 weeks and the dose range was 1 to 4 mg per day.

In Study SPD503-314 there were 221 subjects aged 6 to 12 years exposed to guanfacine in combination with psychostimulants. There were 107 dosed in the morning and 114 dosed in the evening. Median duration of exposure was 9 weeks, with a maximum of 10 weeks and the dose range was 1 to 4 mg per day.

In Study SPD503-315 there were 526 subjects aged 6 to 17 years exposed to up to 7 mg guanfacine per day for up to 13 weeks. In the randomised phase there were 157 subjects exposed to up to 7 mg guanfacine per day for up to 26 weeks. Forty subjects were exposed for ≥ 26 weeks.

In Study SPD503-316 there were 114 subjects with ADHD aged 6 to 17 years exposed to guanfacine up to 7 mg/day for a median of 84 days and a maximum of 113 days.

Long term follow-on studies:

In Study SPD503-303 240 subjects aged 6 to 17 years were exposed to guanfacine extended release in the dose range 1 mg to 4 mg per day. There were 72 subjects exposed for ≥ 12 months and 32 for ≥ 24 months.

In Study SPD503-305 259 subjects aged 6 to 17 years were treated with guanfacine in the dose range 1 mg to 4 mg per day for up to 24 months. There were 206 subjects in monotherapy and 53 co-medicated with psychostimulants. There were 107 subjects treated for ≥ 12 months and 55 treated for ≥ 24 months.

In Study SPD503-318 there were 198 subjects exposed to guanfacine. There were 122 subjects aged 6 to 12 years and 76 aged ≥ 13 years. There were 62 subjects exposed for ≥ 6 months and two subjects exposed for ≥ 12 months.

Phase II studies:

In Study SPD503-201 there were 20 subjects aged 6 to 12 years exposed to immediate release guanfacine, up to 1.5 mg per day, for up to 4 weeks.

In Study SPD503-202 there were 28 subjects aged 6 to 12 years exposed to immediate release guanfacine, up to 1.5 mg/day for up to 5 weeks.

In Study SPD503-205 there were 75 subjects aged 7 to 17 years exposed to up to 4 mg extended release guanfacine per day for up to 7 weeks. There were 42 subjects co-medicated with methylphenidate and 33 with amphetamine.

In Study SPD503-206 there were 121 subjects aged 6 to 17 years exposed to up to 3 mg guanfacine extended release daily for up to 7 weeks.

In Study SPD503-210 there were 62 subjects aged 6 to 17 years treated with guanfacine up to 6 mg/day for up to 14 weeks for anxiety related disorders.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Integrated safety analyses

Overall the rate of TEAEs was higher in the guanfacine extended release group than in the placebo 2046 (84.9%) subjects compared with 620 (63.7%). In the guanfacine group, there were 1467 (85.4%) subjects aged 6 to 12 years with TEAEs and 579 (83.5%) aged 13 to 17 years. Compared to placebo, in the guanfacine group, there was a higher rate of somnolence, headache, fatigue and sedation regardless of dose or age group (Tables 33 and 34).

Table 33: TEAEs reported by ≥5% of subjects in the placebo or guanfacine treatment groups by randomised treatment group – short term fixed dose pool (copied from Table 14, Summary of Clinical Safety).

Preferred Term	Placebo (N=149)	SPD503 1mg[a] (N=61)	SPD503 2mg (N=150)	SPD503 3mg (N=151)	SPD503 4mg (N=151)	SPD503 All Active (N=513)
	n (%) m					
Somnolence	10 (6.7) 10	16 (26.2) 19	31 (20.7) 42	43 (28.5) 54	60 (39.7) 78	150 (29.2) 193
Headache	29 (19.5) 38	16 (26.2) 19	38 (25.3) 60	24 (15.9) 44	44 (29.1) 56	122 (23.8) 179
Fatigue	5 (3.4) 5	6 (9.8) 7	19 (12.7) 22	25 (16.6) 32	22 (14.6)) 33	72 (14.0) 94
Sedation	7 (4.7) 8	1 (1.6) 1	15 (10.0) 19	15 (9.9) 19	20 (13.2) 22	51 (9.9) 61
Abdominal pain upper	11 (7.4) 12	5 (8.2) 5	9 (6.0) 9	15 (9.9) 18	22 (14.6) 29	51 (9.9) 61
Dizziness	6 (4.0) 6	3 (4.9) 3	4 (2.7) 4	11 (7.3) 14	15 (9.9) 17	33 (6.4) 38
Decreased appetite	6 (4.0) 6	3 (4.9) 3	6 (4.0) 6	13 (8.6) 14	9 (6.0) 9	31 (6.0) 32
Irritability	6 (4.0) 6	3 (4.9) 3	13 (8.7) 13	4 (2.6) 4	10 (6.6) 12	30 (5.8) 32
Lethargy	4 (2.7) 4	1 (1.6) 1	5 (3.3) 6	12 (7.9) 15	11 (7.3) 13	29 (5.7) 35
Nausea	3 (2.0) 5	4 (6.6) 4	8 (5.3) 9	8 (5.3) 9	9 (6.0) 10	29 (5.7) 32
Nasopharyngitis	9 (6.0) 9	2 (3.3) 2	5 (3.3) 5	4 (2.6) 4	4 (2.6) 4	15 (2.9) 15
Dry mouth	2 (1.3) 2	0	2 (1.3) 2	9 (6.0) 11	10 (6.6) 10	21 (4.1) 23
Epsitaxis	2 (1.3) 4	4 (6.6) 4	2 (1.3) 2	4 (2.6) 6	2 (1.3) 3	12 (2.3) 15

[a] From SPD503-304 only (no 1mg dosing group in SPD503-301). All other columns include both Studies SPD503-301 and SPD503-304.
Note: An AE is considered treatment-emergent if the start date occurred on or after the first dispensing day or within 3 days (inclusive) of stopping treatment, otherwise it is considered to have occurred either prior to treatment or post-treatment. All AEs with missing start dates are assumed to be treatment-emergent.
AE=adverse event; m=number of events; n=number of subjects

Table 34: TEAEs occurring in ≥5% of all subjects who received SPD503 in Phase II-III studies– overall pool (copied from Table 15, Summary of Clinical Safety).

Preferred term	Placebo 6-12 years (N=643)	Placebo 13-17 years (N=330)	Placebo All (N=973)	SPD503 6-12 years (N=1 718)	SPD503 13-17 years (N=693)	SPD503 All (N=2 411)
	n (%) m					
Somnolence	41 (6.4) 45	56 (17.0) 63	97 (10.0) 108	713 (41.5) 1150	266 (38.4) 439	979 (40.6) 1589
Headache	99 (15.4) 137	60 (18.2) 83	159 (16.3) 220	452 (26.3) 773	208 (30.0) 372	660 (27.4) 1145
Fatigue	28 (4.4) 31	29 (8.8) 32	57 (5.9) 63	306 (17.8) 448	131 (18.9) 180	437 (18.1) 628
Abdominal pain upper	37 (5.8) 40	10 (3.0) 11	47 (4.8) 51	242 (14.1) 322	47 (6.8) 55	289 (12.0) 377
Sedation	10 (1.6) 14	9 (2.7) 11	19 (2.0) 25	184 (10.7) 245	61 (8.8) 78	245 (10.2) 323
Dizziness	24 (3.7) 25	24 (7.3) 26	48 (4.9) 51	129 (7.5) 159	93 (13.4) 120	222 (9.2) 279
URTI	34 (5.3) 35	24 (7.3) 26	58 (6.0) 61	134 (7.8) 167	61 (8.8) 80	195 (8.1) 247
Irritability	19 (3.0) 20	15 (4.5) 15	34 (3.5) 35	143 (8.3) 170	40 (5.8) 47	183 (7.6) 217
Nausea	22 (3.4) 29	30 (9.1) 31	52 (5.3) 60	123 (7.2) 148	59 (8.5) 67	182 (7.5) 215
Decreased appetite	26 (4.0) 35	26 (7.9) 31	52 (5.3) 66	127 (7.4) 143	48 (6.9) 55	175 (7.3) 198
Nasopharyngitis	32 (5.0) 35	14 (4.2) 15	46 (4.7) 50	104 (6.1) 137	60 (8.7) 79	164 (6.8) 216
Insomnia	24 (3.7) 24	13 (3.9) 14	37 (3.8) 38	115 (6.7) 139	40 (5.8) 47	155 (6.4) 186
Vomiting	29 (4.5) 33	14 (4.2) 16	43 (4.4) 49	110 (6.4) 129	34 (4.9) 37	144 (6.0) 166
Diarrhea	27 (4.2) 32	19 (5.8) 22	46 (4.7) 54	96 (5.6) 123	34 (4.9) 45	130 (5.4) 168
Pyrexia	24 (3.7) 24	1 (0.3) 1	25 (2.6) 25	97 (5.6) 112	30 (4.3) 35	127 (5.3) 147
Cough	25 (3.9) 28	14 (4.2) 14	39 (4.0) 42	95 (5.5) 109	26 (3.8) 32	121 (5.0) 141

[a] Please note that meaningful comparison of placebo to SPD503 treatment is limited for the overall pool because this data set included open-label studies for which there was no placebo arm.
m=number of events; n=number of subjects; URTI=upper respiratory tract infection

8.4.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.4.1.3. Pivotal and/or main efficacy studies

In Study SPD503-301 TEAEs were reported in 67 (77.0%) subjects in the 2 mg group, 76 (88.4%) in the 3 mg, 75 (87.2%) in the 4 mg and 55 (64.0%) in the placebo (Table 35). The commonest TEAEs in the guanfacine group were somnolence in 83 (32.0%) subjects, headache

in 68 (26.3%), fatigue in 47 (18.1%), upper abdominal pain in 37 (14.3%) and sedation in 33 (12.7%).

Table 35: Summary of Treatment-Emergent Adverse Events by Randomized Dose for Events Occurring in ≥5.0% of Any Treatment Group (Safety Population) (copied from Table 35, Study SPD503-301 CSR)

Body System	Placebo N=86	SPD503 2mg N=87	SPD503 3mg N=86	SPD503 4mg N=86	All Active N=259
Preferred Term (MedDRA®)	n (%)	n (%)	n (%)	n (%)	n (%)
Total[1]	55 (64.0%)	67 (77.0%)	76 (88.4%)	75 (87.2%)	218 (84.2%)
Gastrointestinal disorders					
Abdominal pain upper	5 (5.8%)	9 (10.3%)	14 (16.3%)	14 (16.3%)	37 (14.3%)
Dry mouth	1 (1.2%)	2 (2.3%)	8 (9.3%)	5 (5.8%)	15 (5.8%)
Nausea	2 (2.3%)	6 (6.9%)	5 (5.8%)	5 (5.8%)	16 (6.2%)
General disorders and administration site conditions					
Fatigue	3 (3.5%)	16 (18.4%)	18 (20.9%)	13 (15.1%)	47 (18.1%)
Lethargy	3 (3.5%)	5 (5.7%)	7 (8.1%)	8 (9.3%)	20 (7.7%)
Pyrexia	3 (3.5%)	2 (2.3%)	0	6 (7.0%)	8 (3.1%)
Infections and infestations					
Upper respiratory tract infection NOS	3 (3.5%)	3 (3.4%)	5 (5.8%)	2 (2.3%)	10 (3.9%)
Metabolism and nutrition disorders					
Appetite decreased NOS	2 (2.3%)	5 (5.7%)	8 (9.3%)	5 (5.8%)	18 (6.9%)
Nervous system disorders					
Dizziness	2 (2.3%)	4 (4.6%)	5 (5.8%)	9 (10.5%)	18 (6.9%)
Headache	21 (24.4%)	23 (26.4%)	19 (22.1%)	26 (30.2%)	68 (26.3%)
Sedation	3 (3.5%)	8 (9.2%)	11 (12.8%)	14 (16.3%)	33 (12.7%)
Somnolence	3 (3.5%)	21 (24.1%)	29 (33.7%)	33 (38.4%)	83 (32.0%)
Psychiatric disorders					
Insomnia	4 (4.7%)	5 (5.7%)	7 (8.1%)	5 (5.8%)	17 (6.6%)
Irritability	3 (3.5%)	9 (10.3%)	2 (2.3%)	5 (5.8%)	16 (6.2%)
Respiratory, thoracic, and mediastinal disorders					
Cough	5 (5.8%)	3 (3.4%)	5 (5.8%)	7 (8.1%)	15 (5.8%)
Nasal congestion	3 (3.5%)	2 (2.3%)	2 (2.3%)	5 (5.8%)	9 (3.5%)
Nasopharyngitis	5 (5.8%)	4 (4.6%)	4 (4.7%)	3 (3.5%)	11 (4.2%)
Pharyngitis	4 (4.7%)	2 (2.3%)	4 (4.7%)	5 (5.8%)	11 (4.2%)

Source: Section 12.1 Table 3.2.4
Note: An AE was considered treatment emergent if the start date occurred on or after the first dispensing day, otherwise it was considered prior to treatment. AEs with missing start dates were assumed to be treatment emergent.
1 Subjects may have experienced more than one TEAE.

In Study SPD503-304 TEAEs were reported in 49 (80.3%) subjects in the 1 mg group, 40 (61.5%) in the 2 mg, 45 (69.2%) in the 3 mg, 55 (84.6%) in the 4 mg and 50 (75.8%) in the placebo. The commonest TEAEs in the guanfacine group were: somnolence in 69 (27.0%) subjects and headache in 53 (20.7%).

In Study SPD-503-307 TEAEs were reported in 114 (83.8%) subjects in the guanfacine group and 45 (57.7%) in the placebo. The commonest TEAEs in the guanfacine group were: somnolence in 69 (50.7%) subjects, headache in 30 (22.1%), sedation in 18 (13.2%), upper abdominal pain in 16 (11.8%) and fatigue in 15 (11.0%).

In Study SPD503-312 667 TEAEs were reported in 147 (93.6%) subjects in the guanfacine group and 413 in 120 (77.4%) in the placebo. The commonest TEAEs in the guanfacine group were: somnolence in 69 (43.9%), headache in 42 (26.8%), fatigue in 35 (15.9%), dizziness in 25 (15.9%), decreased appetite in 23 (14.6%), nausea in 19 (12.1%), nasopharyngitis in 18 (11.5%) and sedation in 18 (11.5%). The Structured Side Effect Questionnaire (SSEQ) demonstrated a higher rate of headache, dizziness, fatigue and somnolence in the guanfacine group.

In Study SPD503-313, TEAEs were reported in 116 (77.3%) subjects in the AM group, 116 (76.3%) in the PM, and 97 (63.4%) in the placebo. The commonest TEAEs in the guanfacine group were headache in 64 (21.2%) subjects and somnolence in 41 (13.6%). TEAEs occurred with similar frequency in the AM and PM groups, except for a higher rate of nausea and insomnia in the PM group.

In Study SPD503-314 TEAEs were reported in 85 (79.4%) subjects in the AM group, 95 (83.3%) in the PM and 64 (57.1%) in the placebo. The commonest TEAEs in the guanfacine group were: somnolence in 98 (44.3%) subjects, headache in 37 (16.7%), sedation in 32 (14.5%) upper abdominal pain in 27 (12.2%) and fatigue in 24 (10.9%).

In Study SPD503-315 in the open label phase, TEAEs were reported in 448 (85.2%) subjects. Somnolence was reported in 255 (48.5%), headache in 144 (27.4%), fatigue in 130 (24.7%) and upper abdominal pain in 60 (11.4%). In the double blind phase, TEAEs were reported in 89 (56.7%) subjects in the guanfacine group and 76 (48.1%) in the placebo. In the guanfacine group, headache was reported in 25 (15.9%) and somnolence in 19 (12.1%).

In Study SPD503-316 there were 509 TEAEs reported in 88 (77.2%) subjects in the guanfacine group, 322 in 73 (65.8%) in the placebo and 424 in 76 (67.9%) in the atomoxetine. Somnolence was more common in the guanfacine than either the placebo or atomoxetine groups, and nausea was more common with atomoxetine. The commonest TEAEs in the guanfacine group were: somnolence in 50 (43.9%), headache in 30 (26.3%), fatigue in 29 (25.4%), and abdominal pain in 19 (16.7%).

8.4.1.4. Other studies

Other efficacy studies

Study SPD503-202 there were 224 TEAEs reported in 28 (100%) subjects in the guanfacine group and 121 in 22 (81.5%) in the placebo. In the guanfacine group, headache was reported in 17 (60.7%) subjects, asthenia in 14 (50.0%), abdominal pain in 12 (42.9%), somnolence in 11 (39.3%), vomiting in six (21.4%), and nausea, pharyngitis, rhinitis, infection, accidental injury, abnormal ECG, and bradycardia each in five (17.9%).

In Study SPD503-205 TEAEs were reported in 69 (92.0%) subjects. Fatigue was reported in 26 (34.7%) subjects, headache in 25 (33.3%), upper abdominal pain in 24 (32.0%), irritability in 24 (32.0%), somnolence in 14 (18.7%), insomnia in 12 (16.0%), and anxiety in 11 (14.7%). The mean (SD) change from baseline in Pediatric Daytime Sleepiness Score (PDSS) was -4.8 (6.23). The Pittsburgh Side Effect Rating Scale (PSERS) reflected the increase in somnolence and headache.

In Study SPD503-206 TEAEs were reported in 96 (79.3%) subjects in the guanfacine group and 40 (70.2%) in the placebo. TEAEs were reported in 11 (78.6%) subjects in the guanfacine 1 mg group, 35 (94.6%) in the 2 mg and 50 (71.4%) in the 3 mg. The commonest TEAEs in the guanfacine group were: somnolence in 50 (41.3%) subjects and headache in 30 (24.8%). TEAEs did not appear to be dose related.

In Study SPD503-303 TEAEs were reported in 209 (87.1%) subjects. Somnolence was reported in 73 (30.4%) subjects, headache in 63 (26.3%), fatigue in 34 (14.2%), and sedation in 32 (13.3%).

In Study SPD503-305 TEAEs were reported in 226 (87.3%) subjects. Somnolence was reported in 79 (30.5%) subjects, headache in 63 (24.3%), fatigue in 36 (13.9%), upper abdominal pain in 33 (12.7%) and sedation in 29 (11.2%).

Studies with evaluable safety data: dose finding and pharmacology

At doses of up to 8 mg guanfacine there was a high rate of adverse effects (Study SPD503-112). TEAEs were recorded in 76 (100%) with guanfacine, 29 (57.4%) with placebo and 46 (63.9%) with moxifloxacin. The commonest TEAEs with guanfacine were: dry mouth in 50 (65.8%)

subjects, dizziness in 47 (61.8%), asthenia in 43 (56.5%), constipation in 32 (42.1%), headache in 23 (30.3%), nausea in 13 (17.1%), tinnitus in 12 (15.8%) and blurred vison in ten (13.2%).

At doses up to 0.12 mg/kg, the rates of somnolence, dizziness, sinus bradycardia and orthostatic hypotension increased with increasing dose (Study SPD503-113). At the 0.12 mg/kg dose level, somnolence was reported in eight (29.6%) subjects, dizziness in seven (25.9%), orthostatic hypotension in seven (25.9%) and sinus bradycardia in four (14.8%).

Studies evaluable for safety only

In Study SPD503-201 (immediate release guanfacine up to 1.5 mg) all subjects had cardiovascular TEAEs: 20 (100%) had tachycardia, 17 (85%) hypotension, 16 (80%) hypertension, 11 (55%) had prolonged QT, and 8 (40%) had bradycardia (Table 36). Headache was reported in four (20%).

Table 36: Overall incidence of adverse events by body system, preferred term, subjects and percent of subjects (copied from Table 5, Study SPD503-201 CSR)

Body System	COSTART Preferred Term	Number of Subjects (n=20)	Percent of Subjects
Body as a Whole	Headache	4	20%
	Accidental Injury	3	15%
	Asthenia	2	10%
	Abdominal Pain	2	10%
	Ear Pain	2	10%
	Chills	1	5%
	Infection	1	5%
Cardiovascular	Tachycardia [1]	20	100%
	Hypotension [2]	17	85%
	Hypertension [3]	16	80%
	QT Prolonged [4]	11	55%
	Bradycardia	8	40%
Digestive	Anorexia	2	10%
	Appetite Increase	1	5%
	Diarrhea	1	5%
Hematologic/Lymphatic	Ecchymosis	1	5%
Metabolic/Nutritional	Weight Increase	2	10%
Nervous	Nervousness	2	10%
	Somnolence	2	10%
	Anxiety	1	5%
	Emotional Lability	1	5%
Skin	Urticaria	1	5%

Source: Appendix Table 4.1.1

[1] Tachycardia defined as increase in heart rate >20% from baseline in any single measurement

[2] Hypotension defined as decrease in blood pressure >20% from baseline in any single measurement

[3] Hypertension defined as increase in blood pressure >20% from baseline in any single measurement

[4] Prolonged QT defined as any Marquette automated derived measurement with QTc>440 ms in any single tracing

In Study SPD503-318 TEAEs were reported in 88 (72.1%) subjects in the 6 to 12 years age group and 41 (53.9%) in the ≥ 13 years age group. The commonest TEAEs were somnolence in 60 (30.3%), headache in 38 (19.2%) and fatigue in 29 (14.6%).

In Study SPD503-210 TEAEs were reported in 51 (82.3%) subjects in the guanfacine group and 13 (61.9%) in the placebo. The commonest TEAEs in the guanfacine group were: headache in 22 (35.5%), somnolence in 17 (27.4%), fatigue in 13 (21.0%), upper abdominal pain in ten (16.1%), dizziness in seven (11.3%) and postural dizziness in seven (11.3%).

8.4.2. Treatment related adverse events (adverse drug reactions)

8.4.2.1. Integrated safety analyses

Overall the rate of treatment related TEAEs was higher in the guanfacine extended release group than in the placebo 1765 (73.2%) subjects compared with 357 (36.7%). In the guanfacine

group, there were 1275 (74.2%) subjects aged 6 to 12 years with TEAEs and 490 (70.7%) aged 13 to 17 years.

8.4.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.4.2.3. Pivotal and/or main efficacy studies

In Study SPD503-301 treatment related TEAEs were reported in 58 (66.7%) subjects in the 2 mg group, 73 (84.9%) in the 3 mg, 68 (79.1%) in the 4 mg and 34 (39.5%) in the placebo. The commonest treatment related TEAEs in the guanfacine group were: somnolence in 82 (31.7%) subjects, headache in 54 (20.8%), sedation in 33 (12.7%) and upper abdominal pain in 28 (10.8%).

In Study SPD503-304 treatment related TEAEs were reported in 42 (68.9%) subjects in the 1 mg group, 28 (43.1%) in the 2 mg, 37 (56.9%) in the 3 mg, 49 (75.4%) in the 4 mg and 36 (54.5%) in the placebo. The commonest treatment related TEAEs in the guanfacine group were: somnolence in 67 (26.2%) subjects and headache in 35 (13.7%).

In Study SPD-503-307 treatment related TEAEs were reported in 100 (73.5%) subjects in the guanfacine group and 27 (34.6%) in the placebo. The commonest treatment related TEAEs in the guanfacine group were: somnolence in 66 (48.5%) subjects, headache in 22 (16.2%) and sedation in 18 (13.2).

In Study SPD503-312, 372 treatment related TEAEs were reported in 125 (79.6%) subjects in the guanfacine group and 176 in 80 (51.6%) in the placebo. The commonest TEAEs in the guanfacine group were: somnolence in 67 (42.7%), fatigue in 31 (19.7%), headache in 26 (16.6%), dizziness in 22 (14.0%), and sedation in 18 (11.5%).

In Study SPD503-313 treatment related TEAEs were reported in 74 (49.3%) subjects in the AM group, 79 (52.0%) in the PM, and 50 (32.7%) in the placebo.

In Study SPD503-314 treatment related TEAEs were reported in 74 (69.2%) subjects in the AM group, 79 (69.3%) in the PM and 41 (36.6%) in the placebo. The commonest treatment related TEAEs in the guanfacine group were: somnolence in 94 (42.5%) subjects, sedation in 32 (14.5%), headache in 28 (12.7%) and fatigue in 22 (10.0%).

In Study SPD503-315 in the open label phase, treatment related TEAEs were reported in 407 (77.4%) subjects. Somnolence was reported in 247 (47.0%), fatigue in 124 (23.6%) and headache in 92 (17.5%). In the double blind phase, treatment related TEAEs were reported in 42 (26.8%) subjects in the guanfacine group and 20 (12.7%) in the placebo.

In Study SPD503-316 there were 277 treatment related TEAEs reported in 70 (61.4%) subjects in the guanfacine group, 136 in 44 (39.6%) in the placebo and 278 in 62 (55.4%) in the atomoxetine. Somnolence was more common with guanfacine but nausea and decreased appetite were more common with atomoxetine.

8.4.2.4. Other studies

Other efficacy studies

In Study SPD503-202 there were 138 treatment related TEAEs reported in 26 (92.9%) subjects in the guanfacine group and 65 in 19 (70.4%) in the placebo. In the guanfacine group, headache was reported in 14 (50.0%) subjects, asthenia in 14 (50.0%), somnolence in 11 (39.3%), and abdominal pain in eight (28.6%).

In Study SPD503-205 treatment related TEAEs were reported in 58 (77.3%) subjects. Upper abdominal pain was reported in 19 (25.3%) subjects, fatigue in 18 (24.0%) subjects, irritability in 17 (22.7%), headache in 15 (20.0%), somnolence in 14 (18.7%), and insomnia in 10 (13.3%).

In Study SPD503-206 treatment related TEAEs were reported in 75 (62.0%) subjects in the guanfacine group and 25 (43.9%) in the placebo. TEAEs were reported in nine (64.3%) subjects in the guanfacine 1 mg group, 29 (78.4%) in the 2 mg and 37 (52.9%) in the 3 mg. The commonest treatment related TEAEs in the guanfacine group were: somnolence in 49 (40.5%) subjects and headache in 18 (14.9%).

In Study SPD503-303 treatment related TEAEs were reported in 178 (74.2%) subjects. Somnolence was reported in 72 (30.0%) subjects, headache in 39 (16.3%), fatigue in 33 (13.8%), and sedation in 30 (12.5%).

In Study SPD503-305 treatment related TEAEs were reported in 190 (73.4%) subjects. Somnolence was reported in 77 (29.7%) subjects, headache in 34 (13.1%), fatigue in 33 (12.7%) and sedation in 28 (10.8%).

Studies evaluable for safety only

In Study SPD503-201 (immediate release guanfacine up to 1.5 mg) prolonged QT was attributed to study drug in 11 (55%) subjects.

In Study SPD503-318 treatment related TEAEs were reported in 67 (54.9%) subjects in the 6 to 12 years age group and 27 (35.5%) in the ≥ 13 years age group. The commonest treatment related TEAEs were somnolence in 55 (27.8%) and fatigue in 23 (11.6%).

In Study SPD503-210 treatment related TEAEs were reported in 42 (67.7%) subjects in the guanfacine group and seven (33.3%) in the placebo. The commonest TEAEs in the guanfacine group were: somnolence in 16 (25.8%), headache in 15 (24.2%), and fatigue in 12 (19.4%).

8.4.3. Deaths and other serious adverse events

8.4.3.1. Integrated safety analyses

There were no deaths in the study program. Overall the rate of SAEs was higher in the guanfacine extended release group than in the placebo 49 (2.0%) subjects compared with eight (0.8%). In the guanfacine group, there were 33 (1.9%) subjects aged 6 to 12 years with TEAEs and 16 (2.3%) aged 13 to 17 years.

8.4.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.4.3.3. Pivotal and/or main efficacy studies

In Study SPD503-301 there were no deaths. SAEs were reported in one (1.2%) subject in the 2 mg group (pneumothorax), and one (1.2%) in the 4 mg (severe asthma).

In Study SPD503-304 there were no deaths. SAEs were reported one (1.5%) subject in the 3 mg (concussion/convulsions) and one (1.5%) in the placebo (lower limb fracture).

In Study SPD-503-307 there were no deaths or SAEs.

In Study SPD503-312 there were no deaths. SAEs were reported in four (2.5%) subjects in the guanfacine group (homicidal ideation, loss of consciousness/concussion, vomiting/withdrawal hypertension, cholecystitis/abdominal pain) and two (1.3%) in the placebo (ruptured ovarian cyst, clavicle fracture/pelvic fracture).

In Study SPD503-313 there were no deaths. SAEs were reported in one (0.7%) subject in the AM group (self-injurious behaviour/ worsening aggression/ adjustment disorder), two (1.3%) in the PM (syncope, poisoning) and none in the placebo.

In Study SPD503-314 there were no deaths. SAEs were reported in one (0.9%) subjects in the AM group (syncope), two (1.8%) in the PM (syncope, self-injurious ideation/suicidal ideation) and none in the placebo.

In Study SPD503-315 there were no deaths. In the open label phase, SAEs were reported in six (1.1%) subjects (syncope [3], sinus bradycardia, aggression and somnolence). In the double blind phase, SAEs were reported in two (1.3%) subjects in the guanfacine group (conduct disorder, grand mal convulsion) and four (2.5%) in the placebo (nephrolithiasis, aggression/ family stress, lower abdominal pain, syncope).

In Study SPD503-316 there were no deaths. SAEs were reported in one (0.9%) subject in the guanfacine group (syncope), one (0.9%) in the placebo (syncope) and none in the atomoxetine.

8.4.3.4. Other studies

Other efficacy studies

In Study SPD503-202 and Study SPD503-205 there were no deaths or SAEs.

In Study SPD503-206 there were no deaths. SAEs were reported in two (1.7%) subjects in the guanfacine group (asthma exacerbation, loss of consciousness) and none in the placebo. Both subjects with SAEs were in the 3 mg group.

In Study SPD503-303 there were no deaths. SAEs were reported in nine (3.8%) subjects. Syncope was reported in two (0.8%) subjects and orthostatic hypotension in one (0.4%).

In Study SPD503-305 there were no deaths. SAEs were reported in 16 (6.2%) subjects. In five (1.9%) subjects SAEs were due to syncope.

Studies evaluable for safety only

In Study SPD503-201 (immediate release guanfacine up to 1.5 mg) there were no deaths or SAEs.

In Study SPD503-318 there were no deaths. SAEs were reported in one (0.8%) subject in the 6 to 12 years age group (severe gastroenteritis) and none in the ≥ 13 years age group.

In Study SPD503-210 there were no deaths or SAEs.

8.4.4. Discontinuations due to adverse events

8.4.4.1. Integrated safety analyses

Overall the rate of DAE was higher in the guanfacine extended release group than in the placebo 261 (10.8%) subjects compared with 13 (1.3%). In the guanfacine group, there were 200 (11.6%) subjects aged 6 to 12 years with DAE and 61 (8.8%) aged 13 to 17 years.

8.4.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.4.4.3. Pivotal and/or main efficacy studies

In Study SPD503-301 there was a dose related increase in DAE. DAEs was reported for nine (10.3%) subjects in the 2 mg group, 13 (15.1%) in the 3 mg, 20 (23.3%) in the 4 mg and one (1.2%) in the placebo. The commonest reasons for DAE in the guanfacine group were somnolence in 11 (4.2%) subjects, sedation in 9 (3.5%) and headache in four (1.5%).

In Study SPD503-304 DAE was reported for two (3.3%) subjects in the 1 mg group, two (3.1%) in the 2 mg, six (9.2%) in the 3 mg, nine (13.8%) in the 4 mg and five (7.6%) in the placebo. The commonest DAE was somnolence in eight (3.1%) subjects in the guanfacine group.

In Study SPD-503-307 DAE was reported for twelve (83.8%) subjects in the guanfacine group and none in the placebo. Four (2.9%) subjects discontinued due to sedation and four (2.9%) due to somnolence.

In Study SPD503-312 DAE was reported for nine (5.7%) subjects in the guanfacine group and three (1.9%) in the placebo. Fatigue led to discontinuation in two subjects in the guanfacine group.

In Study SPD503-313 DAE was reported for four (2.7%) subjects in the AM group, six (3.9%) in the PM, and one (0.7%) in the placebo. Two subjects in the guanfacine group discontinued because of aggression.

In Study SPD503-314 DAE was reported for eight (7.5%) subjects in the AM group, eight (7.0%) in the PM and none in the placebo. Two (0.9%) subjects discontinued due to somnolence, two (0.9%) due to fatigue, and two (0.9%) due to syncope.

In Study SPD503-315 in the open label phase, DAEs was reported for 42 (8.0%) subjects. Somnolence in nine (1.7%), fatigue in five (1.0%), sedation in five (1.0%), dizziness in three (0.6%) and hypotension in three (0.6%). In the double blind phase, DAE was reported for three (1.9%) subjects in the guanfacine group and two (1.3%) in the placebo. No individual term was reported in more than one subject.

In Study SPD503-316 DAE was reported for nine (7.9%) subjects in the guanfacine group, one (0.9%) in the placebo and five (4.5%) in the atomoxetine. In the guanfacine group, three (2.6%) subjects discontinued due to somnolence, two (1.8%) due to irritability and two (1.8%) due to insomnia.

8.4.4.4. Other studies

Other efficacy studies

In Study SPD503-202 there was one (3.6%) subject with DAE in the guanfacine group (premature ventricular contractions) and one (3.7%) in the placebo (rash).

In Study SPD503-205 DAE was reported for five (6.7%) subjects: lethargy, dizziness, headache, somnolence, and rash NOS.

In Study SPD503-206 DAEs was reported for four (3.3%) subjects in the guanfacine group (fatigue/somnolence, pyrexia, viral syndrome, asthma exacerbation) and one (1.82%) in the placebo (essential hypertension).

In Study SPD503-303 DAE was reported for 50 (20.8%) subjects. Four (1.7%) subjects discontinued due to depression, nine (3.8%) due to somnolence, seven (2.9%) due to weight gain and five (2.1%) due to fatigue.

In Study SPD503-305 DAE was reported for 31 (12.0%) subjects. Six (2.3%) subjects discontinued due to somnolence, three (1.2%) due to syncope and three (1.2%) due to depression.

Studies evaluable for safety only

In Study SPD503-201 (immediate release guanfacine up to 1.5 mg) one subject discontinued because of hypertension at the 1 mg dose level.

In Study SPD503-318 DAE was reported for five (4.1%) subjects in the 6 to 12 years age group and two (2.6%) in the ≥ 13 years age group. Somnolence and aggression were each recorded in two subjects.

In Study SPD503-210 DAE was reported for eight (12.9%) subjects in the guanfacine group and none in the placebo. There were two reports of fatigue and two of dizziness.

8.5. Evaluation of issues with possible regulatory impact

8.5.1. Liver function and liver toxicity

8.5.1.1. Integrated safety analyses

In the Summary of Clinical Safety the sponsor states 'Overall, there were no clinically meaningful laboratory results observed during SPD503 studies'.

8.5.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.5.1.3. Pivotal and/or main efficacy studies

In Study SPD503-301 one (1%) subject in the guanfacine group had GGT $\geq$ 3xULN. In Study SPD503-313 one subject in the guanfacine group had an elevation in AST.

In Study SPD503-304, Study SPD-503-307, Study SPD503-312, Study SPD503-314, Study SPD503-315 and Study SPD503-316 there were no clinically significant abnormalities in liver function.

8.5.1.4. Other studies

Other efficacy studies

In Study SPD503-202 there were no subjects with clinically significant abnormalities in liver function.

In Study SPD503-205 one subject had elevated GGT.

In Study SPD503-206 one subject in the guanfacine group had treatment emergent mildly elevated ALT.

In Study SPD503-305 one subject had elevated ALT and GGT that normalised post-study.

8.5.2. Renal function and renal toxicity

8.5.2.1. Integrated safety analyses

There were no clinically significant abnormalities in renal function reported in the integrated safety analysis.

8.5.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.5.2.3. Pivotal and/or main efficacy studies

In Study SPD503-301, Study SPD503-304, Study SPD-503-307, Study SPD503-312, Study SPD503-313, Study SPD503-314 and Study SPD503-316 there were no reports of renal impairment.

8.5.2.4. Other studies

Other efficacy studies

Study SPD503-202, Study SPD503-205, Study SPD503-206 and Study SPD503-305 there were no subjects with clinically significant abnormalities in renal function.

8.5.3. Other clinical chemistry

8.5.3.1. Integrated safety analyses

There were no clinically significant abnormalities in clinical chemistry reported in the integrated safety analysis.

8.5.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.5.3.3. Pivotal and/or main efficacy studies

In Study SPD503-301, Study SPD503-304, Study SPD503-312, Study SPD503-314, Study SPD503-315 and Study SPD503-316 there were no clinically significant abnormalities in other clinical chemistry.

In Study SPD-503-307 two subjects in the guanfacine group had low TSH.

8.5.3.4. Other studies

Other efficacy studies

Study SPD503-202, Study SPD503-206 and Study SPD503-305 there were no subjects with clinically significant abnormalities in other clinical chemistry parameters.

In Study SPD503-205 on subject had decreased TSH.

8.5.4. Haematology and haematological toxicity

8.5.4.1. Integrated safety analyses

There were no clinically significant abnormalities in haematology reported in the integrated safety analysis.

8.5.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.5.4.3. Pivotal and/or main efficacy studies

In Study SPD503-301, Study SPD503-304, Study SPD-503-307, Study SPD503-312, Study SPD503-314, Study SPD503-315 and Study SPD503-316 there were no clinically significant abnormalities in haematology.

8.5.4.4. Other studies

Other efficacy studies

Study SPD503-202, Study SPD503-205, Study SPD503-206 and Study SPD503-305 there were no subjects with clinically significant abnormalities in haematology parameters.

In Study SPD503-303 one subjects had a high WBC reported as an AE.

8.5.5. Other laboratory tests

There were no clinically significant abnormalities in other laboratory tests reported in the integrated safety analysis.

8.5.6. Electrocardiograph findings and cardiovascular safety

8.5.6.1. Integrated safety analyses

Overall, there were few clinically significant ECG changes on treatment and no apparent differences between guanfacine and placebo with the exception of a higher rate of bradycardia with guanfacine.

8.5.6.2. Main/pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.5.6.3. Pivotal and/or main efficacy studies

In Study SPD503-301 discontinuation due to prolonged QTc was reported for three (1.2%) subjects in the guanfacine group and one (1.2%) in the placebo. There was a dose dependent

increase in QTcF, with the greatest mean (SD) increase in the 4 mg group of 9.1 (16.12) msec (Table 37). There was no significant increase in mean QTcB. No subject had an increase from baseline in QTcF ≥ 60 msec. One subject in the 2 mg group had an increase from baseline in QTcB of ≥ 60 msec. No subject had a QTcB ≥ 480 msec or QTcF ≥ 500 msec. In the follow-on study, Study SPD503-303, no subject had an increase in QTcB or QTcF ≥ 60 msec, or QTcB or QTcF ≥ 500 msec.

Table 37: QTcB and QTcF Data by Actual Dose at the Time of the ECG Assessment (Safety Population) (copied from Table 53, Study SPD503-301 CSR)

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

a: Number of subjects who took the specified actual dose at any time during the study.
b: Number of subjects who had an ECG taken while receiving the specified actual dose.
c: For each subject, the Baseline ECG is the mean of multiple ECGs taken at Baseline.
d: Change from Baseline is derived from comparing the ECG taken while on study drug with the Baseline ECG of the same subject.
Source: Section 12.1 Table 3.5.7.

In Study SPD503-304 there was a dose related increase in mean QTcF in the guanfacine group at Week 6: mean (SD) change from baseline 4.3 (12.74) msec for 1 mg, 2.4 (12.32) msec for 2 mg, 7.1 (12.75) msec for 3 mg, 9.7 (15.92) msec for 4 mg and -0.3 (16.31) msec for placebo. There was no corresponding dose related increase in QTcB: mean (SD) change from baseline 1.3 (15.29) msec for 1 mg, -3.1 (15.50) msec for 2 mg, 1.8 (13.28) msec for 3 mg, -2.2 (16.74) msec for 4 mg and -2.7 (17.42) msec for placebo. No subject had an increase in QTcB or QTcF ≥ 60 msec, or QTcB or QTcF ≥ 500 msec. In the follow-on study, Study SPD503-305, the mean (SD) change from baseline in QTcF was 2.2 (13.19) msec for 1 mg, 6.0 (16.24) msec for 2 mg, 5.9 (15.24) msec for 3 mg, and 7.5 (16.69) msec for 4 mg. There was no significant change in QTcB. No subject had an increase in QTcB or QTcF ≥ 60 msec, or QTcB or QTcF ≥ 500 msec.

In Study SPD-503-307 QTcF increased by a mean (SD) of 5.2 (15.74) msec and QTcB decreased by a mean of 5.6 (21.58) msec. No subject in the guanfacine group had an increase in QTcB or QTcF ≥ 60 msec, or QTcB or QTcF ≥ 500 msec.

In Study SPD503-312 no subject in the guanfacine group had an increase in QTcB, or QTcB or QTcF ≥ 500 msec. One subject had an increase in QTcF ≥ 60 msec.

In Study SPD503-313 one subjects in the guanfacine group discontinued because of nodal rhythm. No subject in the guanfacine group had an increase in QTcB or QTcF ≥ 60 msec, or QTcB or QTcF ≥ 500 msec.

In Study SPD503-314 no subject in the guanfacine group had a QTcB or QTcF ≥ 500 msec.

In Study SPD503-315 no subject in the guanfacine group had an increase in QTcB or QTcF ≥ 60 msec, or QTcB or QTcF ≥ 500 msec.

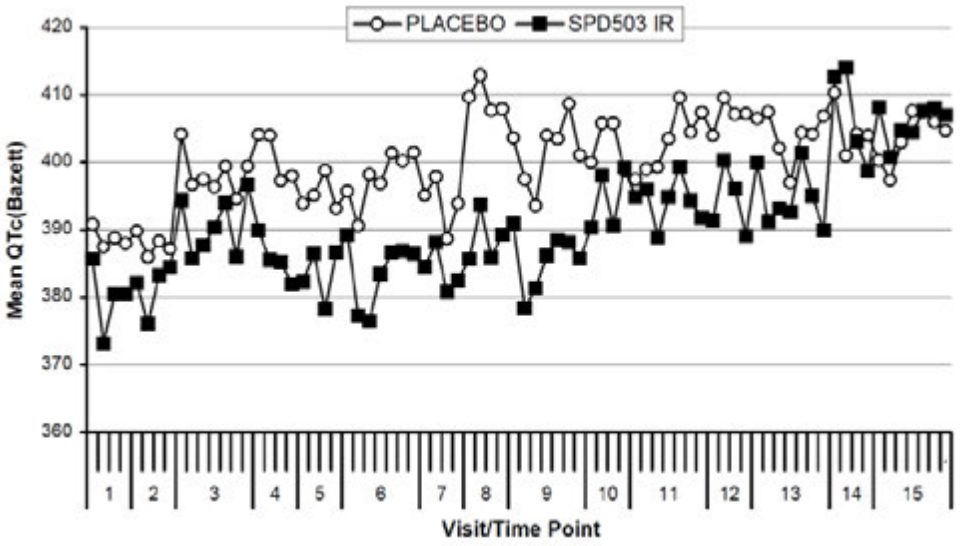
In Study SPD503-316 no subject in the guanfacine group had an increase in QTcB or QTcF ≥ 60 msec, or QTcB or QTcF ≥ 500 msec. One subject in the atomoxetine group had an increase in QTcB ≥ 60 msec.

8.5.6.4. Other studies

Other efficacy studies

In Study SPD503-202 there were no subjects with clinically significant abnormalities in haematology parameters. Mean QTc decreased with treatment in the guanfacine group (Figure 1). There were 27 ECGs from subjects in the guanfacine group with prolongation of QTc >59 msec from baseline, and 14 of these ECGs were from the off-treatment period.

Figure 1: Mean QTc (Bazett) Intervals versus Visit/Time Point for All Randomized Subjects (copied from Figure 17, Study SPD503-202 CSR)



In Study SPD503-205 no subject had a post-baseline increase in QTcB or QTcF $\geq$ 60 msec.

In Study SPD503-206 in the guanfacine group the mean (SD) increase in QTcP was 11.6 (13.65) msec, QTcB was 0.7 (16.41) msec and QTcF was 11.4 (13.49) msec. No subject had an increase in either QTcB or QTcF of ≥ 60 msec.

Studies with evaluable safety data: dose finding and pharmacology

In Study SPD503-102 at dose up to 4 mg daily there was no significant increase in QTcF.

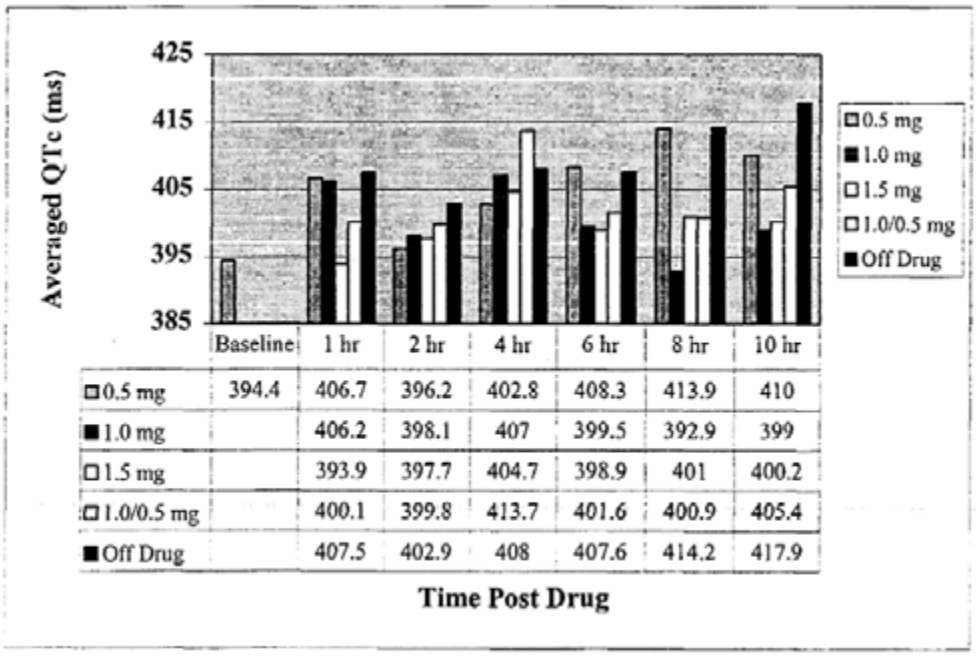
At doses titrated up to 8 mg, there was prolongation of QTcF to the threshold of regulatory concern, but there was no prolongation when QTc was calculated by QTcNi (Study SPD503-112). The mean (90% CI) for difference guanfacine-placebo, change for baseline in QTcF was 3.54 (0.78 to 6.29) at 6 hours post dose, and 7.61 (4.87 to 10.34) at 12 hours post dose. However, heart rate decreased by a mean of 20 bpm in the guanfacine group. The interpretation of these findings, according to the CHMP Guidance, is that ECG data should be collected during the subsequent Phase 2 and 3 studies.

In Study SPD503-203 three (15%) subjects had post-baseline increases in QTcB ≥ 60 msec.

Studies evaluable for safety only

In Study SPD503-201 (immediate release guanfacine up to 1.5 mg) prolonged QT was attributed to study drug in 11 (55%) subjects. The increase in mean averaged QTc was highest off drug (Figure 2). An increase in QTc ≥ 60 msec was reported in 10 (50%) subjects.

Figure 2: Mean averaged QTc values by dosage and time post dose (copied from Figure 11, Study SPD503-201 CSR)



	Baseline	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr
0.5 mg	394.4	406.7	396.2	402.8	408.3	413.9	410
1.0 mg		406.2	398.1	407	399.5	392.9	399
1.5 mg		393.9	397.7	404.7	398.9	401	400.2
1.0/0.5 mg		400.1	399.8	413.7	401.6	400.9	405.4
Off Drug		407.5	402.9	408	407.6	414.2	417.9

Source: Appendix Table 3.5.1

Note: Each data value represented in the figure represents an average of all the values obtained at a given time collected during the clinic visits in a given week.

In Study SPD503-318 no subject had an increase in QTcB or QTcF ≥ 60 msec, or QTcB or QTcF ≥ 500 msec.

8.5.7. Vital signs and clinical examination findings

8.5.7.1. Integrated safety analyses

Decrease in heart rate. SBP and DBP were identified in the integrated safety data. These are discussed in more detail below.

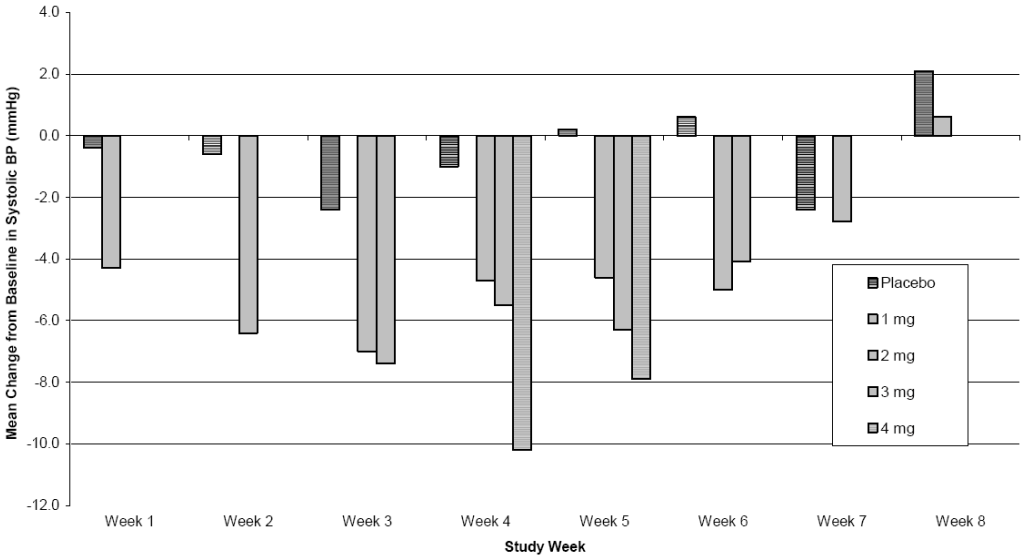
8.5.7.2. Pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.5.7.3. Pivotal and/or main efficacy studies

In Study SPD503-301 SBP decreased in a dose dependent manner, with the greatest decrease in mean SBP being -10 mmHg in the 4 mg group (Figure 3). There was a similar pattern for DBP, with the greatest decrease being -6 mmHg in the 4 mg group at Week 4. There was also a similar pattern for HR with the greatest decrease being -8 bpm in the 4 mg group at Weeks 3 and 4. In the follow-on study, Study SPD503-303, SBP and DBP returned to baseline over several months of treatment but the decrease in HR persisted long term.

Figure 3: Mean Change from Baseline for Systolic Blood Pressure by Actual Dose and Study Week (Safety Population) (copied from Figure 5, Study ASPD503-301 CSR)



In Study SPD503-304 hypotension was reported as a TEAE in ten (3.9%) subjects. Mean SBP and DBP decreased by up to 7.38 mmHg with guanfacine treatment and returned to baseline with tapering. Orthostatic hypotension was recorded in three subjects in the guanfacine group at Week 4. Mean heart rate decreased by up to 9.51 bpm with treatment and returned to baseline with tapering. In the follow-on study, Study SPD503-305, in five (1.9%) subjects SAEs were due to syncope. Two (0.8%) subjects were reported with a postural drop in DBP ≥ 15 mmHg. The decrease in SBP and DBP returned to baseline following up to 5 months of treatment.

In Study SPD-503-307 on treatment there was a decrease in mean SBP up to 4.6 mmHg, DBP up to 3.9 mmHg and pulse rate up to 6.1 bpm. SBP and DBP returned to baseline after tapering. Postural hypotension was more common in the placebo group: diastolic orthostatic drop ≥ 15 mmHg in 20 (15.4%) subjects in the guanfacine group and 17 (22.7%) in the placebo.

Study SPD503-312 one subject in the guanfacine group had syncope recorded as a SAE. In the guanfacine group there was a mean decrease in pulse rate of 3.7 bpm on treatment, a mean decreased in SBP of 4.4 mmHg and a mean decrease in DBP of 2.9 mmHg. Postural hypotension was more common in the guanfacine group: diastolic orthostatic drop ≥ 15 mmHg in 17 (10.0%) subjects in the guanfacine group and nine (5.8%) in the placebo.

In Study SPD503-313 one subject in the guanfacine group had a SAE of syncope. In the guanfacine group, on treatment, there was a mean decrease in pulse rate of 5.6 bpm, SBP of 2.2 mmHg and DBP of 2.1 mmHg. There was a diastolic orthostatic drop ≥ 15 mmHg in 15 (10.1%) subjects in the AM group, eight (5.4%) in the PM and nine (5.9%) in the placebo.

Study SPD503-314 two subjects in the guanfacine group had a SAE of syncope, leading to discontinuation. In the guanfacine group, on treatment, there was a mean decrease in pulse rate of 3.8 bpm, SBP of 3.0 mmHg and DBP of 2.4 mmHg. There was a diastolic orthostatic drop ≥ 15 mmHg in eight (7.7%) subjects in the AM group, five (4.5%) in the PM and six (5.5%) in the placebo.

In Study SPD503-315 in the long term study (26 weeks) there were no significant changes from baseline in pulse rate, SBP or DBP.

In Study SPD503-316 in the guanfacine group, on treatment, mean pulse rate decreased by 3.3 bpm, SBP by 4.3 mmHg and DBP by 2.8 mmHg. There was a diastolic orthostatic drop ≥ 15

mmHg in ten (8.9%) subjects in the guanfacine group, five (4.5%) in the placebo and eight (7.1%) in the atomoxetine.

8.5.7.4. Other studies

Other efficacy studies

In Study SPD503-202 mean SBP decreased with treatment with guanfacine, but rebounded with treatment withdrawal (Figure 4). DBP behaved in a similar manner (Figure 5). Pulse rate also decreased with treatment and rebounded with withdrawal (Figure 6).

In Study SPD503-205 there was a mean decrease in SBP up to 7 mmHg on treatment and increase of up to 5 mmHg after cessation of treatment. There was a mean decrease in DBP up to 5.6 mmHg on treatment and increase of up to 4 mmHg after cessation of treatment. There was a mean decrease in HR up to 10.2 bpm on treatment and increase of up to 8 bpm after cessation of treatment.

In Study SPD503-206 SBP, DBP and HR decreased in the guanfacine group relative to placebo (Figure 4). The decreases did not appear to be dose related. There were six (5.0%) subjects in the guanfacine group and one (1.8%) in the placebo with postural orthostatic decreases in DBP ≥ 15 mmHg.

Figure 4: Mean Systolic Blood Pressure versus Visit and Time Point for All Randomized Subjects (copied from Figure 12, Study SPD503-202 CSR)

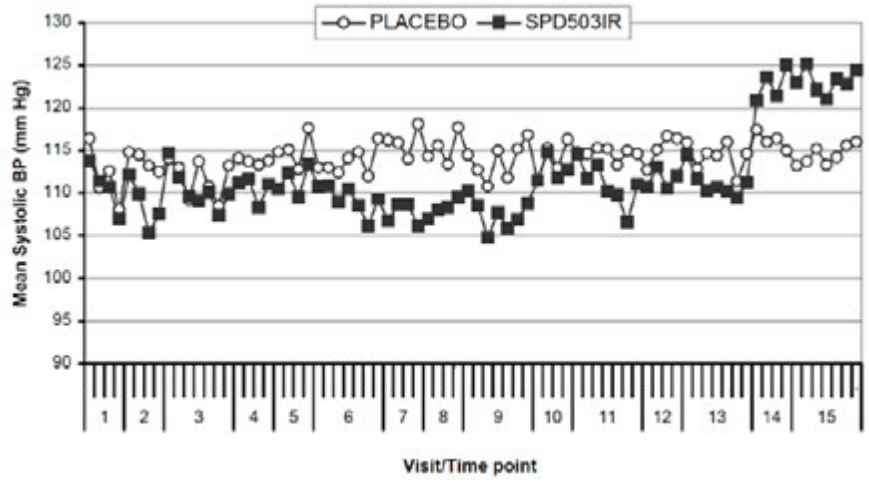


Figure 5: Mean Diastolic Blood Pressure versus Visit and Time Point for All Randomized Subjects (copied from Figure 13, Study SPD503-202 CSR)

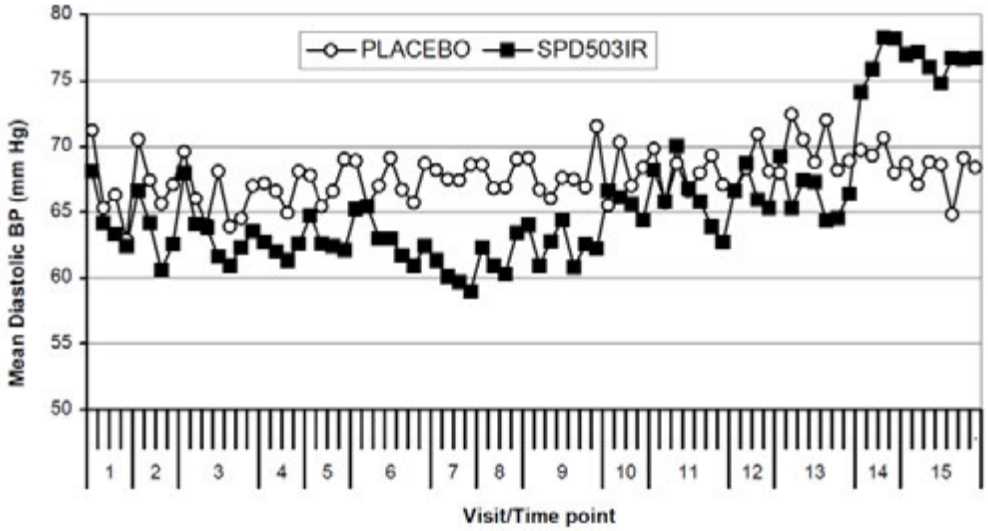
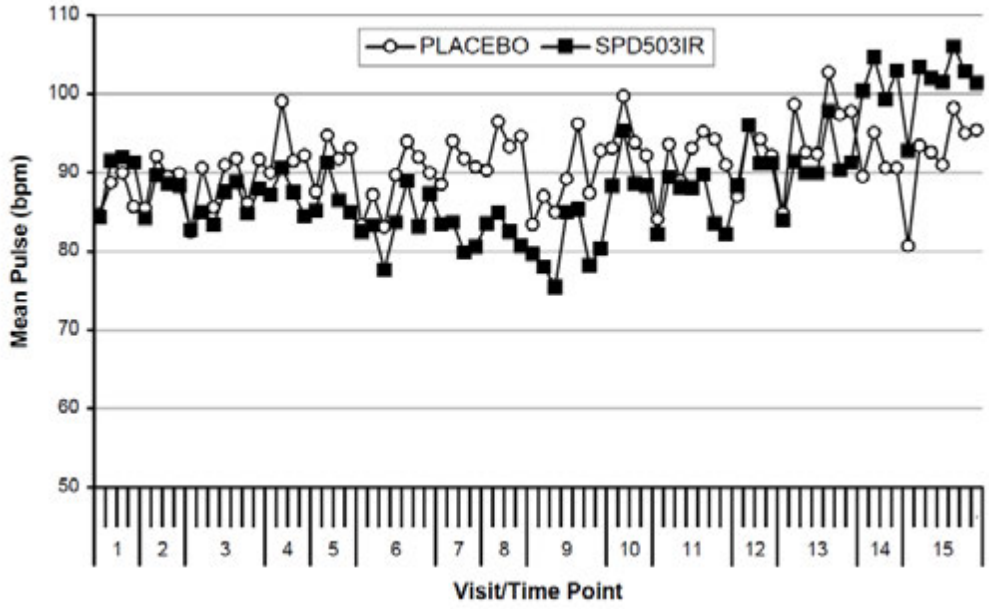


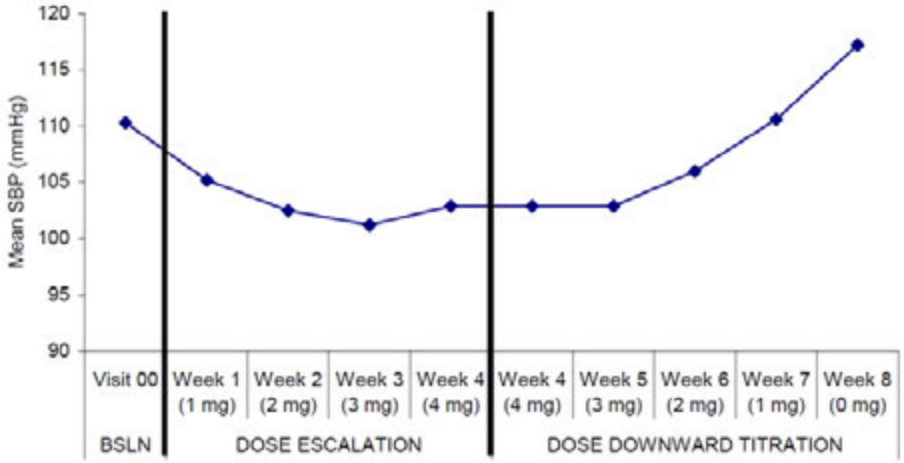
Figure 6: Mean Pulse versus Visit and Time Point for All Randomized Subjects (copied from Figure 14, Study SPD503-202 CSR)



Studies with evaluable safety data: dose finding and pharmacology

In Study SPD503-203 SBP decreased with increasing dose up to guanfacine extended release 3 mg per day, and rebounded following withdrawal (Figure 7). There were similar effects for DBP and pulse rate.

Figure 7: Overall Mean Systolic Blood Pressure By Treatment Week, All Subjects Treated (copied from Study SPD503-203 CSR)



Studies evaluable for safety only

In Study SPD503-201 (immediate release guanfacine up to 1.5 mg daily) there was a mean decrease in SBP of -5.2% and DBP of -9.0% with the first 0.5 mg dose, but there were no significant decreases with subsequent dosing. There was an increase in SBP and DBP from baseline of up to 10% following cessation of treatment. There was a mean increase in heart rate from baseline of 2.7% with the 1.5 mg dose level, and up to 25% off treatment.

8.5.8. Immunogenicity and immunological events

Immunogenicity and/or immunological events were not identified as a safety issue in the clinical data.

8.5.9. Serious skin reactions

Serious skin reactions were not identified as a safety issue in the clinical data.

8.5.10. Sedation / insomnia

8.5.10.1. Integrated safety analyses

Sedation and somnolence were identified as common adverse events with guanfacine in the integrated safety data.

8.5.10.2. Main/pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.5.10.3. Pivotal and/or main efficacy studies

Study SPD503-304 somnolence events increased in frequency with dose: 16 (26.2%) subjects in the 1 mg group, 11 (16.9%) in the 2 mg, 15 (23.1%) in the 3 mg and 27 (41.5%) in the 4 mg. However, there was no significant change in PDSS score relative to placebo for any of the treatment groups.

In Study SPD-503-307 93 (68.9%) subjects treated with guanfacine reported sedation related events compared to nine (11.5%) in the placebo group. The median duration of the event was 26.0 days.

In Study SPD503-312 there were 123 sedative events in 85 (54.1%) subjects in the guanfacine group and 42 in 35 (22.6%) in the placebo.

In Study SPD503-313 sedative events were reported in 27 (18.0%) subjects in the AM group, 28 (18.4%) in the PM, and ten (6.5%) in the placebo.

In Study SPD503-314 sedative events were reported in 61 (57.0%) subjects in the AM group, 62 (54.4%) in the PM and 17 (15.2%) in the placebo. There was a greater decrease in PDSS in the placebo group compared with the PM group: mean (SD) change from baseline -2.4 (5.18) for PM (p = 0.596), -1.5 (6.71) for AM (p = 0.023) and -3.2 (5.76).

In Study SPD503-315 two subjects in the guanfacine group withdrew because of sedative events.

In Study SPD503-316 sedative events were reported in 51 (44.7%) subjects in the guanfacine group, 16 (14.4%) in the placebo and 21 (18.8%) in the atomoxetine

8.5.10.4. Other studies

Other efficacy studies

In Study SPD503-206 sedation was common in comparison with placebo but was not related to dose (Table 38). Sedation did not appear to resolve over the 7 weeks of the study. The mean (SD) change from baseline in PDSS score was -1.3 (3.56) in the guanfacine group and 0.9 (5.31) in the placebo (p = 0.020), indicating a mild decrease in daytime sleepiness in the guanfacine group. There was no significant difference between the treatment groups in PSS.

In Study SPD503-305 sedative events were reported in 127 (29.0%) subjects.

Table 38: Incidence of Sedative Events by Week and Actual Dose (Full Analysis Set/Safety Population) (copied from Table 30, Study SPD503-206 CSR)

Study Week Statistic	Placebo	SPD503 1mg	SPD503 2mg	SPD503 3mg
Week 1				
Number of subjects	57	121		
Number (%) of subjects with sedative events	2 (3.5)	26 (21.5)		
Week 2				
Number of subjects	57	18	100	
Number (%) of subjects with sedative events	7 (12.3)	8 (44.4)	28 (28.0)	
Week 3				
Number of subjects	56	12	29	77
Number (%) of subjects with sedative events	12 (21.4)	7 (58.3)	13 (44.8)	25 (32.5)
Week 4				
Number of subjects	55	11	37	70
Number (%) of subjects with sedative events	10 (18.2)	6 (54.5)	17 (45.9)	14 (20.0)
Week 5				
Number of subjects	55	11	38	69
Number (%) of subjects with sedative events	7 (12.7)	2 (18.2)	15 (39.5)	18 (26.1)
Week 6				
Number of subjects	55	11	37	68
Number (%) of subjects with sedative events	8 (14.5)	2 (18.2)	12 (32.4)	16 (23.5)

Note: Percentages are based on the number of subjects in the FAS/Safety population who received the dose during each week.

Note: Sedative events include somnolence, sedation, fatigue, and lethargy.

8.5.11. Psychiatric changes

8.5.11.1. Integrated safety analyses

The integrated safety data did not identify adverse psychiatric changes as a safety issue.

8.5.11.2. Main/pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.5.11.3. Pivotal and/or main efficacy studies

In Study SPD503-312 there was no significant difference between the treatment groups in BPRS-C total score and the BPRS-C suicidal ideation. There were no 'yes' responses to the suicidal behaviour category of the C-SSRS and no completed suicides while subjects were on-treatment.

In Study SPD503-314 two subjects in the guanfacine group reported yes to the C-SSRS suicidal ideation category while on treatment.

In Study SPD503-315 in the open label phase, seven (1.9%) subjects responded 'yes' to items in the suicidal ideation category of the C-SSRS. In the double blind phase nine guanfacine and 12 placebo subjects responded 'yes' to items in the suicidal ideation category of the C-SSRS.

In Study SPD503-316 suicidal ideation was not more common in the guanfacine group than either placebo or atomoxetine (Table 39).

Table 39: Summary of BPRS-C Item 6 - Suicidal Ideation (Safety Population) (copied from Table 45, Study SPD503-316 CSR)

Visit Response	Placebo (N=111)	SPD503 (N=114)	STRATTERA (N=112)
Baseline (Visit 2/Week 0)			
n	111	114	111
Not present, n (%)	108 (97.3)	113 (99.1)	110 (99.1)
Very mild, n (%)	3 (2.7)	0	1 (0.9)
Mild, n (%)	0	1 (0.9)	0
Visit 15 (Week 10/13)			
n	89	91	88
Not present, n (%)	89 (100.0)	91 (100.0)	87 (98.9)
Very mild, n (%)	0	0	1 (1.1)
Mild, n (%)	0	0	0
Visit 15 (Week 10/13) (LOCF)			
n	102	101	99
Not present, n (%)	101 (99.0)	101 (100.0)	98 (99.0)
Very mild, n (%)	0	0	1 (1.0)
Mild, n (%)	1 (1.0)	0	0

Note: Week number(s) shown represents the week relating to the visit schedule for the 6-12 years age group /13-17 years age group (if different).
Note: BPRS-C response scores were rated using a 7-point scale: 0 (not present), 1 (very mild), 2 (mild), 3 (moderate), 4 (moderately severe), 5 (severe), and 6 (extremely severe). No subjects had scores greater than mild (2).
BPRS-C= Brief Psychiatric Rating Scale for Children; LOCF=last observation carried forward

8.5.11.4. Other studies

Other efficacy studies

In Study SPD503-303 there were no changes in mean Hamilton Anxiety Scale (HAM-A) or Hamilton Depression Scale (HAM-D) scores during the study.

In Study SPD503-305 there were no changes in mean Hamilton Anxiety Scale (HAM-A) or Hamilton Depression Scale (HAM-D) scores during the study.

Studies evaluable for safety only

In Study SPD503-318 suicidal ideation was recorded using the C-CCRS for two subjects.

8.6. Other safety issues

8.6.1. Safety in special populations

There were no further safety data in special populations.

8.6.2. Safety related to drug-drug interactions and other interactions

There were no further safety data with regard to drug-drug interactions.

8.7. Post marketing experience

Guanfacine extended release (SPD503) was first launched in the US in September 2009. There were nine Post-Marketing Safety Update Reports provided in the dossier covering the time period up to 1 September 2015. A total of 3,243 subjects had been treated with SPD503 in clinical trials. The estimated cumulative worldwide patient exposure is 965,432 patient years of treatment.

During the period covered by the reports, there have been no actions taken for safety reasons such as withdrawals, suspensions, limits on indication, or lack of approval for safety reasons taken by regulators.

The Important Identified Risks are:

- Syncope
- Bradycardia
- Hypotension
- Sedative events
- Withdrawal blood pressure increased
- Weight increase

The Important Potential Risks are:

- Cardiac valvulopathy due to binding to 5HT-2B receptors
- QT prolongation
- Off-label use
- Blood glucose disorder

The Missing Information is:

- Use of GXR in pregnant or breastfeeding women
- Use of GXR in patients with renal or hepatic impairment
- Long-term safety (neurocognition in particular but also effects on growth, sexual maturation)
- Drug interactions

8.8. Evaluator's overall conclusions on clinical safety

In the submitted data, overall exposure to guanfacine extended release (SPD503) was 2411 subjects, with 1718 aged 6 to 12 years and 693 aged 13 to 17 years at time of randomisation. There were 482 subjects exposed for ≥ 180 days, 235 subjects exposed for ≥ 360 days and 101 subjects exposed for >720 days. Subjects were exposed to up to 7 mg/day (Table 40) and up to 0.16 mg/kg/day (Table 41). In the post-marketing data, a total of 3,243 subjects had been treated with SPD503 in clinical trials and the estimated cumulative worldwide patient exposure was 965,432 patient years of treatment.

Table 40: Length of treatment exposure by actual dose – randomised pool (copied from Table 7, Summary of Clinical Safety)

Parameter	Placebo (N=820)	SPD503 1mg (N=1414)	2mg (N=1280)	3mg (N=965)	4mg (N=490)	5mg (N=116)	6mg (N=59)	7mg (N=16)
Length of exposure (days)								
n	820	1414	1280	965	490	116	59	16
Mean (SD)	71.2 (44.40)	14.5 (15.64)	20.0 (19.85)	25.4 (30.48)	31.7 (39.57)	31.7 (39.30)	34.4 (26.97)	36.4 (30.17)
Median	63.0	10.0	14.0	14.0	19.0	14.0	42.0	43.0
Min, Max	2, 274	1, 196	1, 192	1, 201	2, 199	1, 173	4, 166	6, 127
Total years exposed	159.9	56.3	70.1	67.0	42.5	10.1	5.5	1.6

Note: Percentages are based on the number of subjects who were dispensed the dosage of investigational product at least once.
Max=maximum; Min=minimum; SD=standard deviation.

Table 41: Length of treatment exposure by weight-adjusted dose – randomised pool (copied from Table 7, Summary of Clinical Safety)

Parameter	Placebo (N=820)	SPD503 0.01-0.04mg/kg (N=1418)	0.05-0.08mg/kg (N=1112)	0.09-0.12mg/kg (N=531)	0.13-0.16mg/kg (N=110)
Length of exposure (days)					
n	820	1418	1112	531	110
Mean (SD)	71.2 (44.40)	23.6 (23.60)	32.1 (31.07)	36.9 (39.95)	34.0 (40.15)
Median	63.0	15.0	23.0	27.0	21.0
Min, Max	2, 274	1, 212	2, 208	1, 197	2, 199
Total years exposed	159.9	91.6	97.7	53.6	10.2

Note: Percentages are based on the number of subjects who were dispensed the dosage of investigational product at least once.
Max=maximum; Min=minimum; SD=standard deviation.

Overall the rate of TEAEs was higher in the guanfacine extended release group than in the placebo 2046 (84.9%) subjects compared with 620 (63.7%). In the guanfacine group, there were 1467 (85.4%) subjects aged 6 to 12 years with TEAEs and 579 (83.5%) aged 13 to 17 years. Compared to placebo, in the guanfacine group, there was a higher rate of somnolence, headache, fatigue and sedation regardless of dose or age group

Overall the rate of treatment related TEAEs was higher in the guanfacine extended release group than in the placebo 1765 (73.2%) subjects compared with 357 (36.7%). In the guanfacine group, there were 1275 (74.2%) subjects aged 6 to 12 years with TEAEs and 490 (70.7%) aged 13 to 17 years. Somnolence, sedation and headache were the most common treatment related TEAEs.

There were no deaths in the study program.

Overall the rate of SAEs was higher in the guanfacine extended release group than in the placebo 49 (2.0%) subjects compared with eight (0.8%). In the guanfacine group, there were 33 (1.9%) subjects aged 6 to 12 years with TEAEs and 16 (2.3%) aged 13 to 17 years. Syncope and sedation were the commonest SAEs in the guanfacine group.

Overall the rate of DAE was higher in the guanfacine extended release group than in the placebo 261 (10.8%) subjects compared with 13 (1.3%). In the guanfacine group, there were 200 (11.6%) subjects aged 6 to 12 years with DAE and 61 (8.8%) aged 13 to 17 years. Somnolence and syncope were the commonest reasons for discontinuation in the guanfacine group.

At doses titrated up to 8 mg, there was prolongation of QTcF to the threshold of regulatory concern, but there was no prolongation when QTc was calculated by QTcNi (Study SPD503-112). The mean (90% CI) for difference guanfacine-placebo, change for baseline in QTcF was 3.54 (0.78 to 6.29) at 6 hours post dose, and 7.61 (4.87 to 10.34) at 12 hours post dose.

However, heart rate decreased by a mean of 20 bpm in the guanfacine group. Subsequently, ECG data were collected for all of the Phase III and Phase II studies and no significant concerns with regard to QTc prolongation were identified in these data. Of note, subjects with known QTc prolongation or who were taking drugs known to prolong QTc were excluded from all of these studies.

HR, SBP and DBP decreased from the first dose of guanfacine, and normalised over several months of treatment. With tapered withdrawal of guanfacine rebound hypertension was not clinically significant. Postural hypotension and syncope was reported in patients treated with guanfacine. The pivotal trials excluded subjects with hypertension or orthostatic hypotension.

Somnolence and sedation were common adverse events. The rate of somnolence/sedation increased with dose in the fixed dose studies, but a dose effect was not apparent in the dose optimisation studies.

Adverse psychiatric changes were not identified as a safety issue. There was no apparent increase in suicidality with guanfacine.

The pivotal clinical trials excluded patients with a broad range of comorbidities and the dossier does not contain safety data for use in these patients. Typical exclusion criteria used in the development program were those from Study SPD503-313:

- Any current, controlled (requiring a prohibited medication or behavioural modification program) or uncontrolled, co-morbid psychiatric diagnosis (except ODD), including any severe co-morbid Axis II disorders or severe Axis I disorders such as Post Traumatic Stress Disorder (PTSD), bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder (OCD), substance abuse disorder, or other symptomatic manifestations or lifetime history of bipolar illness, psychosis or conduct disorder that, in the opinion of the Investigator, contraindicate SPD503 treatment or confound efficacy or safety assessments.
- Subjects who are at suicide risk, any subject who has previously made a suicide attempt or those who are currently demonstrating active suicide ideation.
- Subject has a history of seizure disorder (other than a single childhood febrile seizure occurring before the age of 3 years).
- History or presence of known structural cardiac abnormalities, symptomatic cardiovascular disease, advanced arteriosclerosis, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, syncope, cardiac conduction problems (for example, clinically significant heart block or clinically significant abnormality in QT or QTc interval, etc.), exercise-related cardiac events including syncope and pre-syncope, clinically significant bradycardia or any other serious cardiac problem that may place a subject at increased vulnerability to the effects of a stimulant and/or α2-agonist medication.
- Subject has a family history of sudden cardiac death or ventricular arrhythmia.
- Subject has symptomatic or clinically meaningful orthostatic hypotension based on clinical judgment.
- History of controlled or uncontrolled hypertension.
- Current use of any prohibited medication or other medications, including herbal supplements, that have central nervous system (CNS) effects or affect cognitive performance, such as sedating antihistamines and decongestant sympathomimetics (bronchodilators are permitted).
- Current use of any medication, including herbal supplements, that affects BP or HR or are known to prolong the QT/QTc interval (excluding the subject's current ADHD medication).
- Morbidly overweight or obese, as defined by a BMI >95th percentile.

- Weight less than 55 lbs (25kg).
- Weight greater than 176 lbs (80kg).
- Pregnancy or currently lactating.
- History of alcohol or other substance abuse or dependence, as defined by DSM-IV (with the exceptions of caffeine or nicotine) within the last year.

These exclusion criteria and the conditions they represent should be mentioned in the contraindications and warnings sections of the Product Information document.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Table 42: First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Guanfacine significantly improves ADHD symptomatology in patients aged 6 to 17 years with ADHD There is maintenance of efficacy for up to 24 months. Efficacy was demonstrated for oppositional symptoms in subjects with ADHD with oppositional symptoms. Guanfacine significantly improves ADHD symptomatology in patients aged 6 to 17 years with ADHD who are co-medicated with psychostimulants Guanfacine has not been demonstrated to be superior or non-inferior to any currently approved treatment for ADHD. Efficacy has not been demonstrated in patients with the inattentive subtype of ADHD.	Demonstrated by the pivotal studies: Study SPD503-312, Study SPD503-315 and Study SPD503-316. Study SPD503-315 demonstrated efficacy for 26 weeks. Study SPD503-303 and Study SPD503-305 were supportive of efficacy for up to 2 years. Demonstrated in Study SPD503-307. Demonstrated in Study SPD503-313 Study SPD503-316 was not designed as a comparator controlled study. A subgroup analysis of either an individual study or a pooled analysis that demonstrates efficacy in patients with inattentive subtype of ADHD has not been submitted.

9.2. First round assessment of risks

Table 43: First round assessment of risks

Risks	Strengths and Uncertainties
Guanfacine extended release (SPD503) has a favourable safety profile. Somnolence, sedation, fatigue and headache	There is extensive exposure data to support this including a total of 3,243 subjects treated with SPD503 in clinical trials and an estimated cumulative worldwide patient

Risks	Strengths and Uncertainties
are very common adverse events. There were no deaths in the clinical trials. There were few SAEs. The commonest SAEs were somnolence, sedation and syncope Somnolence and syncope were the commonest reasons for discontinuation due to AE. Guanfacine causes a decrease in HR, SBP and DBP that returns to baseline following several months of treatment. Rebound hypertension can be avoided by tapered withdrawal. QTcF prolongation of regulatory concern was identified in the thorough QT study. Clinically significant prolongation of QTcF or QTcB was not identified in the subsequent clinical trials. Effects on operating machinery and driving have not been evaluated. There are no safety data for the 5 mg to 7 mg dose range in patients co-medicated with psychostimulants.	exposure of 965,432 patient years of treatment. This is supported by the safety data presented in the dossier.

9.3. First round assessment of benefit-risk balance

The clinical evaluator is not in a position to determine the benefit-risk balance. There are a number of issues that require clarification before this can be determined. These issues are:

- Efficacy for guanfacine extended release has not been demonstrated for inattentive subtype ADHD.
- The effects on driving and operating machinery of guanfacine extended release have not been determined.

10. First round recommendation regarding authorisation

The clinical evaluator is deferring recommendation for authorisation until the following issues have been resolved:

- Efficacy for guanfacine extended release has not been demonstrated for inattentive subtype ADHD.
- The effects on driving and operating machinery of guanfacine extended release have not been determined.

11. Clinical questions

1. In the Clinical Rationale for product development the sponsor makes the following statement: '*Several studies published in peer reviewed journals have documented the beneficial effects of guanfacine and other alpha-2-adrenergic agonists (such as clonidine) for treatment of the symptoms of ADHD*.' Can the sponsor please provide the bibliographic details of the studies referred to?

11.1. Pharmacokinetics

The clinical evaluator does not have any questions with regard to pharmacokinetics.

11.2. Pharmacodynamics

The clinical evaluator does not have any questions with regard to pharmacodynamics.

11.3. Efficacy

2. Does the sponsor have evidence of efficacy in patients with inattentive subtype of ADHD?
3. Does the sponsor have evidence of efficacy in comparison with current treatments for ADHD, such as psychostimulants, atomoxetine and/or behavioural treatments?

11.4. Safety

4. Does the sponsor have data regarding the effects on driving and operating machinery for SPD503?
5. Does the sponsor have safety data for guanfacine when administered at doses higher than 4 mg/day in subjects with ADHD co-medicated with psychostimulants?
6. Does the sponsor have any safety data in patients with long QT syndrome?
7. Does the sponsor have any safety data in patients medicated with drugs known to prolong the QT interval?

12. Second round evaluation

The Sponsor has provided the following responses to the Clinical Questions:

12.1. Clinical question 1:

In the Clinical Rationale for product development the Sponsor makes the following statement: 'Several studies published in peer reviewed journals have documented the beneficial effects of guanfacine and other alpha-2-adrenergic agonists (such as clonidine) for treatment of the symptoms of ADHD.' Can the Sponsor please provide the bibliographic details of the studies referred to?

12.1.1. Sponsor's response

The sponsor has provided bibliographic references in support of the statement.

12.1.2. Evaluator's Comments

The sponsor's response is satisfactory.

12.2. Clinical question 2

Does the sponsor have evidence of efficacy in patients with inattentive subtype of ADHD?

12.2.1. Sponsor's response

The sponsor has performed post-hoc pooled analyses to explore the efficacy of guanfacine in patients with inattentive type ADHD. The first analysis explored short-term efficacy. In the first analysis data were extracted from Study SPD503-301 and SPD503-304. Using the FAS, the LS mean difference (95% CI), guanfacine – placebo, in change in ADHD-RS-IV from baseline to last measure before dose tapering (FOTA) was -4.4 (-11.5 to 2.6), p = 0.215, for the 1 mg dose; -4.8 (-9.4 to -0.1), p = 0.044, for the 2 mg dose; -6.9 (-11.8 to -1.9), p= 0.007, for the 3 mg dose; and -5.5 (-10.1 to -0.8), for the 4 mg dose (Table 42).

Table 42: Summary and Analysis in the ADHD-RS-IV Total Score in Subjects with Inattentive ADHD Subtype by Randomized Treatment in the Short-term Fixed Dose Pool SPD503-301 and SPD503-304: Integrated Dose-response FAS (copied from Table 1, S31 Response)

	Randomized Treatment Arm					All Active
	Placebo	1 mg[a]	2 mg	3 mg	4 mg	
n	38	12	42	32	41	127
Mean change from baseline to FOTA[b] (SD)	-9.4 (12.51)	-17.8 (9.29)	-13.1 (10.66)	-15.1 (10.08)	-15.0 (11.54)	-14.7 (10.66)
Difference in LS mean[c] (95% CI)	NA	-4.4 (-11.5, 2.6)	-4.8 (-9.4, -0.1)	-6.9 (-11.8, -1.9)	-5.5 (-10.1, -0.8)	NA
Nominal p-value[d]	NA	0.215	0.044	0.007	0.021	0.065

Source: SPD503-ISE-MAA Tables 1.2.5.1.1 and 1.2.5.1.4

ADHD=attention-deficit hyperactivity disorder; FAS=full analysis set; FOTA=final on-treatment assessment; NA=not applicable

a Only study SPD503-304 had a 1 mg SPD503 randomized treatment arm.

b The FOTA is the last valid ADHD-RS-IV total score postbaseline and before dose tapering.

c Difference in LS mean compared with placebo. A negative difference indicates a positive effect of active over placebo.

d Nominal p-value of active versus placebo from ANCOVA based on LS means.

The second pooled analysis explored a 6 week maintenance dataset. The data were extracted from Study SPD503-312 and Study SPD503-316. The analysis used the FAS with LOCF. For the end of maintenance period assessment, the LS mean difference (95% CI), guanfacine – placebo, in change in ADHD-RS-IV from baseline was -5.2 (-9.2 to -1.2), p = 0.011 (Table 43).

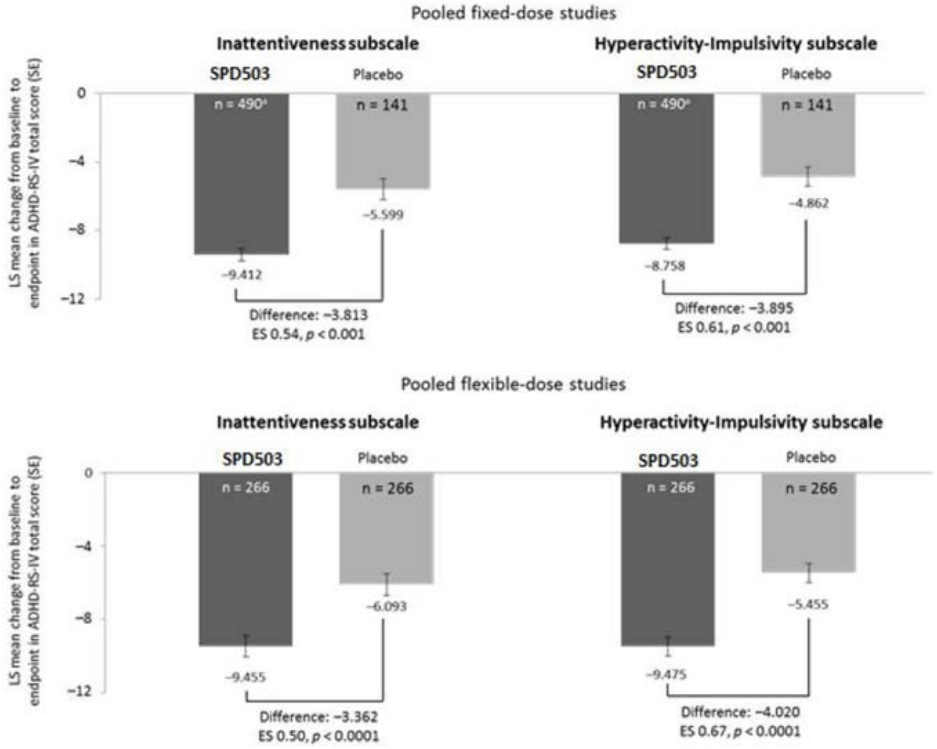
Table 43: ANCOVA Change from Baseline in ADHD-RS-IV Total Score in the Inattentive Subtype of the 6-Week Maintenance Set – Full Analysis Set, LOCF (copied from Table 2, S31 Response)

Day[a] Children/Adolescents		Treatment Arm	
		Placebo N=56	SPD503 N=61
Day 35/56	LS mean (SE)	-16.8 (1.47)	-20.6 (1.38)
	Placebo-adjusted change in LS mean (95% CI)	-3.8 (-7.4, -0.1)	
	Treatment effect size	0.386	
	Nominal p-value[b]	0.042	
Day 42/63	LS mean (SE)	-16.0 (1.47)	-20.8 (1.38)
	Placebo-adjusted change in LS mean (95% CI)	-4.8 (-8.4, -1.2)	
	Treatment effect size	0.490	
	Nominal p-value[b]	0.010	
Day 56/77	LS mean (SE)	-16.2 (1.51)	-21.0 (1.41)
	Placebo-adjusted change in LS mean (95% CI)	-4.8 (-8.6, -1.1)	
	Treatment effect size	0.482	
	Nominal p-value[b]	0.011	
Day 70/91	LS mean (SE)	-16.1 (1.61)	-21.2 (1.51)
	Placebo-adjusted change in LS mean (95% CI)	-5.2 (-9.2, -1.2)	
	Treatment effect size	0.481	
	Nominal p-value[b]	0.011	

Source: SPD503-ISE-MAA Table 1706.25.33111 and Table 1706.25.33112
ADHD-RS-IV=Attention-deficit Hyperactive disorder-Rating Scale-IV; ANCOVA=analysis of covariance; BL=baseline; LOCF=last observation carried forward
Note: The LS mean, standard error, effect size, and p-value were baed on type III sum of squares from an ANCOVA model for the change from baseline, which included treatment group and study as fixed effects and baseline as a covariate.
a Differences in the number of weeks spent in the dose-optimization period between children (4 weeks) and adolescents (7 weeks), result in an offset of the efficacy evaluation days during dose maintenance visits.

The third pooled analysis explored the effect on subscales. The data were extracted from Study SPD503-301, SPD503-304, Study SPD503-312 and Study SPD503-316. For both the inattentiveness and the hyperactivity- impulsiveness subscales there was significant improvement for both short term and maintenance (Figure 8).

Figure 8: ADHD-RS-IV Subscale Scores in the Pooled, Short-term, Fixed-dose Studies SPD503-301 and SPD503-304 and the Pooled Short-term, Flex-dose Studies SPD503-312 and SPD503-316 – Full Analysis Sets (LOCF) (copied from Figure 1, S31 Response)



12.2.2. Evaluator's comments

The sponsor's response is satisfactory. The sponsor has demonstrated efficacy in the subgroup of patients with inattentive type ADHD.

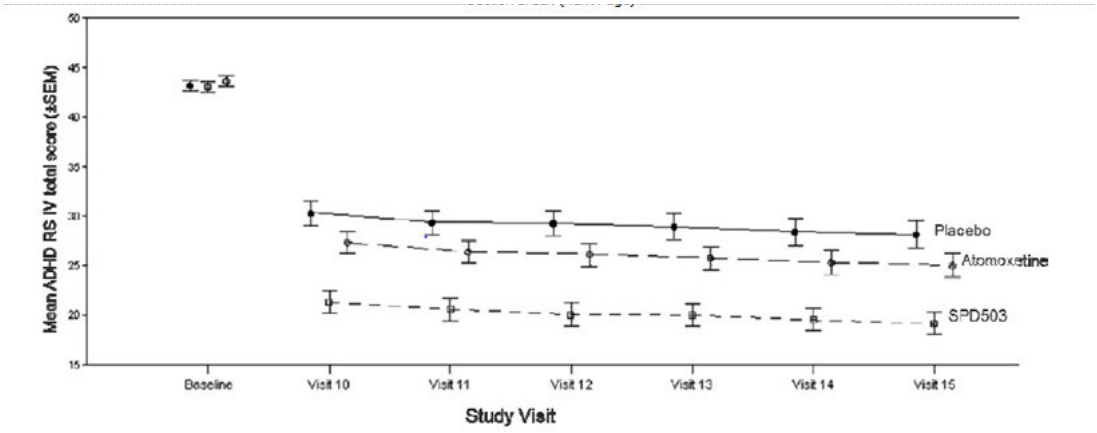
12.3. Clinical Question 3

Does the Sponsor have evidence of efficacy in comparison with current treatments for ADHD, such as psychostimulants, atomoxetine and/or behavioural treatments?

12.3.1. Sponsor's response

The sponsor has responded: '*A direct superiority or non-inferiority study of SPD503 and other ADHD therapeutics has not been conducted in the clinical development program; however an atomoxetine arm was included in study SPD503-316 to provide reference information*.' In addition to the results from Study SPD503-316 previously discussed in Section 7.2.8 the sponsor also draws attention to ADHD-RS-IV by study visit (Figure 9). The evaluator notes the error bars represent the SEM and not 95% CI. The sponsor also draws attention to a subgroup analysis that suggests that patients previously treated with stimulants did not respond to atomoxetine (Table 44).

Figure 9: Mean ADHD-RS-IV Total Score by Visit: Full Analysis Set (LOCF) (copied from Figure 2, S31 Response)



ADHD-RS-IV=Attention-deficit/Hyperactivity-Rating Scale-IV; LOCF=last observation carried forward; SEM=standard error of mean

Table 44: Comparative Change from Baseline in ADHD-RS-IV Total Score by Prior Treatment in Study SPD503-316 (copied from Table 4, S31 Response)

	Treatment Group			
	SPD503		Atomoxetine	
	Stimulant naïve	prior MPH	Stimulant naïve	prior MPH
Placebo-adjusted difference in LS mean change from baseline	-7.6	-9.8	-5.0	-1.8
95% CI	-11.8, -3.3	-14.6, -5.1	-9.4, -0.7	-6.5, 2.9
Effect size	0.65	0.85	0.43	0.15
p value	<0.001	<0.001	0.022	0.452

ADHD-RS-IV=Attention-deficit Hyperactivity Disorder-Rating Scale-IV; CI=confidence interval; LS=least squares; MPH=methylphenidate

Source: Table 6 of the Briefing Document for the SAG Meeting 01 Jun 2015

12.3.2. Evaluator's comments

The sponsor has not provided any new data to demonstrate evidence of efficacy in comparison with current treatments for ADHD, such as psychostimulants, atomoxetine and/or behavioural treatments. This not satisfactory because there are currently a range of effective treatments for ADHD and the Sponsor has not defined the place in management for guanfacine. The proposed therapeutic indication is:

> *INTUNIV is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive).*

This indication does not state whether guanfacine should be first, second or third line.

12.4. Clinical Question 4

Does the sponsor have data regarding the effects on driving and operating machinery for SPD503?

12.4.1. Sponsor's response

The sponsor has responded: '*Briefly as stated in the safety topic report, based on a cumulative review of existing clinical trial data from Phase 1-3 studies of SPD503, postmarketing safety data, and literature through 21 May 2014, no evidence was found to support a causal association between guanfacine-induced hypotension, somnolence, sedation or syncope and negative effects on*

daily functioning. No evidence was found of a relationship between SPD503 and the occurrence of increased risk of injuries, although a causal relationship in some instances of occurring injuries cannot completely be excluded. Lastly, no new safety trends or signals were identified in the preparation of the safety topic report.'

12.4.2. **Evaluator's comments**

The sponsor's response is not satisfactory. The question related specifically to the effects on driving and operating machinery. The sponsor has not provided any data that evaluate these effects. The PI currently states '*Caution patients against operating heavy equipment or driving until they know how they respond to treatment with INTUNIV*'. However, this warning assumes that patients would be able to recognise impaired performance when driving or operating machinery.

12.5. Clinical Question 5

Does the sponsor have safety data for guanfacine when administered at doses higher than 4 mg/day in subjects with ADHD co-medicated with psychostimulants?

12.5.1. **Sponsor's response**

The sponsor has responded '*Concomitant use of psychostimulants was permitted in only one clinical study of SPD503. Study SPD503-313 was a phase 3, double-blind, randomized, placebo-controlled, multicenter, dose optimization study in which the efficacy and safety of SPD503 was evaluated in combination with psychostimulants in children and adolescents aged 6 to 17 years with a diagnosis of ADHD; however, SPD503 doses >4 mg/day were not permitted in study SPD503-313.*'

12.5.2. **Evaluator's comments**

The sponsor's response is not satisfactory. The PI does not currently warn against using doses above 4 mg in patients also treated with psychostimulants. The proposed dosing instructions state only that '*Doses above 4 mg/day have not been studied in co-administration trials.'*

12.6. Clinical Question 6

Does the sponsor have any safety data in patients with long QT syndrome?

12.6.1. **Sponsor's response**

The sponsor has conducted a Thorough QT study, Study SPD503-112. In that study, at no stage did the 90% CI for change in QTcNi cross the boundary for regulatory concern.

The sponsor has not identified concerns regarding QT prolongation in the clinical trials or post-marketing data.

The sponsor also reports one death associated with QT prolongation, with the following description: '*In case [information redacted], the PTs cardiac arrest, ventricular tachycardia, Torsades de pointes, and ventricular fibrillation occurred in a 12-year-old male, weighing 48.1 kg. The child developed Torsades after a cardiac arrest, ventricular tachycardia and ventricular fibrillation that occurred in the context of probable septic shock. He was treated unsuccessfully for a prolonged period with resuscitative efforts and the QT prolongation and Torsades de pointes were assessed as likely related to the intravenous lidocaine administered during these efforts.'*

12.6.2. **Evaluator's comments**

The sponsor's response is unsatisfactory. QTcF prolongation of regulatory concern was identified in the thorough QT study. In the opinion of the evaluator known QT prolongation should be a contraindication to use.

12.7. Clinical question 7

Does the sponsor have any safety data in patients medicated with drugs known to prolong the QT interval?

12.7.1. Sponsor's response

The case previously mentioned in the response to Clinical Question 6 was also medicated with lignocaine and risperidone.

12.7.2. Evaluator's comments

The sponsor's response is unsatisfactory. QTcF prolongation of regulatory concern was identified in the thorough QT study. In the opinion of the evaluator concomitant use of drugs known to prolong the QT interval should be contraindicated.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

Table 45: Second round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Guanfacine significantly improves ADHD symptomatology in patients aged 6 to 17 years with ADHD There is maintenance of efficacy for up to 24 months. Efficacy was demonstrated for oppositional symptoms in subjects with ADHD with oppositional symptoms. Guanfacine significantly improves ADHD symptomatology in patients aged 6 to 17 years with ADHD who are co-medicated with psychostimulants Guanfacine has not been demonstrated to be superior or non-inferior to any currently approved treatment for ADHD. Efficacy has been demonstrated in patients with the inattentive subtype of ADHD.	Demonstrated by the pivotal studies: Study SPD503-312, Study SPD503-315 and Study SPD503-316. Study SPD503-315 demonstrated efficacy for 26 weeks. Study SPD503-303 and Study SPD503-305 were supportive of efficacy for up to 2 years. Demonstrated in Study SPD503-307. Demonstrated in Study SPD503-313 Study SPD503-316 was not designed as a comparator controlled study. Demonstrated by a posthoc analysis of Study SPD503-301, SPD503-304, Study SPD503-312 and Study SPD503-316.

13.2. Second round assessment of risks

Table 46: Second round assessment of risks

Risks	Strengths and Uncertainties
Guanfacine extended release (SPD503) has a favourable safety profile. Somnolence, sedation, fatigue and headache are very common adverse events. There were no deaths in the clinical trials. There were few SAEs. The commonest SAEs were somnolence, sedation and syncope Somnolence and syncope were the commonest reasons for discontinuation due to AE. Guanfacine causes a decrease in HR, SBP and DBP that returns to baseline following several months of treatment. Rebound hypertension can be avoided by tapered withdrawal. QTcF prolongation of regulatory concern was identified in the thorough QT study. Clinically significant prolongation of QTcF or QTcB was not identified in the subsequent clinical trials. Effects on operating machinery and driving have not been evaluated. There are no safety data for the 5 mg to 7 mg dose range in patients co-medicated with psychostimulants.	There is extensive exposure data to support this including a total of 3,243 subjects treated with SPD503 in clinical trials and an estimated cumulative worldwide patient exposure of 965,432 patient years of treatment. This is supported by the safety data presented in the dossier.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Intuniv (guanfacine hydrochloride) 1 mg, 2 mg, 3 mg and 4 mg modified release tablets would be favourable if steps are taken to ameliorate the following risks:

- Use in doses above 4 mg in patients also treated with psychostimulants.
- Use in patients operating heavy equipment or driving
- Use in patients with a history of long QT syndromes
- Use in patients co-medication with drugs known to prolong the QTc interval

14. Second round recommendation regarding authorisation

The application for Intuniv (guanfacine hydrochloride) 1 mg, 2 mg, 3 mg and 4 mg modified release tablets should be rejected for the following indication:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive).*

The reason for rejection is that Intuniv (guanfacine hydrochloride) has not been compared with currently approved treatments for ADHD, and therefore its place in the order of management of the condition is unknown.

Consideration could be given for approval of the following alternative indication:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive) where psychostimulants, atomoxetine and/or behavioural treatments have been ineffective or are contraindicated.*

15. References

Lawrence D, Johnson S, Hafekost J, Boterhoven de Haan K, Sawyer M, Ainley J, Zubrick SR. Mental Health of Children and Adolescents Report on the second Australian Child and Adolescent Survey of Mental Health and Wellbeing. Commonwealth of Australia (2015) ISBN: 978-1-76007-187-5.

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