

Public Assessment Report

Scientific discussion

Elvanse
(lisdexamfetamine dimesylate)

SE/H/1839/01-03

Shire Pharmaceuticals Ireland Limited

This module reflects the scientific discussion for the approval of Elvanse. The Public Assessment Report was written in January 2013 by the previous RMS UK after initial procedure UK/H/3326/001-03/DC. RMS transfer from UK to SE was completed 2018-06-27. For information on changes after this date please refer to the module 'Update'.

Application/Legal Basis	Article 8(3)
Active substance	lisdexamfetamine dimesylate
Pharmaceutical form	capsules, hard
Strength	30 mg, 50 mg and 70 mg
Applicant	Shire Pharmaceuticals Ireland Limited
EU-Procedure number (original)	UK/H/3326/001-03/DC

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Elvanse 30 mg, 50 mg and 70 mg capsules, hard, could be approved.

These products are prescription only medicines indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years of age and over when response to previous methylphenidate treatment is considered clinically inadequate.

The public assessment report (PAR) was written in January 2013 by the previous RMS UK after the initial procedure UK/H/3326/01-03/DC and is attached at the end of this document. Please note that the PAR only covers the strengths 30 mg, 50 mg and 70 mg.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/1839/01-06/II/41	The purpose of this new application is to incorporate the indication for adults (currently stated in SmPC from the procedure SE/H/1825/DC) into the SmPC from the decentralised procedure SE/H/1839/DC which currently only includes the paediatric indication.	Yes	2023-12-08	Approval	The application aimed to simplify the prescription approach for the Healthcare Providers to have both indications within the same SmPC, under one single marketing authorisation. The procedure SE/H/1825/DC may be discontinued in the future. Accordingly, the MAH provided a revised version of the paediatric product information to include the adult indication and to capture appropriately all adult specific information previously included in the approved Product Information from the SE/H/1825/DC procedure.

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Public Assessment Report

Decentralised Procedure

Elvanse 30 mg, 50 mg and 70 mg capsules, hard

Lisdexamfetamine dimesylate

UK/H/3326/001-03/DC

UK licence no: PL 08081/0050-2

Shire Pharmaceuticals Contracts Limited

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Elvanse 30 mg, 50 mg and 70 mg capsules, hard (PL 08081/0050-0052; UK/H/3326/001-003/DC). Elvanse 30 mg, 50 mg and 70 mg capsules, hard will be termed Elvanse 30, 50 and 70mg capsules throughout this PAR for ease of reading. It explains how Elvanse 30, 50 and 70mg capsules were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Elvanse 30, 50 and 70mg capsules, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Elvanse 30, 50 and 70mg capsules and what are they used for?

Elvanse 30, 50 and 70mg capsules are treatments for 'attention deficit hypersensitivity disorder' (ADHD). They are to be used in children and young people between the ages of 6 and 18 who have previously taken a methylphenidate treatment that inadequately treated their ADHD. Elvanse 30, 50 and 70mg capsules may be taken into adulthood if your doctor thinks you are benefiting from treatment.

These products are only prescribed by doctors who have experience in treating people with behaviour problems. Elvanse 30, 50 and 70mg capsules are given as part of a treatment programme, which usually includes psychological, educational and social therapy.

Elvanse is not used as a treatment for ADHD in children under 6 years of age because it is not known if it is safe or of benefit in such young people.

How do Elvanse 30, 50 and 70mg capsules work?

Elvanse 30, 50 and 70mg capsules contains the active substance lisdexamfetamine dimesylate. They improve the activity of certain parts of the brain that are under-active. These medicines can help improve attention, concentration and reduce impulsive behaviour. Elvanse 30, 50 and 70mg capsules are long-acting medicines which work gradually over time.

Each capsule contains 30 mg, 50 mg and 70 mg lisdexamfetamine dimesylate, equivalent to 8.9 mg, 14.8 mg and 20.8 mg of dexamfetamine.

How are Elvanse 30, 50 and 70mg capsules used?

Elvanse 30, 50 and 70mg capsules should be taken in the morning before breakfast. It can be taken with or without food. There are two ways to take these products:

- Swallow the capsules whole with some water
- Open the capsules and empty the contents into a soft food (such as a yoghurt), or a glass of water or orange juice.

Use a spoon to completely break up any bits and stir the yoghurt, water or orange juice until it and the medicine are completely mixed together. Eat all of the yoghurt, or drink all of the water or orange juice, immediately after mixing – do not store it.

You must talk to a doctor if you do not feel better or if you feel worse after 1 month of treatment.

What benefits of Elvanse 30, 50 and 70mg capsules have been shown in studies?

Studies have shown that Elvanse 30, 50 and 70mg capsules improve symptoms of ADHD, and improved function, in children and adolescents. This effect is produced quickly after treatment initiation and maintained for the day. In clinical studies conducted in children and adults, the effects of these products were ongoing at 13 hours after dosing in children and at 14 hours in adults when the product was taken once daily in the morning. In adults it has also been shown that continued long-term treatment is beneficial.

What are the possible side effects of Elvanse 30, 50 and 70mg capsules?

Very common side effects include decreased appetite, weight loss, insomnia (unable to sleep), dry mouth and headache; common side effects include palpitations (uneven heartbeat).

For information about side effects that may occur with using Elvanse 30, 50 and 70mg capsules, please refer to the PIL or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Why are Elvanse 30, 50 and 70mg capsules approved?

It was concluded that Elvanse 30, 50 and 70mg capsules has been shown to have a positive benefit/risk and could be approved for use.

What measures are being taken to ensure the safe and effective use of Elvanse 30, 50 and 70mg capsules?

A Risk Management Plan (RMP) has been developed to ensure that Elvanse 30, 50 and 70mg capsules are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for these products, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Elvanse 30, 50 and 70mg capsules

Denmark, Finland, Germany, Norway, Republic of Ireland, Spain, Sweden and the UK agreed to grant marketing authorisations for Elvanse 30, 50 and 70mg capsules on 16 December 2012. The marketing authorisations in the UK were granted on 01 February 2013.

The full PAR for Elvanse 30, 50 and 70mg capsules follows this summary.

For more information about treatment with Elvanse 30, 50 and 70mg capsules, read the PIL or contact your doctor or pharmacist.

This summary was last updated in February 2015.

TABLE OF CONTENTS

I	Introduction	Page 5
II	Quality aspects	Page 7
III	Non-clinical aspects	Page 8
IV	Clinical aspects	Page 9
V	User consultation	Page 13
VI	Overall conclusion, benefit/risk assessment and recommendation	Page 13
	Table of content of the PAR update for MRP and DCP	Page 17

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Elvanse 30 mg, 50 mg and 70 mg capsules, hard (PL 08081/0050-2; UK/H/3326/001-03/DC) could be approved.

These products are prescription only medicines indicated as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years of age and over when response to previous methylphenidate treatment is considered clinically inadequate.

Treatment must be under the supervision of a specialist in childhood and/or adolescent behavioural disorders. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources. A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

Elvanse is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age and potential for abuse, misuse or diversion.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. The use of Elvanse should always be used in this way according to the licensed indication.

These are full dossier applications for a New Active Substance (NAS), lisdexamfetamine dimesylate (LDX), submitted via the decentralised procedure in accordance with Article 8.3 of Directive 2001/83/EC, as amended. The United Kingdom acted as RMS and Denmark, Finland, Germany, Norway, Republic of Ireland, Spain and Sweden were CMSs.

The drug product, Elvanse, is referred to as SPD489 throughout this report. SPD489 Capsules (under the trade name Vyvanse) were initially approved in the United States for the treatment of ADHD in children aged 6-12 years in February 2007. Subsequently, the US approval was extended to adults aged 18-55 years (April 2008) and adolescents aged 13-17 years (November 2010). In Canada (under the trade name Vyvanse), approval was granted for children in February 2009 and extended to include adolescents and adults in November 2010. In Brazil, SPD489 Capsules (under the trade name Venvanse) were approved for the treatment of ADHD in children aged 6-12 years (July 2010). Marketing Authorisation Applications have not previously been submitted in the EU for these products.

The proposed marketed formulation of SPD489 contains 30, 50, or 70 mg of lisdexamfetamine dimesylate, equivalent to 8.9, 14.8, or 20.8 mg dexamfetamine, respectively.

Lisdexamfetamine dimesylate is the *l*-lysine conjugate of *d*-amphetamine (dexamfetamine), a well established centrally acting non-catecholamine sympathomimetic amine. It is a pharmacologically inactive pro-drug. The stimulant activity of *d*-amphetamine appears to relate to blockade of norepinephrine and dopamine reuptake in the central nervous system (CNS) thereby increasing the availability of these naturally occurring neurotransmitters.

After oral administration, lisdexamfetamine is absorbed intact, as evidenced by relatively high plasma concentration of unconverted drug in the portal blood of rats. *In vitro* studies indicated that the intestinal peptide transporter PEPT-1 is likely to be involved in the uptake of lisdexamfetamine in the intestine. After absorption, lisdexamfetamine is rapidly converted to *d*-amphetamine and *l*-lysine with a $t_{1/2}$ of approximately 1 hour. The major site of the metabolic activation for lisdexamfetamine is believed to be in red blood cells.

The Marketing Authorisation holder (MAH) obtained scientific advice from the Committee for Medicinal Products for Human Use (CHMP) and European National Agencies throughout the development of SPD489. This advice was received in the context of the ongoing SPD489 Clinical Development Programme being conducted in the US and while the European Medicines Agency (EMA) ADHD guidance was being drafted. After a thorough consideration of the scientific advice, the SPD489 Clinical Development Programme was amended to incorporate the key recommendations.

A Paediatric Investigation Plan (PIP) was provided, which covered the age range 6-17 years. A waiver was issued for children aged less than 6 years. A Clinical Development Programme was conducted for SPD489 and this was in compliance with the PIP approved by the Paediatric Committee (PDCO).

Following the feedback received from the PDCO throughout the procedure, the European development programme was further updated to incorporate the following changes:

- An additional assessment to monitor psychiatric adverse events (AEs) Brief Psychiatric Rating Scale for Children (BPRS-C) was added to Studies SPD489-317, SPD489-325 and SPD489-326 for all newly-enrolled subjects. An additional assessment to monitor suicidality (Columbia Suicide Severity Rating Scale, C-SSRS) was added to Studies SPD489-306, SPD489-317, SPD489-325 and SPD489-326.
- A definition and analysis of responders was included as a secondary outcome measure for Studies SPD489-325 and SPD489-326.
- A structured side effects questionnaire (UKU) and Data Monitoring Committee was added to Study SPD489-317. In addition, several changes to the study design (e.g. addition of the 100 mg dose of atomoxetine) were added to the study at the request of the PDCO.
- Study SPD489-404 (2 year safety study) was added to European development programme at the request of the PDCO. Furthermore, the study was required to be initiated prior to EU Marketing Authorisation Application (MAA) submission date.

The guideline on the clinical investigation of medicinal products for the treatment of ADHD was adopted by the CHMP in July 2010 (with an effective date of 1 February 2011). Overall, the SPD489 Clinical Development Programme was conducted in accordance with the recommendations of this guideline. However, because the last patient visit for the EU registration study (Study SPD489-325) was completed in March 2011, one month after the finalisation of the guidance, some deviations from the guideline are to be expected. These deviations are not considered to affect the applicability of the programme results.

Non-clinical studies have been performed with lisdexamfetamine dimesylate specifically to assess non-clinical pharmacokinetics, metabolism, safety pharmacology, single and repeat dose toxicity, genetic toxicity, embryofoetal development and juvenile toxicity. All non-clinical studies were conducted in accordance with Good Laboratory Practice (GLP).

Currently there are both pharmacological (including stimulants and non-stimulants) and non-pharmacological options for the treatment of ADHD. In Europe, when drug treatment is considered appropriate, methylphenidate (MPH), *d*-amfetamine and atomoxetine are recommended as options for the management of ADHD in children and adolescents.

In the Phase 1 Clinical Development Programme, a total of 16 studies have been conducted to characterise the pharmacokinetic and pharmacodynamic properties of lisdexamfetamine and the associated release of *d*-amfetamine following SPD489 administration. All of these studies were conducted in the United States (US).

The Phase 2-4 Clinical Development Programme included 13 completed well-designed short and long-term studies each of which provides evidence for the efficacy and safety of SPD489 in the treatment of ADHD. Nine of the completed studies were short-term controlled studies providing substantial evidence of efficacy. The remaining 4 studies were uncontrolled, open-label safety studies.

Two EU studies were conducted (SPD489-325 and SPD489-326) to demonstrate that the efficacy established in previous US studies was generally applicable and had no region-specific cultural or context-specific dimension. The results of these studies confirmed that the rigorous demonstration of efficacy in the US studies can be generalised to the EU patients.

All clinical studies were conducted in accordance with Good Clinical Practice (GCP).

The quality, non-clinical and clinical expert reports have been written by appropriately qualified experts.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All Member States agreed to grant licences for the above products at the end of procedure (Day 210 – 16th December 2012). After a subsequent national phase, the UK granted a licence for these products on 1st February 2013 (PL 08081/0050-2).

II QUALITY ASPECTS

II.1 Introduction

These are full dossier applications for a New Active Substance (NAS), lisdexamfetamine dimesylate (LDX), submitted via the decentralised procedure in accordance with Article 8.3 of Directive 2001/83/EC, as amended. The United Kingdom acted as RMS and Denmark, Finland, Germany, Norway, Republic of Ireland, Spain and Sweden were CMSs.

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, croscarmellose sodium and magnesium stearate making up the capsule core, the capsule shell consists of gelatin, black ink (shellac and black iron oxide E172), titanium dioxide (E171) and erythrosine (E127) (30 mg and 70 mg) and Brilliant blue FCF (E133) (50 mg and 70 mg).

All strengths of the finished product are packed in high-density polyethylene bottles with a polypropylene child-resistant cap and a foil inner seal. The pack sizes are 28 or 30 capsules. Not all pack sizes may be marketed.

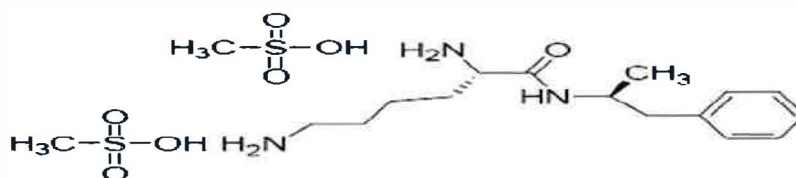
Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

II.2 DRUG SUBSTANCE

rINN: **Lisdexamfetamine dimesylate**

Chemical Name: (2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethanesulphonate

Structure:



Lisdexamfetamine dimesylate

Molecular Formula: C₁₇H₃₃N₃O₇S₂

Molecular Weight: 455.6

Lisdexamfetamine dimesylate is a specific stereoisomer: L-lysine D-amphetamine.

Appearance: A white to off-white solid.

Full details of lisdexamfetamine dimesylate synthesis, control of materials and process validation are provided in the dossier.

Satisfactory controls of materials are in place. The routes of synthesis are adequately described and characterised, and the structure of lisdexamfetamine dimesylate has been confirmed by analytical evidence by both the active pharmaceutical ingredient manufacturers.

The proposed drug substance specification is satisfactory.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed and the proposed retest period of 4 years is justified and a storage statement in line with CHMP guidelines has been proposed.

II.3 DRUG PRODUCT

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of erythrosine (E127) and brilliant blue FCF (E133) which comply with in-house specifications and black iron oxide which complies with United States Pharmacopoeia-National Formulary requirements. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal origin is gelatin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

The applicant has also confirmed that the magnesium stearate used is a vegetable origin.

None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

Finished Product Specification

The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years with a storage condition 'Do not store above 25°C' is set. This is satisfactory.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

These are full dossier applications for a New Active Substance (NAS), lisdexamfetamine dimesylate (LDX), submitted via the decentralised procedure in accordance with Article 8.3 of Directive 2001/83/EC, as amended. The United Kingdom acted as RMS and Denmark, Finland, Germany, Norway, Republic of Ireland, Spain and Sweden were CMSs.

All non-clinical studies were conducted in accordance with Good Laboratory Practice (GLP).

III.2 Pharmacology

Lisdexamfetamine dimesylate is pharmacologically inactive, with its biological actions appearing to be due to *d*-amfetamine released into the systemic circulation following intestinal absorption and metabolism by erythrocytes. The counter-moiety, *l*-lysine, which is also released upon enzymatic hydrolysis of lisdexamfetamine is a naturally occurring amino acid, and the amount generated is small amount of the required daily amount. The systemic delivery of *d*-amfetamine after administration of lisdexamfetamine has been shown to alter its pharmacodynamics and improve therapeutic index in pre-clinical models. The mode of action is the ability to increase synaptic concentrations of the catecholamine neurotransmitters noradrenaline and dopamine in the prefrontal cortex (PFC), and in the striatum.

In vitro radioligand binding screens demonstrated that lisdexamfetamine has no affinity for Dopamine reuptake transporter (DAT) or Norepinephrine reuptake transporter (NET) sites, nor significant affinity for 62 receptors, transporters, ion channels, second messengers, steroids, prostaglandins, growth factors / hormones, brain / gut peptides and enzymes for a range of neurotransmitters, neuropeptides and hormones from a range of species. These data indicate that lisdexamfetamine dimesylate is pharmacologically inactive and its effects *in vivo* are mediated via its metabolite, *d*-amfetamine.

The relevant pharmacodynamic actions of lisdexamfetamine dimesylate appear to be related to systemically released *d*-amfetamine. The data presented show that lisdexamfetamine dimesylate was efficacious in a rodent model of ADHD. It also enhanced catecholaminergic neurotransmission in the brain *in vivo*. Results from head-to-head comparison experiments indicate that lisdexamfetamine dimesylate may have equivalent or greater efficacy in ADHD than *d*-amfetamine or methylphenidate with less potential to induce stimulant adverse events than either drug.

Lisdexamfetamine reduced impulsive behaviour in a delay discounting paradigm in juvenile male Wistar rats, and systemic administration of lisdexamfetamine dimesylate to rats enhanced catecholaminergic neurotransmission in the brain *in vivo*.

Dual-probe microdialysis in the PFC and the striatum of freely-moving rats along with simultaneous measurement of locomotor activity showed that doses of lisdexamfetamine dimesylate that are not overtly stimulant can, nevertheless, potentiate noradrenergic and dopaminergic function in the PFC and dopaminergic function in the striatum. In comparative studies, lisdexamfetamine dimesylate was less behaviourally stimulant than *d*-amfetamine even though it produced substantial increases in striatal dopamine efflux, suggesting that it may have greater differentiation between its therapeutic actions and its unwanted stimulant effects.

The results of the behavioural despair test in the mouse suggest that the drug has modest antidepressant activity on its own, and that there was evidence of augmentation of the efficacy of some anti-depressant drugs. The effects of lisdexamfetamine dimesylate on food

intake, satiety, water intake and bodyweight have been investigated in normal male rats. Lisdexamfetamine dimesylate reduced food intake throughout a 24-hour study period in a dose-dependent manner. In dietary-induced obese female rats lisdexamfetamine dose-dependently reduced food intake, which was most marked in the first week of dosing which was due to specific loss of body fat, with no effect on body protein. Plasma levels of insulin, cholesterol and triacyl glycerol (TAG) were not altered. However, there were significant reductions of plasma glycerol, non-esterified fatty acids (NEFA) and leptin compared with vehicle-treated animals.

There was negligible binding affinity of lisdexamfetamine dimesylate *in vitro* for a range of receptors, ion channels, enzymes, allosteric binding sites and transporters that are known to mediate the pharmacological action of drugs of abuse.

Lisdexamfetamine dimesylate was resistant to enzymatic metabolism. Incubation of lisdexamfetamine with various rat and human tissues and cells indicate that hydrolysis of lisdexamfetamine is primarily due to enzymatic activity in red blood cells.

Overall, the data show that lisdexamfetamine dimesylate can produce subjective effects in rats and monkeys that are similar to those of *d*-amphetamine. However, the potential of lisdexamfetamine dimesylate for abuse appears to be lower than that of *d*-amphetamine or methylphenidate because of the pre-requisite for metabolic activation which results in slower delivery of *d*-amphetamine to the brain and a slower onset of its pharmacological effect. Importantly, as activation occurs in the blood, the potency of lisdexamfetamine dimesylate is not increased by switching from the oral to the parenteral route of administration.

III.3 Pharmacokinetics

Non-clinical data indicate that lisdexamfetamine dimesylate is absorbed intact via an active transport process likely mediated by Peptide transporter (PEPT-1). It is then hydrolysed primarily by peptidase(s) associated with red blood cells to the naturally occurring amino acid, *l*-lysine, and active drug, *d*-amphetamine. This mechanism of activation appears to prevent the rapid release of a bolus of *d*-amphetamine and provides a pharmacokinetic profile that appears to support once-daily administration. The delivery of *d*-amphetamine to the blood and brain after administration of lisdexamfetamine dimesylate appears to alter its pharmacodynamics and improve the therapeutic index in pre-clinical models.

Systemic exposures to both lisdexamfetamine dimesylate and *d*-amphetamine were broadly linear across a wide range of doses except possibly at those that exceeded the Maximum Tolerated Dose (MTD). As expected for a polar compound, lisdexamfetamine dimesylate did not penetrate the brain and *d*-amphetamine levels in the brain reflect those in the systemic circulation in a manner that parallels *d*-amphetamine derived from administration of amphetamine sulphate.

The major metabolite of lisdexamfetamine dimesylate is *d*-amphetamine and there are no significant alternate metabolic pathways. Elimination occurs primarily by metabolism, the major excretory products being *d*-amphetamine and a glucuronide metabolite of *d*-amphetamine in the urine. Lisdexamfetamine dimesylate itself has no clinically relevant interactions with cytochrome (CYP) P450s or membrane transporter proteins and therefore drug-drug interactions mediated by these enzymes/proteins are considered not to be important for lisdexamfetamine dimesylate. Although *d*-amphetamine has been reported to inhibit CYP2D, *in vitro* studies suggest that this only occurs at exposures far greater than those expected from the clinical use of lisdexamfetamine dimesylate.

III.4 Toxicology

The programme with lisdexamfetamine dimesylate omitted fertility, pre and post-natal development studies and carcinogenicity testing. The applicant submitted an acceptable rationale for the lack of reproductive toxicity studies and carcinogenicity studies.

Single dose toxicity studies suggest that lisdexamfetamine dimesylate is less acutely toxic than *d*-amfetamine at equivalent amfetamine doses.

In the repeated dose rat studies there were some early deaths in particular in the 6-month study. Most deaths on this study were considered to be incidental but the causes were not always established; behaviour changes associated with treatment, leading to broken teeth, may have been contributory.

The most consistently observed overt signs of toxicity were increased activity following oral dosing in both rats and dogs and in all studies. In the rat, self-mutilation was reported in the short-term studies at $\geq 80\text{mg/kg}$, often resulting in premature sacrifice. In dogs increased activity was almost always accompanied by various forms of abnormal behaviour and by panting. Salivation, ocular discharge, bloodshot eyes and self mutilation were reported in the short-term studies at $\geq 6\text{mg/kg/day}$.

All of these overt signs of toxicity were attributed to the *d*-amfetamine moiety and a very similar range of signs was observed in both rats and dogs in reference control groups treated with equivalent doses of *d*-amfetamine sulphate. None of the observed signs except thin build was persistent for more than about a day on withdrawal from treatment. The signs in 3 of the pivotal studies were subject to a detailed post hoc analysis to confirm the absence of any signs of tolerance or withdrawal. Consistent with the lack of abuse potential, there were no similar signs in dogs following intranasal dosing at 7mg/day .

At all doses in both rats and dogs and in all studies, there were dose-related reductions in body weight gain that persisted throughout treatment. Body weight gain increased during withdrawal from treatment showing substantial recovery from this effect. Also in all studies and at all doses in both species there were initial temporary significant reductions in food intake. Similar changes in food intake and bodyweight were observed in rats treated with *d*-amfetamine sulphate at equivalent doses. Appetite suppression and associated weight loss is a well known pharmacological effects of *d*-amfetamine.

There were no treatment-related findings in either gross necropsy observations or microscopic histopathology on any of the repeat dose toxicology studies. In a specific assessment for potential proliferative changes in the rat 6-month study, the number of hepatocyte nuclei immunolabeled by anti-Ki-67 antibodies was unaffected by treatment with lisdexamfetamine.

All of the observed changes could be ascribed to the pharmacological actions of *d*-amfetamine. There was no evidence of neurotoxic changes in any of the studies presented by the applicant. Lisdexamfetamine dimesylate was not genotoxic when tested *in vitro* in the Ames test and the mouse lymphoma assay or *in vivo* in the mouse bone marrow micronucleus test.

Lisdexamfetamine dimesylate had no effect on embryo-foetal development or survival when administered orally to pregnant rats and rabbits and effects were consistent with those expected for *d*-amphetamine. As a comprehensive reproduction toxicity package, including fertility, embryo-foetal development and pre- and post-natal development studies has been

conducted on mixed amphetamine salts to modern testing standards, further studies with lisdexamfetamine dimesylate were not considered necessary to support its safety.

Amphetamine (*d*- to *l* enantiomer ratio of 3:1) did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day. A number of studies in rodents indicate that pre-natal or early post-natal exposure to amphetamine (*d*- or *d*, *l*-) at doses similar to those used clinically can result in long-term neurochemical and behavioural alterations. Reported behavioural effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

Juvenile toxicity evaluations demonstrate no significant irreversible toxicities. The changes observed in developmental and behavioural characteristics were those expected from exposure to *d*-amphetamine and there was no evidence of significant irreversible change.

III.5 Environmental Risk Assessment

Based on a maximum daily dose for lisdexamfetamine of 70 mg, *d*-amphetamine is considered unlikely to represent a risk for the environment following the prescribed usage of the product.

In conclusion, all of the observed changes could be ascribed to the pharmacological actions of *d*-amphetamine. Noteworthy, there appeared to be no evidence of neuro-toxic changes in any of the studies sponsored by the applicant.

III.6 Discussion on non-clinical aspects

There are no objections to the approval of Elvanse 30 mg, 50 mg and 70 mg capsules, hard from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction

These are full dossier applications for a New Active Substance (NAS), lisdexamfetamine dimesylate (LDX), submitted via the decentralised procedure in accordance with Article 8.3 of Directive 2001/83/EC, as amended. The United Kingdom acted as RMS and Denmark, Finland, Germany, Norway, Republic of Ireland, Spain and Sweden were CMSs.

All clinical studies were conducted in accordance with Good Clinical Practice (GCP).

IV.2 Clinical Pharmacology

A total of 16 studies have been conducted to characterise the pharmacokinetic (PK) and pharmacodynamic (PD) properties of lisdexamfetamine and the associated release of *d*-amphetamine following SPD489 administration. All of these studies were conducted in the US.

- 3 bioavailability studies (Studies NRP104.101, NRP104.102, SPD489-111)
- 1 dose proportionality study in children with ADHD (Study NRP104.103)
- 1 efficacy and safety study in children with ADHD with a secondary objective to evaluate PK profile and PK/PK relationship with multiple dosing (Study NRP104.201)
- 1 ADME study in healthy adults (Study NRP104.106)
- 1 dose-escalating, PK study in healthy adults (Study SPD489-109)
- 1 special populations (elderly) study in adults ≥ 55 years of age (Study SPD489-116)
- 1 steady-state dosing study in healthy adults (Study NRP104.104)
- 3 drug-drug interaction studies in healthy adults (Study SPD489-113 – co-administration with omeprazole, Study SPD489-117 - co-administration with venlafaxine and Study SPD503-115, co-administration with the ADHD medication guanfacine)

- 3 abuse potential studies in adults with a history of stimulant abuse (Studies NRP104.A01, NRP104.A02 and NRP104.A03)
- 1 Exploratory Study designed to evaluate the sensitivity and responsiveness of a standardised, validated, neuropsychometric tests to the potential effects of SPD489 in adults with ADHD (Study SPD489-115).

Absorption and activation of parent drug

After oral administration, lisdexamfetamine is absorbed intact, as evidenced by relatively high plasma concentration of unconverted drug in the portal blood of rats. *In vitro* studies indicated that the intestinal peptide transporter PEPT-1 is likely to be involved in the uptake of lisdexamfetamine in the intestine. Based on the very low inter- and intra-subject variability in lisdexamfetamine pharmacokinetics observed clinically, the potential for interactions with co-administered drugs or with food substances at the level of the PEPT-1 transporter is considered to be very low. The absolute oral bioavailability of lisdexamfetamine is close to 100% (96.4% of radioactivity was recovered in a human 0-120hr urine collection). Bioequivalence was shown for the fed versus fasting state. The bioavailability of lisdexamfetamine clearly meets the biopharmaceutics classification system (BCS) criteria for a highly permeable drug.

After absorption lisdexamfetamine is rapidly converted to *d*-amfetamine (the active substance) and *l*-lysine with a $T_{1/2}$ of less than 1 hour. The major site of the metabolic activation for lisdexamfetamine to *d*-amfetamine is believed to be in red blood cells (hydrolysis). Both intra- and inter-subject pharmacokinetic variability in *d*-amfetamine C_{max} and AUC were demonstrated to be low (<20%). AUC of lisdexamfetamine is non dose-linear, with a greater than proportional increase in AUC and C_{max} with increasing dose. This would appear to be due to differences in the clearance of lisdexamfetamine (i.e. conversion to *d*-amfetamine) and not to dose non-linearity of bioavailability. If absorption kinetics were not linear we would expect to see comparable differences in dose adjusted AUC also for the metabolite *d*-amfetamine but this was not the case. Presumably there is a degree of saturation of the metabolising enzymes in the red blood cells that reduces the clearance of lisdexamfetamine at the higher dose. This is not problematic as kinetics for the active drug is essentially dose linear.

Non-clinical studies demonstrated that the hydrolysis of lisdexamfetamine to *d*-amfetamine occurred primarily by red blood cells. The capacity of this process was investigated *in vitro* by incubating lisdexamfetamine with various dilutions of red blood cells. Lisdexamfetamine was hydrolysed to *d*-amfetamine at all red blood cell dilutions, and the rate of hydrolysis was not substantially affected until the red blood cells were diluted to 25% of normal haematocrit. Thus the conversion of lisdexamfetamine to *d*-amfetamine is a high capacity and linear process that is unlikely to be saturated at higher doses. This is confirmed when single doses of lisdexamfetamine up to 250 mg demonstrated linear dose proportionality of *d*-amfetamine. Further study of the enzyme(s) responsible for the hydrolysis of lisdexamfetamine to *d*-amfetamine, with a view to identifying any potentially significant drug – drug interactions at this level, is under investigation.

At steady state, peak levels are about 90 ng/ml and trough levels are about 20 ng/ml. That is not a small degree of peak to trough fluctuation and is greater than that seen for many prolonged release products where low peak to trough fluctuation is considered advantageous. The situation is a little more complicated for stimulant treatments for ADHD as therapeutic drug levels at night may not be required or even desirable (e.g. insomnia as an undesirable effect). The situation is further complicated by the possibility suggested in the literature that a phase of rapid increase in plasma levels is necessary to achieve full therapeutic effect. This is

said to be the reason a conventional monophasic prolonged release methylphenidate was found to lack efficacy but newer biphasic formulations such as Concerta XL and Equasym XL were more successful.

The PK profile for *d*-amfetamine after dosing of SPD489 70mg to steady state meet these criteria for a successful stimulant treatment for ADHD. The initial rise in plasma levels is reasonably sharp; not as rapid probably as a biphasic prolonged release formulation with a substantial immediate release component but this could have advantages for undesirable effects and abuse potential. Ultimately whether the PK profile of SPD489 is preferable to the currently marketed products containing *d*-amfetamine can only be established by comparative clinical efficacy and safety data.

Oral administration of SPD489 resulted in generally predictable pharmacokinetic parameters for lisdexamfetamine and *d*-amfetamine (AUC and C_{max}). AUC and C_{max} values were generally higher in children than in adults, broadly proportional to their weight differences.

Plasma concentrations of unconverted lisdexamfetamine are low and transient. Plasma levels are very low after 3 to 4 hours and are generally non-quantifiable by 8 hours after administration. Both lisdexamfetamine and *d*-amfetamine are eliminated in the urine but very little of the former is found in urine as most of an administered dose is hydrolysed to *d*-amfetamine. Only 2.2% of the administered dose was detected as lisdexamfetamine in the 0-48hr urine sample. T_{max} values for lisdexamfetamine after oral administration were extremely consistent with mean values in the range 1.0 hours to 1.3 hours. The exceptions were the delayed T_{max} in the fed state (2.1 hours in adults, attributed to delayed gastric emptying) and in the elderly aged over 75 years (1.8 hours).

For *d*-amfetamine, mean T_{max} values after oral administration were also consistent, in the range 3.3 hours to 4.6 hours. In the very elderly (over 75 years), T_{max} was prolonged to about 5 hours.

The data for the parent lisdexamfetamine are consistent with a drug that is reliably well absorbed and the data for the active *d*-amfetamine are consistent with a predictable and consistent rate of conversion from the pro-drug parent. These findings are generally reassuring.

Metabolism

It has been sufficiently established that lisdexamfetamine has a single primary metabolite, *d*-amfetamine. *D*-amfetamine is a well established drug and its metabolic pathway is reasonably well established, further work to characterise its metabolic pathway is not required. Sufficient information has been provided on the enzyme systems responsible for the various metabolic steps, on the pharmacokinetics of the main metabolites, the pharmacological activity of the metabolites and the potential for drug-drug interactions.

Elimination

The primary metabolites, *d*-amfetamine and hippuric acid, are excreted in urine. After oral administration of ^{14}C -radiolabeled SPD489 70mg, approximately 67% of the dose was excreted as *d*-amfetamine (41.5%) or hippuric acid (24.8%) in the 0-48hr urine sample. Very little (2.2%) was excreted as unmetabolised lisdexamfetamine. Neither biliary nor faecal excretion played a major role in elimination. After 7 days of once-daily dosing of SPD489 70mg, there was no accumulation of lisdexamfetamine. Steady-state for *d*-amfetamine was achieved by Day 5, with a mean $t_{1/2}$ on Day 7 that was essentially the same as after a single dose.

No studies in impaired renal function are provided and information in the SmPC is based on the PK data in normal subjects. This is acceptable given the well established nature of *d*-amphetamine and the pharmacological inactivity of lisdexamfetamine.

Interactions

No human tissue *in vitro* interaction studies have been performed. There are data in the literature from *in vitro* studies that suggest that CYP2D6, CYP1A2, and CYP3A4 may be weakly inhibited by *d*-amphetamine or other metabolites. However, in a study conducted with extended release (ER) mixed amphetamine salts, *d*- and *l*-amphetamine at concentrations 4 to 30-fold in excess of those anticipated clinically, did not produce notable inhibitory effects on the marker reactions of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, the major human CYP forms involved in the metabolism of most clinically used drugs. It is agreed that there is a low potential for CYP mediated drug-drug interactions. Additional human tissue *in vitro* interaction studies investigating the potential for drug-drug interactions relating to hepatic metabolism are not considered necessary.

IV.3 Pharmacodynamics

Lisdexamfetamine dimesylate is the *l*-lysine conjugate of *d*-amphetamine, a well established centrally acting non-catecholamine sympathomimetic amine. The stimulant activity of *d*-amphetamine appears to relate to blockade of norepinephrine and dopamine reuptake in the central nervous system thereby increasing the availability of these naturally occurring neurotransmitters.

Lisdexamfetamine is an inactive parent drug. *In vitro* studies showed that lisdexamfetamine does not bind to the sites responsible for the reuptake of norepinephrine or dopamine. In receptor binding studies, lisdexamfetamine at concentrations up to 10^{-5} M had no detectable binding affinity to the human recombinant norepinephrine or dopamine transporters. It is difficult to prove a negative, i.e., the parent lisdexamfetamine has no pharmacological activity. Nevertheless the package of *in vitro* studies is fairly comprehensive and seems sufficient for the purpose of this application to justify the contention that lisdexamfetamine is unlikely to have major pharmacological activity that would need to be further addressed in the clinical safety evaluation.

Although not fully understood, the mechanism of action of stimulants including *d*-amphetamine in the treatment of ADHD is reasonably well characterised and further data are not required.

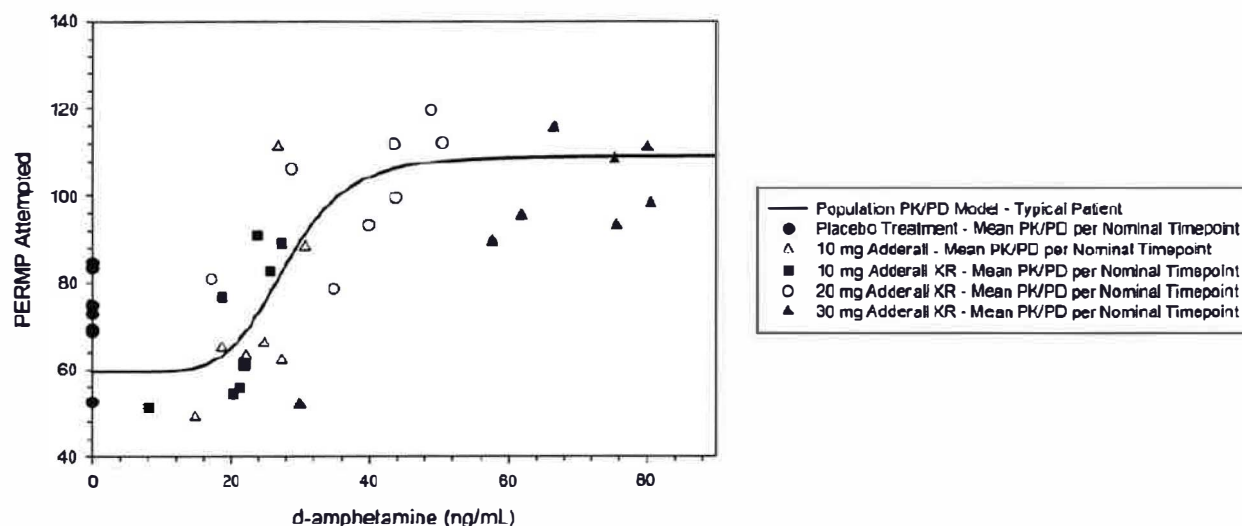
The potential cardiovascular effects of lisdexamfetamine have been evaluated. In the human Ether-à-go-go related gene (hERG) assay, 50 µg/mL lisdexamfetamine produced no inhibition of hERG tail current. The available data showing little or no potential for *d*-amphetamine to prolong QT interval are sufficient and no further data are required.

The effects of a single 50 mg oral dose of lisdexamfetamine on blood pressure and pulse rate were investigated in study SPD489-116, which was primarily a pharmacokinetic study in healthy, elderly male and female subjects in three age groups (55-64, 65-74 and ≥ 75 years). These data indicated that SPD489 causes increases in blood pressure and pulse rate that if maintained with maintenance long-term treatment, might be expected to be associated with significantly increased risk of serious cardiovascular and cerebrovascular adverse events in susceptible patients. This would be an important consideration in the risk-benefit assessment for adults especially and is considered further in the clinical safety section.

PK-PD relationship

Population pharmacokinetic/ pharmacodynamic models for the change in plasma *d*-amphetamine concentration over time have been developed based on an analogue classroom assessment of an immediate release (IR) mixed amphetamine salts product (MAS), an extended release (ER) MAS product, and placebo administered to children with ADHD (McCracken et al. 2003). The pharmacodynamic parameters were based on the Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale (SKAMP) and Permanent Product Measure of Performance (PERMP) scores. The data best fit a sigmoid model in which the *d*-amphetamine plasma concentration required to achieve 50% maximum effect is approximately 24-28 ng/mL and lower plasma concentrations can be considered as sub-therapeutic. Maximal treatment effect was seen at plasma concentrations about 50 ng/mL.

Figure 1



Abuse Potential

The results from three single-dose, abuse potential studies are provided.

In Study NRP104.A01 (oral administration) the applicant's claim that, compared to *d*-amphetamine sulphate 40 mg, SPD489 doses of 30-150mg produced less drug liking.

In Study NRP104.A02 (intravenous administration) reduced drug liking compared to *d*-amphetamine was shown. It can be hypothesised that because of the pro-drug nature of lisdexamfetamine, and its need for metabolic activation even after IV administration, the initial rise in plasma levels after injection of SPD489 prepared for injection is much slower than for *d*-amphetamine sulphate. C_{max} is also substantially lower for SPD489. Both of these factors would be expected to substantially reduce abuse potential by the intravenous route and indeed the data show this.

In Study NRP104.A03 (oral administration), the applicant's claim that SPD489 showed less abuse potential than *d*-amphetamine sulphate at an equimolar dose of amphetamine free base is much more reasonable in this study than in study NRP104.A01. Fast rate of initial increase in plasma levels (fastest with intravenous use) is generally desired for drugs of abuse so it is to be expected that the slower delivery of active drug into the circulation from SPD489 would make it less desirable for abuse than immediate release *d*-amphetamine.

Combining the two oral administration studies, it can be concluded that there is reasonable evidence that SPD489 does indeed have slightly or moderately reduced abuse potential

compared to an equivalent dose of *d*-amphetamine, although the evidence is inconsistent and statistically rather weak.

The applicant has demonstrated a significantly lower potential for non medical use (abuse and misuse). The most compelling reason is that the gradual bioconversion from prodrug to active *d*-amphetamine in red blood cells makes it impossible to achieve the rapid rise in plasma levels that many abusers of *d*-amphetamine desire, and obtain by using the transmucosal or intravenous routes of administration. The applicant has shown that there is significant additional morbidity when the drug is abused in this way. As diversion and abuse of amphetamines is a very real concern this represents a significant advantage for lisdexamfetamine over *d*-amphetamine, even though the former remains a highly abusable drug.

IV.4 Efficacy

Elvanse (lisdexamfetamine dimesylate) is intended as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate. The claim is also made that continuation of treatment into adulthood is appropriate for adolescents who have shown clear benefit from treatment.

The proposed starting dose is 30 mg taken once daily in the morning. The dose may be increased by 20 mg increments at weekly intervals to a maximum of 70 mg.

The CHMP 'Guideline on the clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD)' is applicable here.

- It states that dose finding should be conducted, comparing at least three doses to placebo for a duration of at least 4 weeks on stable medication. Confirmatory trials for short-term efficacy should be randomised, double-blind, parallel group comparisons to placebo and active control. The duration of these trials should be at least 6 weeks on stable dose (8-12 weeks if maintenance of effect is to be demonstrated with a randomised-responder design). Long-term efficacy (maintenance of effect) can be demonstrated using either a 6-month placebo controlled study or a randomised withdrawal design.
- Studies should show both a reduction of symptoms (using a scale such as the Conner's rating scale or the ADHD Symptoms Rating Scale (ADHD-SRS)) and an improvement in functioning (CGI could be used). For both endpoints a responder analysis should be presented as well as difference in mean scores.
- Efficacy should be shown separately in children and adolescents (and adults if applicable). Adult indications can only include patients where it can be verified the symptoms were first present in childhood.

A total of 14 studies have been completed, including 10 randomised controlled efficacy studies.

All studies were designed to enrol subjects in 1 of 4 specific age ranges: children 6-12 years of age, adolescents 13-17 years of age, children and adolescents 6-17 years of age, or adults 18-55 years of age. Three of the controlled studies enrolled children, 1 enrolled adolescents, 1 enrolled children and adolescents and 4 enrolled adults.

In addition there is an efficacy study (317) which is a 9-week active comparator (atomoxetine) controlled parallel-group trial (no placebo control) in children and adolescents

who have an insufficient response to methylphenidate. No data were submitted for this study with the initial decentralised procedure.

There are three 52-weeks, open-label extension trials that primarily assess safety and tolerability, one each in children, adolescents and adults (studies 302, 306 and 304 respectively). There is also a 7-week uncontrolled open-label dose optimisation trial in children (study 310).

There are also trials (all in adults) in major depressive disorder, schizophrenia (negative symptoms), acute sleep deprivation and binge eating disorder.

The completed double blind, randomised, controlled clinical efficacy trials are summarised below.

Controlled efficacy studies in children

Study 201 - Phase 2, 3 week placebo / active controlled crossover trial
 Study 301 - 4 week placebo controlled parallel group trial (dose finding study)
 Study 311 - 2 week placebo controlled crossover trial (classroom analogue)

Controlled efficacy studies in children and adolescents

Study 325 - 7 week placebo / active controlled parallel group trial (dose optimisation)
 Study 326 - 32 week placebo controlled randomised withdrawal trial (dose optimisation phase)

Controlled efficacy studies in adolescents

Study 305 - 4 week placebo controlled parallel group trial (dose finding study)

Controlled efficacy studies in adults

Study 303 - 4 week placebo controlled parallel group trial (dose finding study)
 Study 316 - 2 week placebo controlled crossover trial (workplace environment)
 Study 401 - 6 week (maximum) placebo controlled randomised withdrawal trial
 Study 403 - 10 week placebo controlled parallel group trial (dose optimised)

The programme is generally in-line with the guidance. There are separate 4-week dose finding trials with 3 doses in children, adolescents and adults. Then there is a 7-week confirmatory trial in children and adolescents, and a 10-week confirmatory trial in adults.

Only the study in children and adolescent compares Elvanse to placebo and active control. The lack of an active comparator in the adult 10-week confirmatory trial is potentially an issue. Maintenance of effect in adults was studied in a randomised withdrawal trial.

Efficacy measures

The main measures of ADHD symptomatology were the Attention Deficit / Hyperactivity Disorder Rating Scale (ADHD-RS) and the Conner's Parent Rating Scale (Revised Short Version; [CPRS-R]). The ADHD-RS was assessed in all studies except the exploratory study NRP104.201. The ADHD-RS-IV and CPRS are well established ADHD efficacy measures that have been accepted for a number of previous EU regulatory submissions. The ADHD-RS with Adult Prompts is a well known and established ADHD efficacy measure validated for use in adults. The three are suitable primary efficacy measures.

The main measures of functional outcome were the Clinical Global Impression Scales of Severity and Improvement (CGI-S and CGI-I), the Weiss Functional Impairment Rating Scale-Parent (WFIRS-P), the Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale (SKAMP), and the Permanent Product Measure of Performance (PERMP). CGI-I was assessed in all paediatric studies. In two studies, the exploratory crossover study NRP104.201 and the dose optimisation crossover study SPD489-311, the evaluation of efficacy was conducted in an analogue classroom setting using assessment tools appropriate to this environment, the SKAMP scale being the primary efficacy measure and the PERMP and CGI-I being secondary efficacy measures.

The validity and reliability of a number of other rating scales that were either primary efficacy measures or important secondary efficacy measures in the short-term efficacy studies have been sufficiently justified.

General methodological aspects

All Phase 3 trials studied the 30, 50, and 70 mg doses of SPD489 for which registration is being sought. Of the eight short/medium term double-blind, randomised studies, five were parallel-group designs (301, 305, 325 in children and adolescents, 303 and 403 in adults). The other three were crossover designs, the exploratory (Phase 2) 3-week study 201, the classroom analogue study 311 and the adult workplace environment study 316. A crossover design is acceptable in principle for the exploratory trial 201 and for the studies in controlled settings, since there is unlikely to be significant carryover of pharmacological activity into the second period. For confirmatory trials randomised, double-blind, parallel-group studies are necessary and the applicant has complied with this requirement.

Of the parallel-group designs, the three dose finding studies 301, 303 and 305 had 4 week randomised treatment durations, while the pivotal efficacy studies had a treatment duration 7 weeks (325, paediatrics) and 10 weeks (403, adults). According to the ADHD guideline the randomised treatment periods in the pivotal short-term trials should be of at least 6 weeks duration. The pivotal trials 325 and 403 meet this requirement. The 4-week treatment duration in the dose finding studies is satisfactory.

All studies have included a placebo control. Of the short-term pivotal trials only the one in children and adolescents (325) included an active comparator arm (Concerta XL controlled-release methylphenidate). The only other study that included an active comparator arm was the exploratory (Phase 2) 3-week study 201 which included Adderall XR (Extended Release mixed amphetamine salts) as a comparator. An active comparator is generally considered to be important in trials of drugs in psychiatry because assay sensitivity of trials varies considerably and without an active comparator of known efficacy it can be difficult to draw conclusions on the clinical relevance (in the context of existing treatment options) of an observed difference from placebo. As such it would have been preferable for all of the studies to be placebo and active controlled. The choice of Concerta XL as the active comparator in the European study 325 is acceptable as it is considered to be a treatment of choice for treating children with ADHD (immediate release methylphenidate is generally less favoured) and like SPD489 it is administered once daily which helps the study blinding. The choice of Adderall XR (Extended Release mixed amphetamine salts) is probably less suitable for this European application as this product is not marketed in the UK and not in the EU (licensing status in all EU member states is not known). It would have been preferable to use a European approved *d*-amphetamine product as one of the active comparators.

Four of the five controlled studies in children and adolescents enrolled subjects from the US only, and the fifth (SPD489-325) enrolled only subjects from Europe. All studies enrolled more males than females, reflecting the known higher incidence of ADHD in male children and adolescents. The proportion of females ranged from approximately 20% in Study SPD489-325 (European children and adolescents) to approximately 40% in Study 201 (children only). In all 5 studies, the majority of subjects were white, particularly in the European study SPD489-325 in which approximately 98% of the subjects were white. The CHMP scientific advice in December 2005 stated that data from an EU population would be required as significant differences between the populations in US ADHD trials and the EU ADHD population can be expected. The European clinical studies 325 and 326 are considered sufficient in principle to meet this requirement. The studies in US populations will still be of major importance in the overall assessment of efficacy and safety for the treatment of ADHD.

Patient populations - children and adolescents

The inclusion and exclusion criteria in the paediatric trials are generally satisfactory. The restriction to ADHD-RS-IV Total Score of ≥ 28 at baseline is acceptable and reflects at least a moderate level of symptoms. The approvable indication will reflect this. Drug treatment is in any case not normally advocated for mild symptoms so this restriction is clinically appropriate. The restriction, in this study exclusively in children, to either the combined or hyperactive-impulsive ADHD subtype is acceptable but could have implications for the approvable indication, depending on the data for the inattentive subtype in study 305.

In all five paediatric studies the majority of subjects had the combined ADHD subtype. The measure of ADHD symptoms (ADHD-RS-IV) and disease severity (CGI-S) were similar across studies. For the 4 studies (Studies NRP104.301, SPD489-311, SPD489-305, and SPD489-325) where ADHD-RS-IV Total Score was measured, the baseline ADHD-RS-IV Total Score was approximately 40. In these 5 studies, the majority of subjects were moderately, markedly, or severely ill at baseline as reported by the CGI-S. This is an appropriate patient population. Stimulants are generally a preferred treatment only for patients with only moderate to severe functional impairment.

Patient populations - adults

The inclusion criteria in the adult trials are generally satisfactory. In particular the exclusion of a major comorbid psychiatric diagnosis but not of mild to moderate psychiatric comorbidity strikes the right balance between ensuring that the study population is truly an ADHD population and excluding so many patients that the wider applicability of the studies could be questionable. The exclusion from the pivotal efficacy study 403 of subjects that had previously failed to respond to amphetamine therapy is probably reasonable. Very few patients screened for inclusion in the trial had previously tried and failed amphetamine therapy so this exclusion criterion is not a concern.

The applicant has provided a reasonable justification of the applicability to the EU adult ADHD patient population of the clinical trial programme in adults, which was conducted entirely in the US. This included a detailed consideration of differences between the US and the EU in the diagnosis and management of adult patients with ADHD as well as baseline data (disease characteristics, baseline ADHD scores, co-morbidities etc) from the clinical trials in the US and EU. There is considerable overlap of ADHD type symptoms in adults with other psychiatric, personality and social disorders and for regulatory purposes in the EU the verifiable presence of first symptoms in (early) childhood (e.g. by medical records/school reporting etc) is considered mandatory for the diagnosis of ADHD in adults. The applicant provided satisfactory details of how this requirement was met for the diagnosis of ADHD in

the adult studies. The applicant also provided reassurances regarding how patients were recruited into the key trials 403 and 401.

Dose finding studies

Three randomised, double-blind, placebo-controlled, parallel-group, dose finding trials were conducted. Study 301 in children (6-12 years), study 305 in adolescents (13-17 years) and study 303 in adults (18-55 years). All three studies compared Elvanse 30 mg daily, 50 mg daily and 70 mg daily to placebo.

The studies were conducted over approximately 6 weeks. Six visits were scheduled, one to screen candidates (Visit 1: Screening), one to randomise subjects to double-blind treatment (Visit 2: Baseline), and four at weekly intervals to assess the result of treatment (Visits 3, 4, 5, 6). After the screening visit eligible subjects discontinued any psychoactive medications they were currently taking and entered the (at least) 7 day washout period. Patients were required to have a baseline (after washout) ADHD-RS score ≥ 28 to continue in the trial. Eligible subjects were then randomised and received 4 weeks treatment. A forced titration was employed in the Elvanse arms. The table below shows the doses of Elvanse that were taken during the treatment phase of each study.

Figure 2

Titration of Elvanse by treatment group

Study	Week 1	Week 2	Week 3	Week 4
Elvanse 30mg	30mg	30mg	30mg	30mg
Elvanse 50mg	30mg	50mg	50mg	50mg
Elvanse 70mg	30mg	50mg	70mg	70mg

The primary efficacy endpoint was the change from baseline to the patient's final assessment in the ADHD-RS total score (this is equivalent to analysing the change from baseline to week 4 using last observation carried forward (LOCF) to impute missing data). This was analysed using analysis of covariance with baseline score, treatment and site as covariates (site was not included in study 305). To account for the multiplicity of comparing three treatment groups to placebo, Dunnett's test was used to calculate p-values and 95% confidence intervals. The results for the primary efficacy analyses are as follows:

Study 301- children

	Placebo	Elvanse 30 mg	Elvanse 50 mg	Elvanse 70 mg
n	72	69	71	73
Baseline - mean (sd)	42.40 (7.13)	43.17 (6.68)	43.25 (6.74)	45.08 (6.82)
Endpoint	36.64 (12.64)	21.22 (13.02)	19.63 (14.49)	17.88 (14.41)
Change from baseline	-5.76 (10.48)	-21.96 (12.70)	-23.62 (14.43)	-27.21 (14.04)
Adjusted change*	-6.19	-21.77	-23.40	-26.69
Difference*		-15.58	-17.21	-20.49
95% CI**		(-20.78,-10.38)	(-22.33,-12.08)	(-25.63,-15.36)
p-value vs. placebo**		p<0.0001	p<0.0001	p<0.0001

*from ANOVA ** from Dunnett's test

Study 305 - adolescents

	Placebo	Elvanse 30 mg	Elvanse 50 mg	Elvanse 70 mg
n	76	76	72	75
Baseline# - mean (sd)	38.5 (7.11)	38.3 (6.71)	37.3 (6.33)	37.0 (7.30)

Endpoint	25.4 (12.68)	20.0 (13.03)	16.6 (10.34)	16.8 (9.40)
Change from baseline	-13.0 (10.70)	-18.6 (13.15)	-20.9 (10.11)	-20.4 (10.78)
Adjusted change*	-12.8	-18.3	-21.1	-20.7
Difference*		-5.5	-8.3	-7.9
95% CI*		(-9.7,-1.3)	(-12.5,-4.1)	(-12.1,-3.8)
p-value vs. placebo**		p=0.0056	p<0.0001	p<0.0001

n=77, 78, 76, 78 *from ANOVA ** from Dunnett's test

Study 303 - adults

	Placebo	Elvanse 30mg	Elvanse 50mg	Elvanse 70mg
n	62	115	117	120
Baseline - mean (sd)	39.40 (6.42)	40.52 (6.21)	40.81 (7.30)	41.02 (6.02)
Endpoint	31.60 (11.24)	24.26 (12.69)	23.31 (12.16)	22.23 (11.61)
Change from baseline	-7.81 (9.28)	-16.26 (12.67)	-17.50 (11.65)	-18.78 (11.85)
Adjusted change*	-8.20	-16.24	-17.36	-18.61
Difference*		-8.04	-9.16	-10.41
95% CI**		(-12.14,-3.95)	(-13.25,-5.08)	(-14.49,-6.33)
p-value vs. placebo**		p<0.0001	P<0.0001	p<0.0001

*from ANOVA ** from Dunnett's test

All three studies demonstrated a highly statistically significant advantage over placebo for all three doses of Elvanse and the differences were seen from week 1. The largest benefit was seen in children. In children and adults a dose response is seen, though the additional benefit of increasing dose was small compared to the benefit of initiating treatment. In adolescents the doses did not rank in ascending order, although 50 mg and 70 mg performed better than 30 mg.

Responder analysis for the symptom scores (with the denominator all patients randomised and treated) were presented and confirmed clinically and statistically significant efficacy.

To observe for an improvement in functioning, CGI Improvement (CGI-I) was included as a secondary endpoint. All three studies demonstrated a highly statistically significant improvement in functioning for Elvanse patients (all doses) compared to placebo. The results were highly consistent with those for the primary endpoint in that the largest differences were seen for children, a clear dose response was seen for both children and adults, and in adolescents 50 mg and 70 mg seem better than 30 mg but did not separate from each other.

Confirmatory trials

Two randomised, double-blind, placebo-controlled, parallel-group, studies were conducted using the flexible dosing scheme proposed in the Summary Product Characteristics (SmPC); study 325 in children (6-12 years), adolescents (13-17 years) and study 403 in adults (18-55 years). Both studies compared Elvanse 30, 50 and 70 mg daily to placebo. The trial in children and adolescents also included Concerta XL 18-54 mg as an active comparator.

The full analysis set (FAS) was defined to include all randomised patients who received treatment and at least one post-baseline ADHD-RS assessment. This was the primary population for efficacy analysis. In a double-blind trial, it is acceptable to include only all treated patients, but the exclusion of patients with no post-treatment data creates a potential bias, as these withdrawals may be treatment related. There were a larger number of patients excluded in the Elvanse group although this had no effect on conclusions.

Studies 325 and 403 were generally well designed.

There are no obvious baseline differences between treatment groups. Patients were predominantly white so race / ethnicity in this US patient population is not markedly different from an EU population.

The primary efficacy measure for study 325 was the Attention-Deficit/Hyperactivity Disorder Rating Scale- IV (ADHD-RS-IV). The primary efficacy measure for study 403 was the Subject reported Behavioural Rating Inventory of Executive Function – Adult Version Global Executive Composite T-Score (BRIEF-A GEC T-score). The Adult Attention-Deficit/Hyperactivity Disorder Rating Scale with Prompts (Adult ADHD-RS with prompts) was a key secondary endpoint for study 403.

Study 325 (children/adolescents) - Change from baseline to last observation in ADHD-RS-IV

	Placebo	Elvanse	Concerta XL
n	104	98	103
Baseline# - mean (sd)	41.0 (7.14)	40.7 (7.31)	40.5 (6.72)
Endpoint##	34.8 (11.89)	16.0 (10.44)	21.7 (13.30)
Change from baseline	-6.3 (10.02)	-24.7 (10.15)	-18.9 (12.92)
Adjusted change*	-5.7	-24.3	-18.7
Difference*		-18.6	-13.0
95% CI*		(-21.5,-15.7)	(-15.9,-10.2)
p-value vs. placebo*		P<0.001	p<0.001

n=105, 102, 106 ## n=104, 100, 104 *from ANOVA

Highly statistically significant advantages over placebo were seen in the overall study population. The results are extreme and robust to any issues regarding handling of missing data. Highly statistically significant differences were seen from week 1. The results for Elvanse were numerically superior to Concerta XL. No responder analysis was presented. The results were similar for the children and adolescents analysed separately.

Study 403 (adults) - Change from baseline to last observation in subject reported BRIEF-A GEC T-score

	Placebo	Elvanse
n	75	79
Baseline - mean (sd)	79.4 (8.68)	79.5 (8.01)
Endpoint	68.3 (17.12)	57.2 (14.11)
Change from baseline	-11.1 (16.19)	-22.3 (14.19)
Adjusted change*	-11.1	-22.3
Difference*		-11.2
95% CI**		(-15.9,-6.4)
p-value vs. placebo**		p<0.0001

*from ANOVA

Study 403 (adults) - Change from baseline to last observation in Adult ADHD-RS with prompts (Investigator assessed) Total score

	Placebo	Elvanse
n	75	79
Baseline - mean (sd)	39.9 (6.83)	39.9 (7.37)
Endpoint	29.6 (14.32)	18.5 (12.31)

Change from baseline	-10.3 (12.70)	-21.4 (11.27)
Adjusted change*	-10.3	-21.4
Difference*		-11.1
95% CI**		(-14.9,-7.3)
p-value vs. placebo**		p<0.0001

*from ANOVA

As for study 325 highly statistically significant advantages over placebo were seen, which was sufficiently extreme to be robust to any issues regarding handling of missing data. Highly statistically significant differences were seen from week 1. Responder analysis was presented

Both studies clearly demonstrated the efficacy of Elvanse. The subgroup analyses by age in study 325 were also both positive, so efficacy has been independently demonstrated for children, adolescents and adults. Study 325 showed treatment effect in comparison to an established product (i.e. Concerta). The NICE guideline recommends that drug treatment is the first-line treatment for adults with ADHD with either moderate or severe levels of impairment, and that methylphenidate is the first-line drug. No stimulant currently has a licensed indication for adult ADHD. However section 4.2 of the SPC for Concerta XL states *“In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood. However, start of treatment with CONCERTA XL in adults is not appropriate”*. This is similar to the indication being sought for Elvanse (in section 4.2 of the SmPC) and Concerta XL would therefore have been an appropriate active comparator. The lack of an active comparator in the adult study 403 is non-compliant with the ADHD guideline and could have been problematic if the results had been of uncertain clinical relevance. However the treatment effect is clearly very substantial and obviously clinically relevant so this is not considered to be a major concern.

Long-term efficacy - adults

A single study, 401, was presented to provide evidence of long-term efficacy in adults.

Study 401 was a randomised withdrawal study. Patients were recruited who had been on stable treatment with Elvanse 30, 50 or 70 mg daily for at least 6 months and were responding (Adult ADHD-RS with prompts total score < 22 and CGI-S ≤ 3 at screening) with acceptable tolerability.

Eligible patients went into a 3-week, open-label treatment phase where they continued on the same dose of Elvanse they were already receiving. Patients who had ADHD-RS score ≥ 22 or CGI-S score > 3 at visit 3 (week 3) were withdrawn from the study.

The remaining patients continued into the double-blind treatment phase and were randomised to either continue on the same dose of Elvanse or switch to placebo for a maximum of 6 weeks, which was considered to be sufficient to observe a meaningful difference between treatments in ADHD symptom.

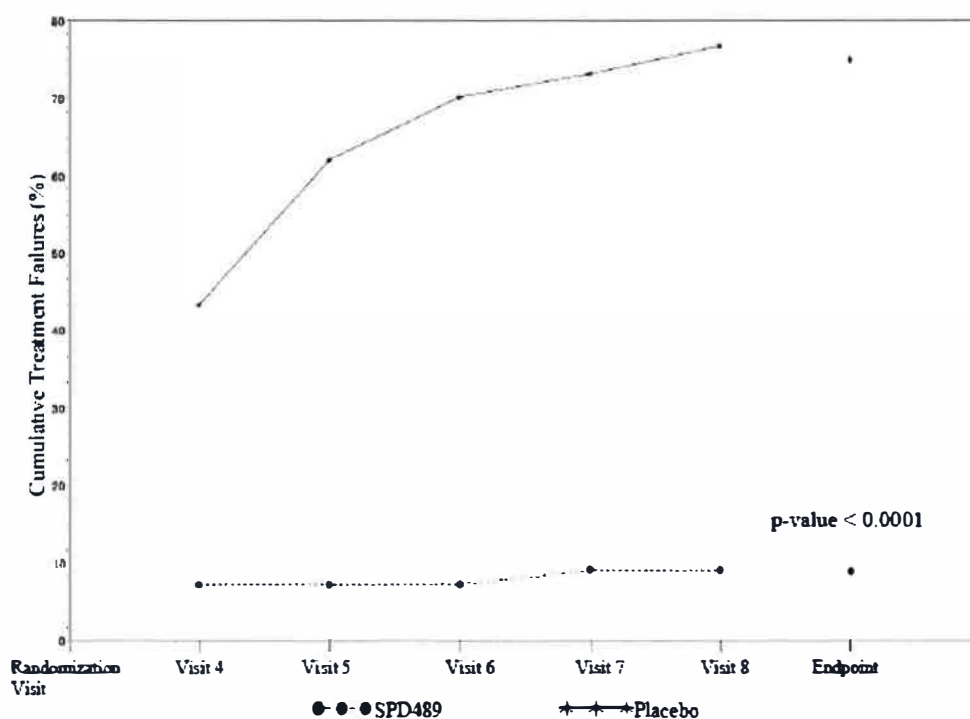
During the double-blind randomised withdrawal phase, patients who had both a ≥ 50% increase in ADHD-RS and a ≥ 2 point increase in CGI-S relative to visit 3, were discontinued from the trial and classified as a treatment failure. The primary end-point compared the proportion of patients with treatment failure across the two groups.

Results

	Placebo	Elvanse
N	60	56
Relapsed		
Visit 4	26	4
Visit 5	10	0
Visit 6	4	0
Visit 7	1	1
Visit 8	2	0
Visit 9	0	0
Withdrew without providing data at withdrawal visit	2	0
Total	45 (75.0%)	5 (8.9%)
p-value		p<0.0001
Any withdrawal = failure	47 (78.3%)	6 (10.7%) p<0.0001

The relapse rate was clearly higher for those who had treatment withdrawn. Hence it seems clear that in patients who respond to short-term treatment, there is benefit in continuing treatment to the long-term.

Figure 3: Cumulative Proportion of Treatment Failures by Visit (FAS)



There is clear evidence in adults that patients receiving clinically important benefit from Elvanse can expect to receive further benefit if treatment is continued.

Long-term efficacy - children and adolescents

Study SPD489-326 was presented to provide evidence of long-term efficacy in children and adolescents. This was a randomised withdrawal study.

Patients were aged 6-17 years and met the DSM-IV-TR criteria for a primary diagnosis of ADHD based on a detailed psychiatric evaluation.

Eligible patients went into a 4-week, open-label optimisation period (up to a maximum of 70 mg and down to a minimum of 30 mg). Following titration to an optimal dose subjects

continued daily morning treatment for a minimum of 20 weeks in the open-label maintenance period. After this they entered the 2-week open-label fixed dose period. In this period patients were discontinued immediately if they required further dose adjustments, if they experienced unacceptable tolerability, or if the ADHD-RS-IV total score was >22 or the CGI-S score was ≥ 3 . Overall, patients successfully completing the open-label treatment phases of the trial would have received at least 26 weeks (6 months) treatment with open-label SPD489.

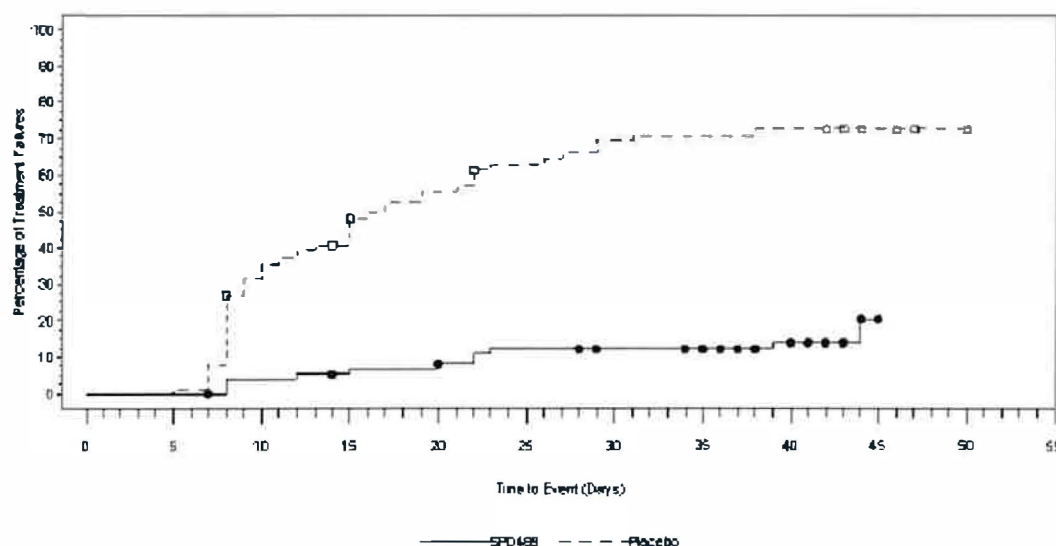
During the double-blind randomised withdrawal phase, patients who had both a $\geq 50\%$ increase in ADHD-RS-IV total score and a ≥ 2 point increase in CGI-S relative to the randomisation visit were discontinued from the trial and classified as a treatment failure. Subjects who withdrew without providing efficacy data at the time of withdrawal were also classified as treatment failures. Patients withdrawing for other reasons and providing successful ADHD-RS-IV/CGI-S data at withdrawal were not classified as failures, though a supportive analysis was conducted where all withdrawals were counted as failures. The primary end-point compared the proportion of patients with treatment failure across the two groups.

There were 276 patients enrolled. The largest group of randomised patients came from Germany with 57, followed by Sweden 27, United States 21, Hungary 20, Italy 14, France 9, Belgium 4, Poland 3, UK 2.

Results

The treatment failure rate was substantially higher for those who had treatment withdrawn. Hence it seems clear that in patients who respond to short-term treatment, there is benefit in continuing treatment to the long-term.

Figure 4: Kaplan-Meier Plot of Time to Treatment Failure (Randomized Full Analysis Set)



Excludes subjects at Site 24

The symbols represent censored observations.

The benefit of continuing treatment was shown separately for both children and adolescents with $p < 0.001$ in both subgroups.

Study SPD489-326 provides clear evidence that for children and adolescents who respond to short-term treatment, there is benefit in continuing treatment to the long-term.

Supportive studies

Studies 311 and 316 were randomised, double-blind, two-way crossover studies comparing Elvanse to placebo. Study 311 was in children aged 6-12. Study 316 was in adults aged 18-55. These studies were conducted in a controlled setting and give a picture of efficacy throughout the day. In the study in children the controlled setting was an analogue classroom session. In the adult study, the controlled setting was an Adult Workplace Environment (AWE). Although no substitute for studies in the natural setting, these studies in controlled settings provide useful additional information on which aspects of mental functioning and behaviour respond positively to treatment.

As already noted the SKAMP is not well established as a key efficacy measure for EU regulatory purposes but it is designed specifically to assess classroom behaviour and seems to be appropriate for the analogue classroom setting. As it is not a pivotal efficacy study and provides efficacy information that is complementary to those studies there are no concerns about the use of the SKAMP as the primary efficacy measure in this study.

These studies showed that the onset of effect is quick and is maintained long enough to cover the school/working day. The SKAMP data suggest the effect may begin to wear off after about 13 hours.

Overall conclusions on clinical efficacy

This is a very extensive package of data which addresses all the points raised in the guideline. For all age groups there is a clear short-term effect, shown to be at least comparable to Concerta XL in children/adolescents, seen in both symptoms and improved function. This effect is produced quickly after treatment initiation and maintained for the school/working day. In adults it is also shown that continued long-term treatment is beneficial. In all trials the differences from placebo are highly statistically significant and robust to choices of analysis and handling of missing data. The magnitude of the difference from placebo was consistently of clear clinical significance for all strengths and for functional measures as well as ADHD symptom scores.

IV.5 Clinical Safety

Stimulants have been used as pharmacological treatments for ADHD over many years and two are currently approved in the UK for this indication, methylphenidate and *d*-amfetamine. Of these, methylphenidate is the preferred first line pharmacological treatment choice in children and adolescents. More recently the non-stimulant atomoxetine (Strattera) has been available as an alternative treatment option. NICE (2007) recommends that *d*-amfetamine is reserved for patients showing insufficient response to a maximum tolerated dose of methylphenidate and atomoxetine (as part of a comprehensive treatment programme). In adults pharmacological treatment is the treatment of choice and methylphenidate is the first line drug. The reasons for preferring methylphenidate over *d*-amfetamine include issues relating to undesirable effects and abuse potential.

The common adverse effects of stimulant therapies for ADHD including *d*-amfetamine are fairly well defined after years of clinical experience. The applicant has provided reasonably persuasive data indicating that lisdexamfetamine is pharmacologically inactive. The safety profile of Elvanse might therefore be expected in general terms to reflect that of the marketed *d*-amfetamine, perhaps with some differences attributable to the different PK and PD profile for the active *d*-amfetamine.

Amfetamines cause increases in pulse and blood pressure and awareness and management of cardiovascular undesirable effects is an important part of managing these patients (NICE 2007). The applicant states that recent published studies have not demonstrated any increased risk of QT prolongation, torsades de point or sudden death for stimulants.

Overall, in the Phase 2-4 Studies, 1941 subjects received at least 1 dose of SPD489. The median duration of exposure was 52 days (range 1 to 431 days). Total exposure to SPD489 in the safety population was 809.6 subject-years. Given the well established use of *d*-amfetamine for the treatment of ADHD in children and adolescents the extent of patient exposure in this population is sufficient. There is much less experience with *d*-amfetamine for the treatment of ADHD in adults. The extent of SPD489 exposure in adults is reasonably substantial but numbers treated long-term are likely to be insufficient to detect for example any increase in cardiovascular risk. The extent of SPD489 exposure in adults is sufficient.

Adverse events

Of the 1941 subjects who received SPD489 in the 13 Phase 2-4 studies, 82.0% had at least 1 treatment emergent adverse event (TEAE), and 70.8% had at least 1 TEAE that was considered by the investigator to be related to the investigational product. In subjects participating in double-blind, parallel-group studies, the incidence of any TEAE was greater among SPD489-treated subjects (72.8%) than among placebo-treated subjects (52.3%). The majority of all TEAEs were mild or moderate in severity; 6.6% of SPD489-treated subjects had 1 or more severe TEAEs. In double-blind, parallel-group, placebo-controlled studies, the percentage of SPD489 subjects with at least 1 severe TEAE (3.7%) was slightly higher than for placebo subjects (2.2%).

In Phase 2-4 studies, the most commonly occurring TEAEs were those typically associated with stimulant therapy, including decreased appetite, insomnia, headache, dry mouth, irritability, upper abdominal pain, and weight decrease. In placebo-controlled, parallel-group studies, these events occurred more frequently among SPD489-treated subjects than among placebo-treated subjects, in line with expectations. Commonly occurring TEAEs not typically associated with stimulant therapy, such as upper respiratory tract infection and nasopharyngitis, occurred with similar frequency in the SPD489 and placebo groups. They are not likely to be treatment related.

It is potentially misleading to compare the data for children and adolescents with those in adults because these are cross trial comparisons. Nevertheless there is a suggestion that decreased appetite and weight loss might be less of an issue in adults than in the paediatric populations. Dry mouth and anxiety might be more of an issue in adults although this cannot be established with any degree of certainty.

The results for study 325 are of particular interest as it provides a comparison with a standard treatment of first choice, Concerta XL (OROS methylphenidate). The numbers of individual adverse events (AEs) in this study is too small to draw clear conclusions on causality or relative incidence. Weight decrease and insomnia seemed to be more common for SPD489 than Concerta XL but this could be a chance finding.

In like for like comparisons there was a trend to a higher incidence of AEs at the 70 mg dose than 30 mg or 50 mg. Adverse events leading to discontinuations were more common for 50 mg and 70 mg than for 30 mg, although numbers are too small to be sure that this difference is attributable to dose. Overall there was no clear dose-response relationship for stimulant related side effects although there is a suggestion from study 303 that there might be a moderately increased incidence at the 70 mg dose. This would be in line with expectations as

stimulant related undesirable central nervous system (CNS) effects are likely to be dose related to some extent. There do not seem to be particular concerns with the 70 mg dose.

Among the 1941 subjects in the Phase 2-4 studies, there was 1 death (a 22-year-old male). It is agreed that this death appears to be unrelated to study medication.

Twenty seven of the 1941 subjects (1.5%) treated with SPD489 in the Phase 2-4 studies reported one or more serious treatment-emergent adverse events (SAEs). In the double-blind parallel-group studies the incidence of serious TEAEs was not higher for the SPD489 group (4 subjects, 0.4%) than for placebo (4 subjects, 0.9%). Serious treatment-emergent adverse events that occurred in more than 1 subject included syncope (5 subjects), aggression (2 subjects) and foot fracture (2 subjects). In each of the 3 age groups, the majority of SAEs reflected intercurrent illnesses, accidental injuries, or potential comorbidities of ADHD. The majority of SAEs were considered by the investigator to be unrelated to SPD489 treatment. Six reports of syncope (plus 2 more in adults not reported as SAEs), two of aggression (in adolescents) and one each of sinus arrest and mania (both in children) were identified as potential concerns.

Discontinuation rates were generally reasonable and in line with expectations. Provided there is adequate monitoring of blood pressure, weight and clinical response the events leading to discontinuations should be manageable without major safety problems arising.

Adverse Events of Special Interest

The integrated AE database was systematically searched for AEs of special interest in the areas of psychiatric events (including suicidality), neurological syndromes, cardiovascular events, growth and development, and sexual dysfunction. This covers the less common AEs that are of most interest for stimulant treatment in ADHD patients. More common AEs of particular interest are covered in the general AE section. The potential for abuse and drug diversion is covered separately.

Most of these AEs of interest were in the open-label studies, which is to be expected as the duration of treatment is much longer in these studies than in the placebo controlled studies. The numbers of individual AEs in the placebo controlled studies are for the most part too small for clear conclusions on causality to be drawn although the total frequency of 2.8% for SPD489 compared with 0.9% for placebo is suggestive that some of these AEs are treatment related. The sexual dysfunction AEs make up most of the difference between the active and placebo groups.

Myocardial ischemia: There was no indication of treatment related events of myocardial ischemia in the clinical trial programme. Nevertheless amfetamines do have known cardiovascular effects that can be expected to increase the risk of such events in susceptible patients, almost all of whom will be middle aged or older adults. Patients with known ischaemic heart disease were excluded from clinical trials and the extent of exposure of adults of an age at risk of coronary events is insufficient to quantify the increased risk associated with amfetamine treatment.

Arrhythmias: ECG analyses showed no sign of treatment related QT interval prolongation. Syncope was experienced by a total of 9 (0.5%) SPD489-treated subjects in the completed SPD489 Phase 2-4 studies, including 4 children (0.5%), 3 adolescents (0.9%) and 2 adults (0.3%). There is no indication that these episodes of syncope are treatment related. The narrative summaries do not reveal features suggesting a serious underlying cause such as

serious arrhythmias. Total exposure to SPD489 in the safety population was 810 subject-years and the number of reported events of syncope is not likely to represent an excess over the expected event rate. There was no excess incidence for SPD489 over placebo. It is considered that there is no need to include syncope in the SmPC section 4.8. One event of sinus arrest seems to be related to a pre-existing medical condition (presumably sick sinus syndrome) although the possibility that it might have been precipitated by stimulant treatment in a susceptible patient cannot be excluded.

Psychosis: The only serious psychiatric AE in SPD489-treated subjects in the Phase 2-4 clinical trial programme was one event of mania. The temporal relationship (after 6 months of treatment) does not suggest a causal relationship to SPD489 treatment. Nevertheless there are historical reports that administration of stimulants may exacerbate symptoms of behaviour disturbance and thought disorder in patients with pre-existing psychotic disorders and this is stated in the SmPC.

Depression / suicidality: Suicide and related events (SREs) were systematically examined across the full SPD489 development programme using multiple sources of information including spontaneously reported AEs (events coding to suicidal ideation or behaviours), a retrospective analysis of controlled clinical trial data using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) and prospectively obtained information on suicidal ideation and behaviours of clinical trial subjects using the Columbia-Suicide Severity Rating Scale (C-SSRS). In addition one item (Item 6) from the BPRS-C, collected in Study SPD489-325, assessed suicidal ideation and behaviours. In Phase 2-4 studies, there were no serious cases of depressed mood or flat/blunted/restricted affect and no reported suicide attempts. In the controlled clinical trials there were no cases of suicidal behaviour or ideation in SPD489 treated patients but there was one case in a placebo-treated subject (0.2%). Suicidal ideation was reported for two SPD489 treated children and one adolescent in the open-label trials (0.2%). The applicant has provided a well reasoned argument, supported by a thorough review of the SPD489 safety data and literature references, that the available evidence suggests that SPD489 does not increase the incidence of suicide and related events (SREs). The fact that there were no reports of completed suicides, no suicide attempts (either interrupted or aborted), and no suicidal preparatory acts or behaviours in the safety database covering 810 subject – years would seem to be reassuring. The three reported brief and self-limited episodes of suicidal ideation without associated behaviours reported in 3 children or adolescents treated with SPD489 in the long-term open-label trials represented the same incidence as in the placebo treated population (0.2%) and does not suggest an association with SPD489 treatment. Nevertheless caution is required in patients showing evidence of suicidal ideation and the SmPC warnings reflect this.

Behavioural undesirable effects: Two subjects (Subjects 032-006 and 041-003, both in Study 306) experienced SAEs of aggression, both rated as moderate in intensity. Such events can occur in adolescents with ADHD and there is no evidence to attribute them to treatment with SPD489.

Tics: Patients with tic disorders were excluded from the clinical trials so there are limited data on the effect of SPD489 and Concerta XL on inducing or exacerbating tics. However the SmPC appropriately reflects clinical experience that *d*-amfetamine can exacerbate motor and phonic tics and Tourette's syndrome.

Seizures: No subject in a Phase 1-4 study reported a seizure or other epilepsy-related TEAE.

Sexual dysfunction: A total of 24 SPD489-treated subjects (1.2%) had sexual dysfunction TEAEs of special interest, including libido decreased (12 subjects [0.6%]), erectile dysfunction (11 subjects [0.6%]), libido increased (1 subject [0.1%]), and painful erection (1 subject [0.1%]). In the double-blind, parallel-group studies, TEAEs of special interest relating to sexual dysfunction occurred in 1.6% of subjects in the SPD489 group and in no placebo subjects.

Growth and Development: Mean decreases from baseline in weight in SPD489-treated subjects seemed to be small in the short-term studies but became much more significant in the long-term studies. The presented mean values for decreases in weight from baseline in the long-term trials are likely to underestimate the situation in patients treated *de novo* with stimulants as many patients would have been taking another stimulant (most commonly methylphenidate) prior to being recruited into the trials. It will be important to investigate whether SPD489 seems to cause more weight loss than methylphenidate. The applicant addressed this by presenting mean the equivalent analyses for treatment naïve patients and for patients who were effectively switched to SPD489 in the clinical trial having previously been on a stable regimen of methylphenidate. Weight loss is of more concern in patients starting with a low body mass index (BMI) at baseline. The data on the proportions of patients who shift from a “normal” BMI (5th to <85th centile) to a below normal BMI (below the 5th centile), 2.1% for SPD489 and 0.7% for placebo, are reasonably reassuring that a serious weight loss problem in the trial populations was not common. This is a well known issue and as advised in the SmPC patients need to be appropriately monitored. If significant appetite suppression persists and growth delay becomes a concern, consideration should be given to alternative treatments. Major problems relating to these effects of treatment should not arise if patients are appropriately managed.

Cardiovascular parameters: The results for blood pressure did not indicate either a substantial mean increase for SBP or DBP and nor was there a clear or consistent excess of potentially clinically important blood pressure changes in SPD489 treated subjects compared with placebo. Given the known effect of amfetamines on cardiovascular parameters this might seem surprising but at least it does not raise new concerns. The effect of SPD489 on pulse rate was more clear. From these data it was not of a magnitude that would represent a major safety problem although it is likely to represent an additional risk factor for serious cardiovascular and cerebrovascular events in susceptible patients, in particular older adults. This is an important risk management issue.

Laboratory findings: There is no signal of an adverse effect of SPD489 treatment on any clinical chemistry or haematology values. There is no evidence of hepatotoxicity.

Long-term Safety

As long-term treatment of ADHD in adults is proposed, it is important to consider the safety implications of long-term treatment. Although evidence suggests that the long-term effects of ADHD stimulant medication on blood pressure, heart rate, and growth are limited, and that occurrences of suicidal, psychotic and manic symptoms are rare (van de Loo-Neus et al. 2011), the potential for side effects that may develop after many months of exposure, or side effects that are rare and of significant clinical concern warrants exploration.

Evidence for the long-term safety of SPD489 comes from the three 1 year, open-label studies (1 each in children [study 302], adolescents [306], and adults [304]). As in the short-term studies, the most frequently occurring TEAEs in the long-term, follow-on studies were events typically associated with stimulant treatment, as well as nasopharyngitis and upper respiratory tract infection. In the 3 long-term safety studies, there were no clinically

concerning trends in laboratory results. Increases in blood pressure and pulse rate were small and there were no concerning trends in ECG results. Mean weight decreases from baseline appeared to be unaximal after about 4-5 months of treatment and declined thereafter.

Long-term effects on cognitive ability and academic outcomes have not been examined in the SPD489 programme. However it is noted that the efficacy of SPD489 was demonstrated across multiple outcome measures (symptomatic, functional, and health-related quality of life) administered by multiple raters (clinician and parent) in the 3 long-term safety studies within the limitations of the open-label study design. Although not a long-term study, an improvement in executive function was associated with SPD489 treatment in the 10-week Study SPD489-403.

Study SPD489-404 (ongoing) was designed to further evaluate the long-term effects of SPD489 in children and adolescents over a 2-year treatment period. This open-label study will collect data on specific endpoints such as sexual development and cognition.

In conclusion there is a reasonable amount of open-label, long-term safety data and no major safety problems have identified. There are some well known potential issues such as cardiovascular risk. Evidence for a positive risk-benefit of SPD489 in the long-term is limited by the lack of a control group in the long-term studies and the limited extent of exposure beyond one or two years of treatment. This is of particular potential concern for the proposed adult indication for which *d*-amfetamine is not licensed.

Abuse potential

A review and analysis of treatment emergent adverse events (TEAEs) indicative of potential cases of abuse in the clinical trial programme was conducted. The first Tier search was related to actual behaviours directly coding to MedDRA terms of abuse and misuse. The second Tier search was used to examine drug effects that are potentially indicative of abuse potential (i.e., have face validity, such as “euphoria”) and common to some drugs of abuse. In addition similar searches were run to identify cases originated from clinical trials in the Shire Global Safety System within the Pharmacovigilance Department. Overall rates of TEAEs related to misuse and abuse for completed Phase 2-4 clinical studies in Tier 1 and 2 were low, especially in the controlled trials. In the open-label trials “any behaviour related to misuse or abuse” was reported in 11 (0.6%) patients, 8 of which were accidental overdose. Only 2 cases of drug misuse behaviour were reported as TEAEs.

These results will inevitably represent considerable under-reporting of potential cases of abuse of SPD489 in the clinical trial programme and the true extent in the controlled settings of clinical trials is likely to be less than what may occur in a more general clinical setting. Abuse and diversion of *d*-amfetamine is a well recognised problem and is one of the reasons methylphenidate is preferred as first line treatment. These data are not considered to provide much information on the abuse potential of SPD489 in comparison with other stimulants. This information must come from the abuse liability studies which are reported in the pharmacodynamics section of this report.

Withdrawal and Rebound

Data from the randomised withdrawal study 401 in adults were evaluated for AEs related to drug withdrawal and rebound effects associated with cessation of SPD489 treatment in the placebo group at the beginning of the randomised withdrawal phase. However, no AEs related to drug withdrawal or rebound were reported based on terms from the SMQ topic of drug withdrawal.

The SPD489 Phase 2-4 AE database was examined for the occurrence of possible withdrawal and rebound events. Rebound effect was reported for 6 subjects (7 events) in the 2 paediatric, open-label studies (Studies 310 and 302). One event described as a rebound effect in Study 310 (which was severe and considered not related to investigational product) occurred after treatment with SPD489 had been discontinued. Of the remaining 6 events of rebound effect, none were serious, none led to discontinuation, and all were mild or moderate in intensity. It is unclear to what extent the events described as rebound in studies 310 and 302 represent true rebound i.e. a return of symptoms worse than baseline upon cessation of treatment. It is hard to see how a true rebound event might be considered not treatment related. At least some of these events seemed possibly to represent a loss of efficacy with falling plasma levels at the end of the day.

The best way to look for true rebound is to evaluate symptoms at baseline (off treatment), during a short period (e.g. 4 weeks) of SPD489 treatment and after treatment cessation. A return to near-baseline symptoms upon treatment cessation might be expected and the occurrence of episodes of true rebound could be explored. The applicant provided these analyses from the appropriate short-term studies and no evidence of rebound symptoms was seen.

The randomised withdrawal design, Study SPD489-326 showed no evidence of rebound symptoms in children and adolescents.

Safety related to drug-drug interactions

No AEs relating to drug interactions have been reported.

Post marketing experience

SPD489 was first approved in the US on 23 Feb 2007 for ADHD in patients aged 6 to 12 years of age. It is currently indicated for the treatment of ADHD in the US, Canada, and Brazil. The safety summary provides post-marketing safety data accumulated during 4 years of post marketing use, from first marketing authorisation to 22 Feb 2011. This review included all current ongoing safety topics including sudden death, ischaemic cardiac events, cardiomyopathy, syncope, ischemic and hemorrhagic stroke, growth retardation, developmental delay, serious skin reactions, abuse, misuse, and diversion. In the first 4 years of marketing, a total of 1846 medically confirmed spontaneous, literature, and health authority case reports with SPD489 were identified. Of these 1842 were spontaneous reports, 1 was from literature surveillance, and 3 were from health authorities. Of the 1846 case reports, 289 reports were serious and 1557 were non-serious. The estimated patient exposure since for this time period was 1.5 million person-years of treatment.

Out of a total of 12 cases reporting a fatal outcome, there were 5 deaths of a sudden nature with a potential cardiac component. Of these 5 cases, 1 was reported as sudden death in a 7-year-old patient with a structurally abnormal heart on autopsy; 1 as circulatory collapse in a 17-year-old confounded by clonidine and olanzapine treatment; 1 as idiopathic seizure disorder in a 23-year-old confounded by obstructive sleep apnea and narcolepsy; 1 as an arrhythmia leading to death in a 20-year-old (in a case which provided insufficient information for medical assessment); and 1 as a cardio-respiratory arrest in a 17-year-old confounded by marijuana abuse and depression.

Other reported serious adverse events of potential concern included 3 reports of possible myocardial ischaemia, 3 reports of cardiomyopathy, 20 syncope-related events, 5 events of cerebrovascular accident, 2 of cerebrovascular spasm and 2 events of cerebral / cerebellar

haemorrhage. There were 2 reports of growth retardation and 2 reports of Stevens-Johnson syndrome.

As tends to be the case with such data it is very difficult to assess possible causality for many of the reported serious adverse events. The proposed SmPC already states that stimulants have been associated with sudden death and serious cardiovascular adverse events. It is possible that some of the deaths, particularly the five reported as being of a sudden nature with a potential cardiac component, could be related to SPD489 treatment, regardless of the presence of underlying pathology or other risk factors. The five cases described were all in young people (ages from 7 to 23). The applicant is asked to relate this to the incidence of sudden cardiac death in a healthy but otherwise comparable population.

Cardiomyopathy has been reported with chronic amphetamine use. The three reports of cardiomyopathy are of interest and represent a possible signal that is included as an ongoing safety topic in the EU Risk Management Plan. There were no reports of possible cardiomyopathy in the clinical trial programme. Cardiomyopathy is included in Section 4.8 of the SmPC (frequency not known; all populations).

The conclusion that there is insufficient evidence to support a reasonable causal relationship between syncope and SPD489 is probably reasonable. Syncope is not listed in the SmPC at the present time and as there was no evidence of an excess incidence over placebo in the clinical trial programme, and vasovagal syncope is not uncommon in a normal population, this is acceptable.

Safety conclusions

In general the safety profile described for SPD489 is in line with expectations based on well established experience with *d*-amphetamine for the licensed indication treatment of children and adolescents with ADHD. No new safety concerns have been identified. There are insufficient data to permit a clear and reliable comparison of the safety and tolerability profiles with either of the active comparators used in two studies, Adderall XR (Extended Release mixed amphetamine salts) and Concerta XL (prolonged release methylphenidate). Weight decrease and insomnia seemed to be more common for SPD489 than for Concerta XL but this could be a chance finding. In the small exploratory study 201, the only study that included *d*-amphetamine product as an active comparator, the number of subjects reporting any AE was just 8 for SPD489 and 9 for Adderall XR so meaningful AE comparisons are impossible and the applicant is not able to claim that SPD489 has a superior safety profile to dexamphetamine “based on this study”.

The main safety issue is in the adult population, who could potentially require treatment for many years and for whom treatment with *d*-amphetamine is not licensed. Although narcolepsy is an approved indication in adults for *d*-amphetamine there are big differences between the two pathologies in terms of safety issues and risk – benefit considerations. Identified safety issues additional to those that are well known for the paediatric population include cardiovascular events and stroke (related to sympathetic stimulation) and long-term effects on various psychiatric and behavioural aspects.

Although *d*-amphetamine is not licensed for the treatment of ADHD in adults it is used off label for this indication and the NICE guideline recommends that *d*-amphetamine (or atomoxetine) can be tried if methylphenidate (the first-line treatment of choice for adults with ADHD with either moderate or severe levels of impairment) is ineffective.

Provided that efficacy is sufficiently demonstrated in adult ADHD, including clinically important benefits in social and employment functioning, the safety profile is considered acceptable, subject to appropriate clinical monitoring as set out in the SmPC.

IV.6 Risk Management Plan

The marketing authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Elvanse 30 mg, 50 mg and 70 mg capsules, hard.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Tachycardia	Routine pharmacovigilance	Cardiac prescreening stipulation in Section 4.2 of the SmPC Cardiovascular status warning in Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC Educational tools
Cardiomyopathy	Routine pharmacovigilance	This risk is addressed in Sections 4.2, 4.3, and 4.4 of the proposed SmPC Educational tools
Increased blood pressure	Routine pharmacovigilance	Cardiac prescreening stipulation in Section 4.2 of the SmPC Hypertension Contraindication in Section 4.3 of the SmPC Blood pressure monitoring Warning in Section 4.4 of the SmPC Pharmacodynamic Interactions detailed in Section 4.5 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC Educational tools
Anorexia	Routine pharmacovigilance	Pretreatment screening for weight and ongoing monitoring of weight and appetite stipulation in Section 4.2 of the proposed SmPC This risk is addressed in Section 4.8 (Undesirable effect) of the proposed SmPC Educational tools
Growth restriction and Developmental delay	Routine pharmacovigilance SPD 489-404	Pretreatment growth monitoring stipulation in Section 4.2 of the SmPC Growth warning in Section 4.4 of the SmPC This risk is addressed in Section 4.8 (Undesirable effect) of the proposed SmPC Educational tools

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Hallucinations (auditory, skin sensation, visual disturbance)	Routine pharmacovigilance	Pretreatment screening for psychiatric disorders stipulation in Section 4.2 of the proposed SmPC Psychiatric AEs warning in Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC Educational tools
Psychosis/Mania	Routine pharmacovigilance	Pretreatment screening for psychiatric disorders stipulation in Section 4.2 of the proposed SmPC Psychiatric AEs warning Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC Educational tools
Hostility/Aggression	Routine pharmacovigilance	Pretreatment screening for psychiatric disorders stipulation in Section 4.2 of the proposed SmPC Contraindication in Section 4.3 of the SmPC Psychiatric AEs warning in Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC Educational tools
Depression	Routine pharmacovigilance	Pretreatment screening for psychiatric disorders stipulation in Section 4.2 of the proposed SmPC Psychiatric AEs warning Section 4.4 of the SmPC Also addressed in Section 4.8 (Undesirable effect) of the SmPC Educational tools
Tics	Routine pharmacovigilance	Tics/Tourette's Syndrome Warning in Section 4.4 of the SmPC Undesirable effect in Section 4.8 of the SmPC Educational tools
Intentional drug misuse and Drug abuse	Routine pharmacovigilance	Misuse and abuse monitoring stipulation in Section 4.2 of the

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		proposed SmPC Drug abuse and misuse warning in Section 4.4 of the proposed SmPC Educational tools
Serious skin reactions	Routine pharmacovigilance	Addressed in Section 4.8 (Undesirable effect) of the SmPC Educational tools
Diversion	Routine pharmacovigilance and supply chain monitoring	Diversion monitoring stipulation in Section 4.2 of the proposed SmPC Diversion warning in Section 4.4 of the proposed SmPC Educational tools
Ischaemic cardiac events	Routine pharmacovigilance	This risk is addressed in Sections 4.2, 4.3, and 4.4 of the proposed SmPC Educational tools
Sudden death	Routine pharmacovigilance	Cardiac prescreening stipulation in Section 4.2 of the SmPC Existing cardiac disease Contraindication in Section 4.3 of the SmPC Sudden death Warning in SmPC Section 4.4 Educational tools
Withdrawal syndrome	Routine pharmacovigilance	This risk is addressed in Section 4.4 of the proposed SmPC
Suicidality	Routine pharmacovigilance	This risk is addressed in Sections 4.2 and 4.4 of the proposed SmPC Educational tools
Migraine	Routine pharmacovigilance	No risk minimisation activities proposed
Syncope	Routine pharmacovigilance	Exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease warning in Section 4.4 of the SmPC. Educational tools
Carcinogenicity	Routine pharmacovigilance	Preclinical data summary in section 5.3 of the SmPC
Neonatal cardio-respiratory toxicity (neonatal foetal tachycardia, respiratory distress/apnoea)	Routine pharmacovigilance	This risk is addressed in Section 4.6 of the proposed SmPC Educational tools
Neonatal effects on growth (via lactation)	Routine pharmacovigilance	This risk is addressed in Section 4.6 of the proposed SmPC Educational tools
Off-label use	Routine pharmacovigilance Drug utilisation study	Off-label age groups addressed in Section 4.2 (Special populations) of the proposed SmPC Educational tools
Cerebrovascular disorders (Ischemic and Hemorrhagic stroke)	Routine pharmacovigilance	This risk is addressed in Sections 4.2, 4.3, and 4.4 of the proposed SmPC Educational tools
Raynaud's phenomenon	Routine pharmacovigilance	No risk minimisation activities proposed
Long-term safety (cardiovascular, cerebrovascular, and psychiatric effects)	Routine pharmacovigilance SPD 489-404 ADDUCE study	Long-term use is addressed in Section 4.2 of the proposed SmPC
Safety in pregnant women	Routine pharmacovigilance	Pregnancy is addressed in Section 4.6 of the proposed SmPC
Safety in the elderly	Routine pharmacovigilance	Elderly addressed in Section 4.2 (Special populations) of the proposed SmPC

IV.7 Discussion of the clinical aspects

There are no objections to the approval of these applications from a clinical point of view.

V USER CONSULTATION

A user consultation with target patient groups on the PIL has been performed and the results provided are acceptable.

VI. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of Elvanse 30 mg, 50 mg and 70 mg capsules, hard are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

There appeared to be no evidence of neuro-toxic changes in any of the studies carried out by the applicant. All of the observed changes are attributed to the pharmacological actions of *d*-amfetamine. The applicant has provided an acceptable explanation for the absence of carcinogenicity studies with *d*-amfetamine mesylate. All non-clinical points raised for consideration have been addressed adequately. There are no objections to the authorisation of these products on non-clinical grounds.

EFFICACY

The dossier for lisdexamfetamine dimesylate has been compiled reasonably well and includes an extensive package of data of pharmacology studies, and efficacy studies. For all age groups there is a clear short-term effect in children/adolescents, seen in both symptoms and improved function. This effect is produced quickly after treatment initiation and maintained for the school/working day. In adults it is also shown that continued long-term treatment is beneficial. In all trials the differences from placebo are highly statistically significant and robust to choices of analysis and handling of missing data. The magnitude of the difference from placebo was consistently of clear clinical significance for all strengths and for functional measures as well as ADHD symptom scores.

SAFETY

In general the safety profile described for SPD489 is in line with expectations based on long clinical experience with *d*-amfetamine for the licensed indication treatment of children and adolescents with ADHD. No new safety concerns have been identified. In the small exploratory study 201, the only study that included *d*-amfetamine product as an active comparator, the number of subjects reporting any AE was just 8 for SPD489 and 9 for Adderal XR, so meaningful comparisons are impossible and the applicant is not able to claim that SPD489 has a superior safety profile to *d*-amfetamine.

Identified safety issues additional to those that are well known for the paediatric population include cardiovascular events and stroke (related to sympathetic stimulation) and long-term effects on various psychiatric and behavioural aspects.

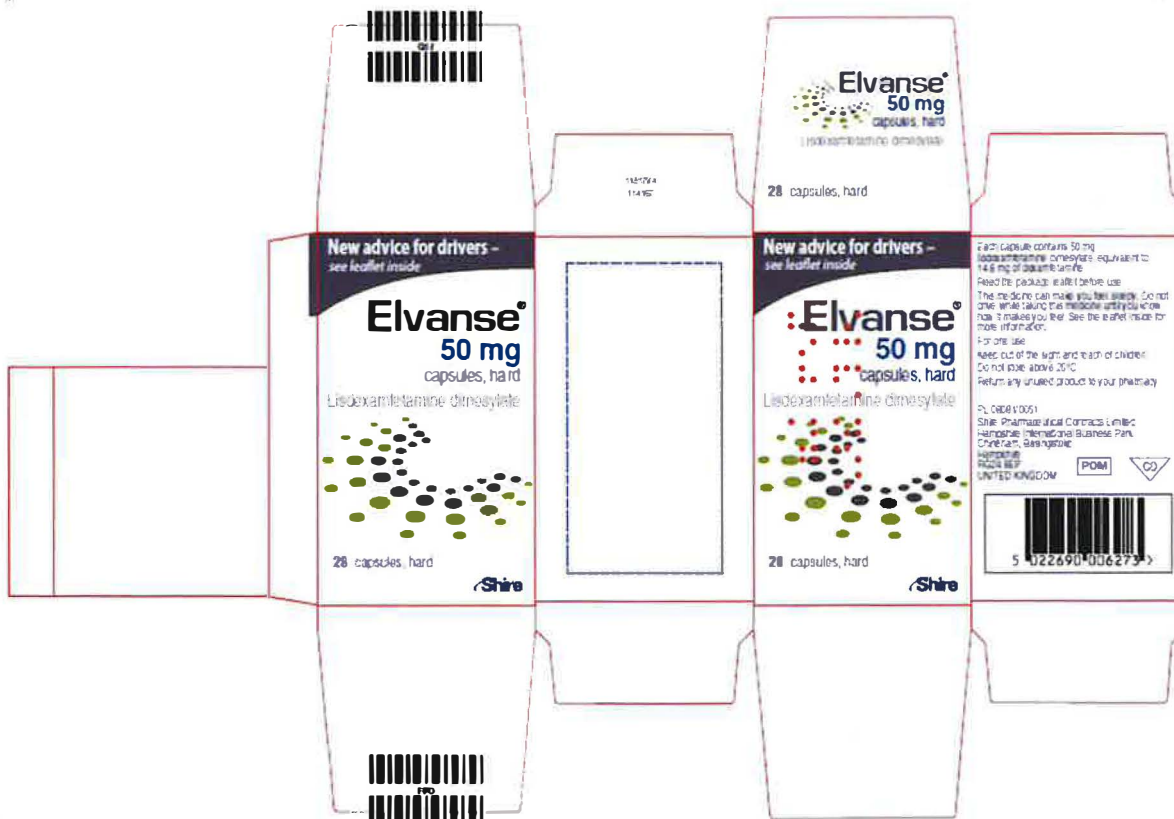
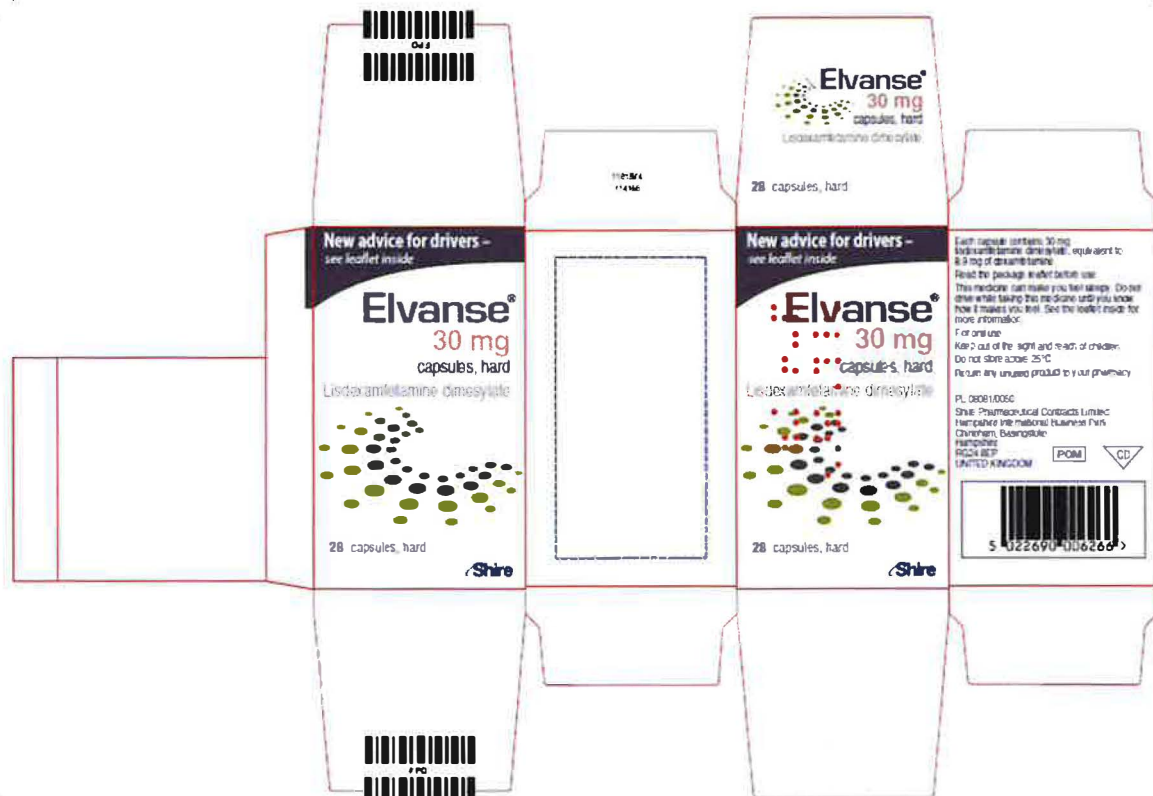
Although *d*-amfetamine is not licensed for the treatment of ADHD in adults it is used off label for this indication and the NICE guideline recommends that *d*-amfetamine (or atomoxetine) can be tried if methylphenidate (the first-line treatment of choice for adults with ADHD with either moderate or severe levels of impairment) is ineffective.

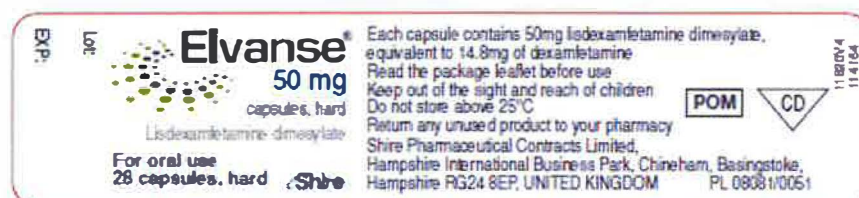
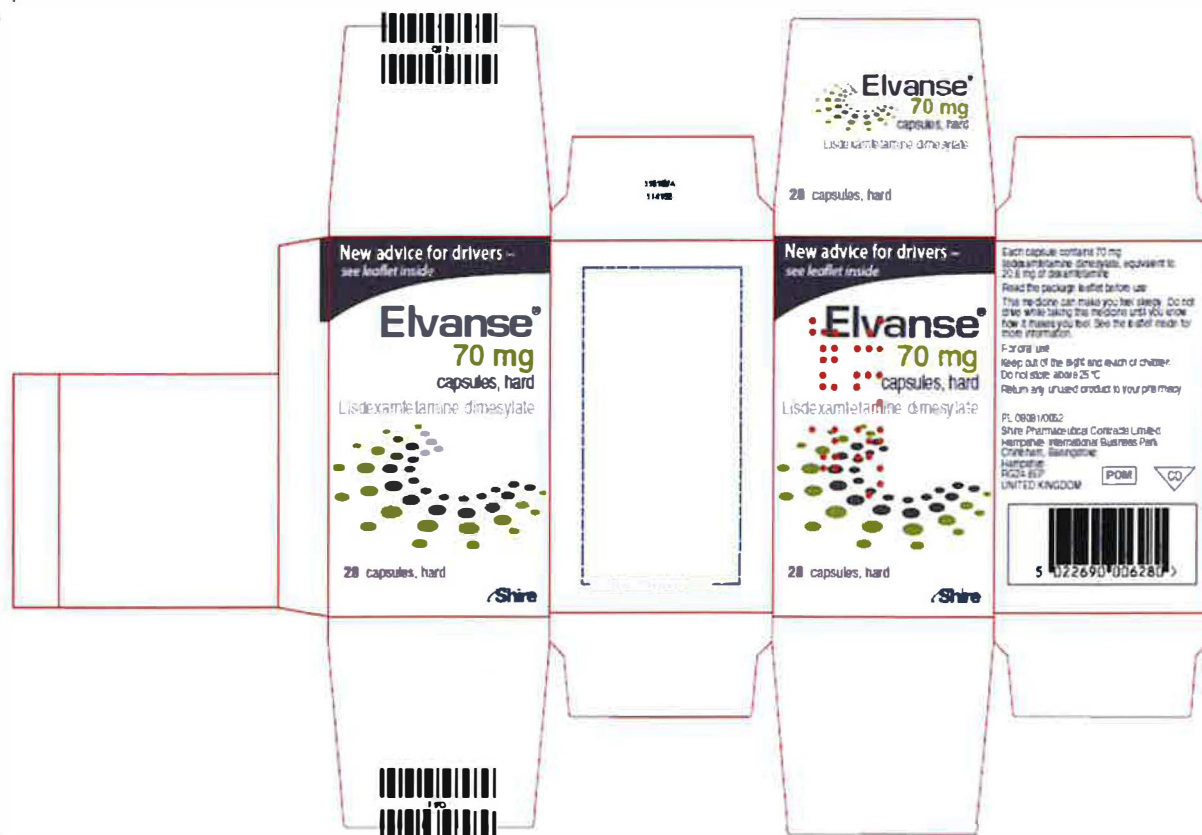
Provided that efficacy is sufficiently demonstrated in adult ADHD, including clinically important benefits in social and employment functioning, the safety profile could be considered acceptable, subject to appropriate clinical monitoring as set out in the Summary Product Characteristics.

PRODUCT LITERATURE

The approved SmPCs and PILs are satisfactory and in-line with those for products of this type. The final labelling is satisfactory and in-line with current guidelines.

The current approved UK SmPCs and PIL are available on the MHRA website. The current approved UK labelling is provided below.





RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and any non-clinical or clinical safety concerns have been fully resolved. The risk benefit is, therefore, considered to be positive.

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)
II	UK/H/3326/001-003/II/001	SmPC/PIL	18/07/2013	31/03/2014	Approval	Yes
II	UK/H/3326/001-003/II/006	SmPC/PIL	18/06/2014	07/01/2015	Approval	Yes
II	UK/H/3326/001-003/II/007	SmPC/PIL	23/06/2014	07/01/2015	Approval	Yes

Annex I

Reference:	PL 08081/0050-0002 (UK/H/3326/001/II/001); PL 08081/0051-0003 (UK/H/3326/002/II/001); PL 08081/0052-0003 (UK/H/3326/003/II/001);
Product:	Elvanse 30, 50 & 70mg Capsules, hard
Marketing Authorisation Holder:	Shire Pharmaceuticals Contracts Limited.
Active Ingredients:	Lisdexamfetamine dimesylate
Reason:	To update Section 5.1 of the SmPC to include the efficacy results of a recently completed study (Study SPD489-317). To update section 4.8 (Undesirable effects) of the SmPC regarding the reporting of adverse effects To update the SmPC and PIL to reflect the updated QRD template pertaining to the new Pharmacovigilance legislation.

Background

This assessment primarily concerns Study SPD489-317, a Phase IIIb, double-blind, randomised, active-controlled, parallel-group study to evaluate the safety and efficacy of lisdexamfetamine dimesylate (previously known as SPD489) to atomoxetine hydrochloride in children and adolescents aged 6-17 years with attention-deficit/hyperactivity disorder (ADHD) who have had an inadequate response to methylphenidate therapy.

The study is stated to have been conducted in compliance with the Declaration of Helsinki and in compliance with the International Conference on Harmonisation Good Clinical Practice Guidelines (1996), and European Guidelines.

Supporting Evidence**Study SPD489-317**

Study SPD489-317 was a randomised, double-blind, multicenter, parallel-group, active-controlled, dose-optimisation study designed to evaluate the safety and efficacy of lisdexamfetamine and atomoxetine (Strattera) in the treatment of children and adolescents (6-17 years of age, inclusive) with attention-deficit/hyperactivity disorder (ADHD) who had an inadequate response (current or historical) to methylphenidate (MPH).

Strattera was chosen as the comparator drug for this study based on guidance from the National Institute for Health and Clinical Excellence (NICE Clinical Guideline 72 2008) and European ADHD guidelines (European Network on Hyperkinetic Disorders [EUNETHYDIS]; Taylor et al. 2004) endorsing its use in the management of ADHD in children and adolescents.

All test products were over-encapsulated and appeared identical to protect the study blind.

Inadequate response to MPH was based on investigator judgment and included, but was not limited to, the presence of some residual symptoms, an inadequate duration of action and/or variability of symptom control, and/or the investigator felt the subject may have derived benefit from an alternative treatment to MPH therapy.

Other inclusion criteria included DSM-IV-TR criteria for a primary diagnosis of ADHD based on a detailed psychiatric evaluation, an ADHD-RS-IV total score ≥ 28 at the Baseline Visit, functioning at an age-appropriate level intellectually, and blood pressure measurements within the 95th percentile.

Subjects were excluded from the study if they had taken more than one different MPH treatment. This did not include subjects who had taken immediate-release MPH for dose titration on a short-term basis (e.g., ≤ 4 weeks) with an adequate response. Subjects were also excluded if they had failed to respond to more than one previous course of MPH treatment. Failure to respond included worsening of symptoms or no change/minimal improvement of symptoms. Subject who had previously been exposed to Strattera or to amphetamine therapy were also excluded, as were those with major psychiatric comorbidity or conduct disorder (but not oppositional defiant disorder).

Subjects who met eligibility criteria entered the study and were randomised (1:1) to lisdexamfetamine or Strattera and subsequently treated in a double-blind fashion for 9 weeks (4 weeks of dose optimisation followed by 5 weeks of dose maintenance). Subjects returned to the site approximately 7-9 days following their last dose of investigational product for a Safety Follow-up Assessment.

The original protocol was amended to utilise a group sequential clinical trial methodology in order to potentially stop the trial early based on interim results for the primary efficacy measure (time to response), the results of which were to be assessed in accordance with a pre-defined charter. However, no interim analyses were performed.

Following an initial Screening Period (Days -14 to -3), which included a washout phone call on Day -7, subjects were randomised to lisdexamfetamine or Strattera (1:1) at the Baseline Visit (Week 0) and subsequently began a 9-week Double-blind Treatment Period, which consisted of 4 weeks of dose optimisation and 5 weeks of dose maintenance, to evaluate safety and efficacy. Subjects returned to the study site for a Safety Follow-up Visit approximately 7-9 days after the last dose of investigational product. The total duration of the study was up to 12 weeks.

Study objectives

The primary objective of this study was to compare the time to response of lisdexamfetamine with that of Strattera in subjects who were judged by the investigator to have had an inadequate response to MPH treatment.

The primary efficacy measure was time to response, where response was assessed at each double-blind visit (Visits 1-9 or early termination [ET]) on an individual subject level and was defined as a Clinical Global Impression – Global Improvement (CGI-I) score of 1 or 2.

There were a number of other secondary efficacy measures, including improvements on the ADHD-RS-IV, the proportion of responders (assessed using the CGI-I) and a functional measure (Weiss Functional Impairment Rating Scale – Parent [WFIRS-P]).

Statistical and Analytical Plans

Summary statistics for time to response (days) are presented for each treatment group (Elvanse and Strattera) and overall. The proportion of responders (n, %) is summarised at each visit (using observed data) by treatment group and overall.

The primary efficacy analyses were performed on the time to response for all subjects randomised, using a Peto-Peto-Prentice test stratified by country group.

Subjects who withdrew early from the study, or, subjects who completed the study through to Visit 9 without meeting response criteria, were censored and classified as non-responders in the efficacy analyses.

For the secondary efficacy measures, the following analyses were applicable:

- The Last Observation Carried Forward (LOCF) methodology was used to handle missing data. Based on this approach, data from baseline were never carried forward into the treatment phase and data collected after the last on-treatment post baseline visit were always excluded.
- In cases where observed data were summarised, an endpoint measurement was derived and defined as the last on-treatment post-baseline visit of the dose optimization or dose maintenance periods (Visits 1-9/ET) with a valid value.
- Visit 9 LOCF is equivalent to observed values endpoint.
- An non-responder imputation (NRI) approach was used, such that a missing post baseline value was classed as a non-response, for the proportions of responders and sustained responders.

Study subjects

One subject was randomised to Strattera, but actually received lisdexamfetamine due to a drug dispensing error that occurred at the site. For the efficacy analyses, which were based on the intention-to-treat principle, this subject was included in the Strattera treatment group. For the safety analysis, this subject was included in the lisdexamfetamine group. In the below primary efficacy measure, two analyses are performed, with the subject in each of the treatment groups.

Of the 267 subjects who were enrolled and randomised, five subjects were not dosed and were excluded from the Full Analysis Set. 200 subjects (74.9%) completed the study through Visit 10, one subject (lisdexamfetamine) completed up to Visit 9 but did not have a Visit 10 clinic visit or telephone call and was, therefore, not considered a study completer, and 66 subjects (24.7%) were prematurely discontinued. When presented by treatment group, similar percentages of randomised subjects in the lisdexamfetamine and Strattera groups completed the study (74.4% and 75.4%, respectively).

In general, the two treatment groups were well-balanced at baseline in terms of age, age group, sex, ethnicity, race, height, weight, BMI, time since ADHD diagnosis, ADHD subtype, ADHD-RS-IV Total and Subscale Scores, CGI-S rating, and WFIRS-P Overall Score.

Overall, the most frequently reported reason for early termination was adverse events (18 subjects, 6.7%). When presented by treatment group, the most frequently reported reasons for early termination were adverse events (AEs) and withdrawal by subject within the lisdexamfetamine group (each reported for 8 subjects, 6.0%); and lack of efficacy (13 subjects, 9.7%) and AEs (ten subjects, 7.5%) within the Strattera group.

Table 7: Summary of Subject Disposition (All Subjects)			
	SPD489 (N=133) n (%)	STRATTERA (N=134) n (%)	Total (N=267) n (%)
Subjects Who Were:			
Randomized	133 (100.0)	134 (100.0)	267 (100.0)
Safety Population ^a	128 (96.2)	134 (100.0)	262 (98.1)
Full Analysis Set ^{b,c}	127 (95.5)	135 (100.0)	262 (98.1)
Study Completers ^d	99 (74.4)	101 (75.4)	200 (74.9)
Early Termination	33 (24.8)	33 (24.6)	66 (24.7)
Completed Visits 0-9 ^e	1 (0.8)	0	1 (0.4)
Reason for Discontinuation:			
Adverse Event	8 (6.0)	10 (7.5)	18 (6.7)
Withdrawal by Subject	8 (6.0)	4 (3.0)	12 (4.5)
Protocol Violation	7 (5.3)	2 (1.5)	9 (3.4)
Lost to Follow-up	5 (3.8)	1 (0.7)	6 (2.2)
Lack of Efficacy	2 (1.5)	13 (9.7)	15 (5.6)
Other	3 (2.3)	3 (2.2)	6 (2.2)

^a The Safety Population includes all subjects who were randomized and who received at least 1 dose of investigational product.

^b The Full Analysis Set includes all subjects who were randomized and who received at least 1 dose of investigational product.

^c Subject 278-0006 was randomized to receive STRATTERA but actually received SPD489. Based on the intention-to-treat principle, this subject is included in the STRATTERA arm for the efficacy analysis. For the safety analysis, this subject is included in the SPD489 arm.

^d A subject was defined as a study completer if Visit 0 through Visit 10 were completed, with Visit 10 being a clinic visit or a telephone call.

^e One subject (166-0001) completed the study through Visit 9 but did not have a Visit 10 clinic visit or telephone call. Because this subject is not considered a study completer, the number of study completers plus the number of early terminations does not equal the number randomized.

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

Source: Section 14.1, Table 1.1.3 and Appendix 16.2, Listings 1.2 and 4.1.

Results

Primary efficacy measure - Time to First Response

The time to response was shorter for the SPD489 group compared to the Strattera group, ($p=0.001$). The median time to first response was 13.0 days for the lisdexamfetamine group and (21.0) days for Strattera. Analyses are presented below with the subject that received SPD489 when they were randomised to the Strattera treatment arm presented in either the Strattera treatment group (Table 13) or the SPD489 group (Table 1).

Table 13: Summary and Analysis of Time to First Response Presented by Treatment Group (Full Analysis Set)		
	SPD489 (N=127)	STRATTERA (N=135)
Kaplan-Meier Estimates		
n	127	135
Total Responders	113	102
Total Censored	14	33
Median Time to First Response (days) ^a (95% Confidence Interval)	12.0 (8.0, 16.0)	21.0 (15.0, 23.0)
Treatment Difference from STRATTERA	p=0.001 ^b	

^a Response was defined as a CGI-I value of 1 (very much improved) or 2 (much improved) recorded post-baseline.

^b The p-value was based on Peto-Peto-Prentice Wilcoxon test, stratified by country group.

Note: The time to first response was defined as the date of response minus the date of first dose + 1 for subjects who responded. Subjects who did not respond and completed the study had their data censored at their Visit 9 date and subjects who were prematurely discontinued from the study without responding had their data censored at 64 days.

Source: Section 14.1. Table 3.1.1.1.

Table 1: Summary and Analysis of Time to First Response Presented by Actual Treatment Group (Full Analysis Set)		
	SPD489 (N=128)	STRATTERA (N=134)
Kaplan-Meier Estimates		
n	128	134
Total Responders	113	102
Total Censored	15	32
Median Time to First Response (days) ^a (95% Confidence Interval)	13.0 (8.0, 16.0)	21.0 (14.0, 23.0)
Treatment Difference from STRATTERA	p=0.003 ^b	

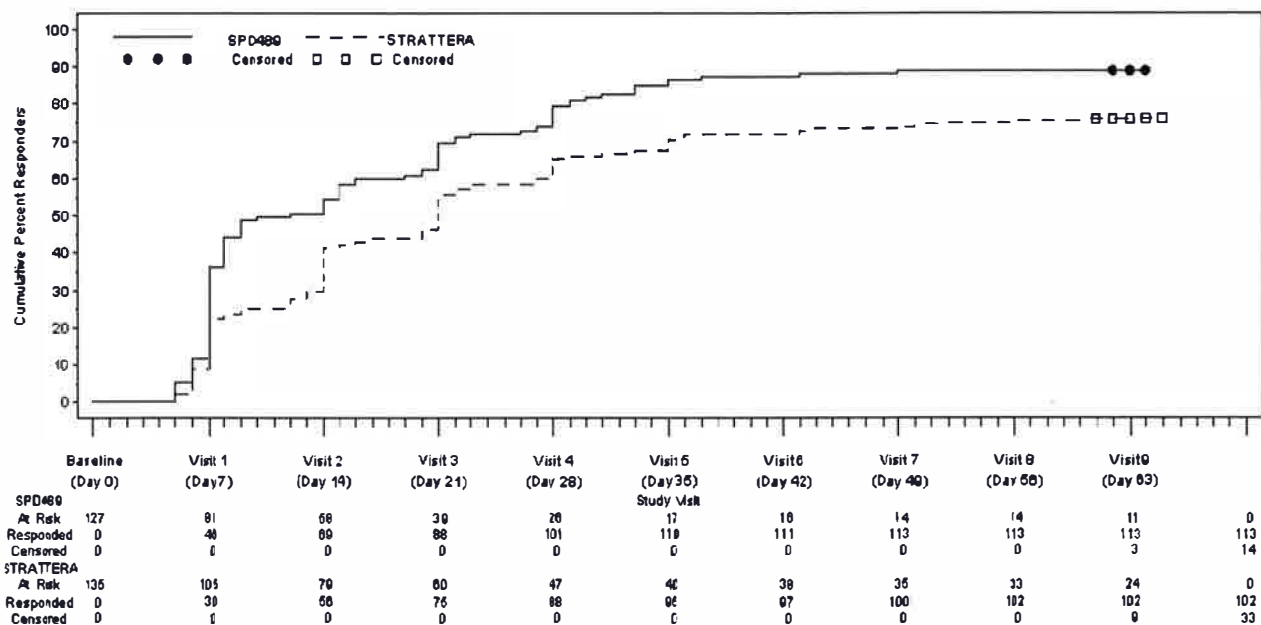
^a Response was defined as a CGI-I value of 1 (very much improved) or 2 (much improved) recorded post-baseline.

^b The p-value was based on Peto-Peto-Prentice Wilcoxon test, stratified by country group.

Note: The time to first response was defined as the date of response minus the date of first dose + 1 for subjects who responded. Subjects who did not respond and completed the study had their data censored at their Visit 9 date and subjects who were prematurely discontinued from the study without responding had their data censored at 64 days.

Note: Subject 278-0006 was randomised to receive Strattera, but actually received SPD489. The subject is included in the SPD489 arm for this analysis.

A graph of the times to first response based on the primary analysis is presented by treatment group in Figure 3.

Figure 3: Time to First Response for the Primary Efficacy Analysis (Full Analysis Set)

Note: Response was defined as CGI-I value of 1 (very much improved) or 2 (much improved) recorded post-baseline. Time to first response=(date of response) – (date of first dose + 1), for subjects who responded. Subjects who did not respond and who completed the study were censored at their Visit 9 date. Subjects who prematurely discontinued the study without responding were censored at 64 days.

Source: Section 15, Figure 3.1.1.1.1.

A pattern favourable for Elvanse is seen, with the biggest difference apparent at Week 1.

Consistently higher proportions of subjects in the SPD489 group compared to Strattera had a CGI-I dichotomized result of responder, with the difference between treatment groups being statistically significant at each post-baseline double-blind treatment visit (Table 14).

Furthermore, within both treatment groups, the proportions of responders increased steadily over time between Visits 1 and 4, inclusive, with minimal changes noted thereafter from Visits 5 through 9. At Visit 9, the proportions of responders in the SPD489 and Strattera groups were 81.7% and 63.6%, respectively ($p=0.001$).

Table 14: Summary and Analysis of Dichotomized CGI-I Results – LOCF (Full Analysis Set)			
Visit Dichotomized CGI-I Result^a		SPD489 (N=127)	STRATTERA (N=135)
Visit 1 (Day 7)			
Responder ^b	n (%)	63 (50.0)	34 (25.8)
Non-responder	n (%)	63 (50.0)	98 (74.2)
95% CI for % responder		41.3, 58.7	18.3, 33.2
p-value ^c		<0.001	
Visit 2 (Day 14)			
Responder ^b	n (%)	72 (57.1)	50 (37.9)
Non-responder	n (%)	54 (42.9)	82 (62.1)
95% CI for % responder		48.5, 65.8	29.6, 46.2
p-value ^c		0.002	
Visit 3 (Day 21)			
Responder ^b	n (%)	84 (66.7)	67 (50.8)
Non-responder	n (%)	42 (33.3)	65 (49.2)
95% CI for % responder		58.4, 74.9	42.2, 59.3
p-value ^c		0.008	
Visit 4 (Day 28)			
Responder ^b	n (%)	98 (77.8)	80 (60.6)
Non-responder	n (%)	28 (22.2)	52 (39.4)
95% CI for % responder		70.5, 85.0	52.3, 68.9
p-value ^c		0.002	
Visit 5 (Day 35)			
Responder ^b	n (%)	103 (81.7)	83 (62.9)
Non-responder	n (%)	23 (18.3)	49 (37.1)
95% CI for % responder		75.0, 88.5	54.6, 71.1
p-value ^c		<0.001	
Visit 6 (Day 42)			
Responder ^b	n (%)	104 (82.5)	80 (60.6)
Non-responder	n (%)	22 (17.5)	52 (39.4)
95% CI for % responder		75.9, 89.2	52.3, 68.9
p-value ^c		<0.001	
Visit 7 (Day 49)			
Responder ^b	n (%)	104 (82.5)	83 (62.9)
Non-responder	n (%)	22 (17.5)	49 (37.1)
95% CI for % responder		75.9, 89.2	54.6, 71.1
p-value ^c		<0.001	

Table 14: Summary and Analysis of Dichotomized CGI-I Results – LOCF (Full Analysis Set)			
Visit		SPD489 (N=127)	STRATTERA (N=135)
Dichotomized CGI-I Result^a			
Visit 8 (Day 56)			
Responder ^b	n (%)	102 (81.0)	84 (63.6)
Non-responder	n (%)	24 (19.0)	48 (36.4)
95% CI for % responder		74.1, 87.8	55.4, 71.8
p-value ^c		0.002	
Visit 9 (Day 63)			
Responder ^b	n (%)	103 (81.7)	84 (63.6)
Non-responder	n (%)	23 (18.3)	48 (36.4)
95% CI for % responder		75.0, 88.5	55.4, 71.8
p-value ^c		0.001	

^a The numbers of subjects evaluated for CGI-I were 126 for the SPD489 group and 132 for the STRATTERA group. Percentages are based on the 'n' at that visit in each treatment group.

^b Response was defined as CGI-I value of 1 (very much improved) or 2 (much improved) recorded post-baseline. Non-response includes all other categories.

^c P-value is based on Cochran-Mantel-Haenszel test, stratified by country group.

Note: Visit 9 LOCF is equivalent to Observed Values Endpoint.

Note: Not assessed is treated as a missing value in the LOCF analysis.

CGI-I=Clinical Global Impressions – Improvement; CI=confidence interval; LOCF=last observation carried forward

As can be seen, the difference was significant at all time points, the lowest level of significance being $p = 0.008$ (Visit 3).

Across all of the double blind treatment visits, the proportion of responders in the SPD489 group was consistently higher than the proportion of responders in the atomoxetine group. The difference ranged from 16-24 percentage points.

Secondary Efficacy Measurements

Various different responder analyses by CGI are presented in the CSR and they follow the general pattern presented above i.e. the majority of patients overall responded, with a trend in favour of Elvanse.

The results for ADHD-RS-IV Total Score are considered important for this application as symptom control at the endpoint of the study is of much greater clinical relevance than the time to achieve symptom control (response).

Mean ADHD-RS-IV total scores were similar between treatment groups at baseline. Mean decreases from baseline (representing improvement) were noted for both treatment groups at every post-baseline double-blind treatment visit and were consistently of greater magnitude for subjects in the lisdexamfetamine group compared to the Strattera group (Table 16). At Visit 9, the mean (SD) changes from baseline in ADHD-RS-IV Total Score for subjects in the lisdexamfetamine and Strattera groups were -26.3 (11.94) and -19.4 (12.82), respectively.

The differences in least-squares mean changes from baseline in ADHD-RS-IV Total Score between lisdexamfetamine and Strattera were statistically significant across all post-baseline double-blind treatment visits (Table 17). At Visit 9, the least square mean changes from baseline for lisdexamfetamine and Strattera were -26.1 and -19.7, respectively ($p < 0.001$).

Table 16: Mean and Mean Changes from Baseline Over Time in ADHD-RS-IV Total Score – LOCF (Full Analysis Set)				
Visit	SPD489 (N=127)		STRATTERA (N=135)	
	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Baseline (Day 0)				
n	127		135	
Mean (SD)	42.6 (6.17)		41.9 (6.68)	
Min. Max	28. 54		28. 53	
Visit 1 (Day 7)				
n	126	126	133	133
Mean (SD)	28.2 (13.45)	-14.4 (13.24)	33.5 (11.71)	-8.4 (9.92)
Min. Max	1. 54	-44. 8	1. 54	-43. 7
Visit 2 (Day 14)				
n	126	126	133	133
Mean (SD)	24.4 (12.81)	-18.2 (12.67)	29.3 (12.55)	-12.5 (11.26)
Min. Max	0. 53	-53. 3	0. 54	-45. 5
Visit 3 (Day 21)				
n	126	126	133	133
Mean (SD)	21.3 (11.74)	-21.3 (11.80)	26.4 (12.99)	-15.4 (12.26)
Min. Max	0. 48	-53. 4	0. 54	-47. 8
Visit 4 (Day 28)				
n	126	126	133	133
Mean (SD)	19.4 (11.14)	-23.2 (10.98)	24.5 (13.05)	-17.4 (12.34)
Min. Max	0. 48	-53. 2	0. 54	-47. 8
Visit 5 (Day 35)				
n	126	126	133	133
Mean (SD)	18.2 (10.93)	-24.4 (11.06)	23.7 (13.20)	-18.2 (12.20)
Min. Max	0. 48	-53. 2	0. 54	-48. 8
Visit 6 (Day 42)				
n	126	126	133	133
Mean (SD)	17.7 (10.95)	-24.9 (11.28)	23.5 (12.97)	-18.4 (12.39)
Min. Max	0. 48	-53. 2	0. 54	-47. 8
Visit 7 (Day 49)				
n	126	126	133	133
Mean (SD)	16.9 (10.92)	-25.7 (11.33)	23.0 (12.70)	-18.9 (12.23)
Min. Max	0. 48	-53. 2	0. 54	-47. 8
Visit 8 (Day 56)				
n	126	126	133	133
Mean (SD)	16.7 (10.89)	-25.8 (11.60)	22.7 (13.14)	-19.2 (12.85)
Min. Max	0. 48	-53. 2	0. 54	-50. 8
Visit 9 (Day 63)				
n	126	126	133	133
Mean (SD)	16.3 (11.16)	-26.3 (11.94)	22.5 (13.21)	-19.4 (12.82)
Min. Max	0. 48	-53. 2	0. 54	-50. 8

Note: Visit 9 LOCF is equivalent to Observed Values Endpoint.

Note: A decrease from baseline indicates an improvement in symptoms.

ADHD-RS-IV=Attention-deficit/Hyperactivity Disorder Rating Scale – IV; LOCF=last observation carried forward; Max=maximum; Min=minimum; SD=standard deviation

Table 17: Analysis of Change from Baseline in ADHD-RS-IV Total Score Presented by Study Visit and Treatment Group - LOCF (Full Analysis Set)

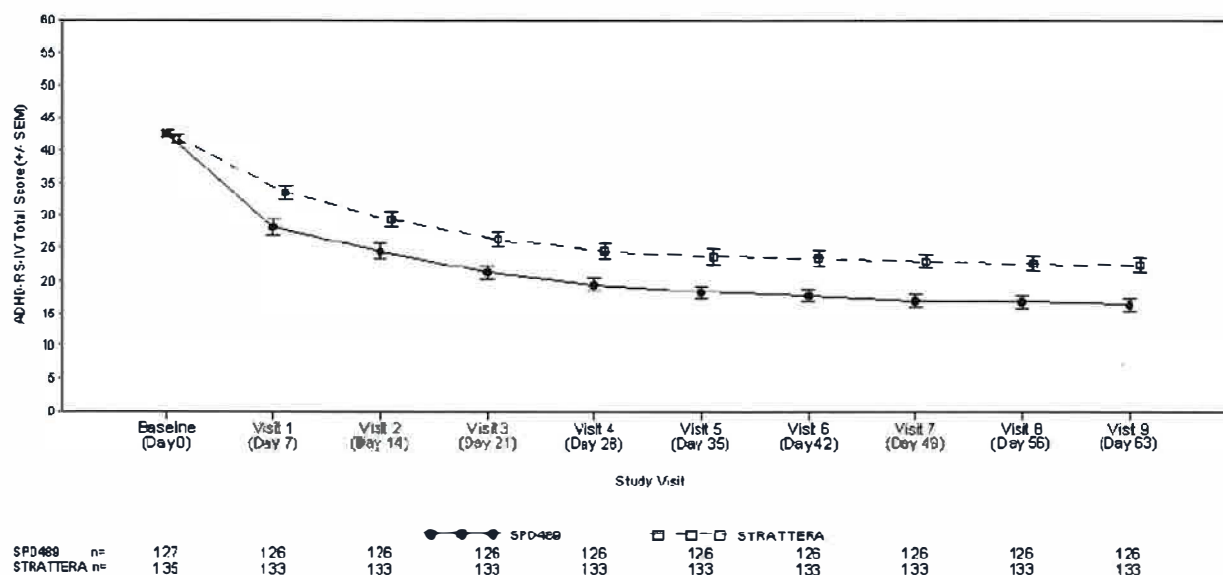
SPD489 vs STRATTERA Visit	Least Square Mean ^a		Difference in LS Mean (SPD489 - STRATTERA) (95% CI)	Effect Size ^a (95% CI)	p-value ^a
	SPD489	STRATTERA			
Visit 1 (Day 7)	-15.0	-9.2	-5.8 (-8.6, -3.1)	0.52 (0.27, 0.76)	<0.001
Visit 2 (Day 14)	-18.4	-13.0	-5.4 (-8.2, -2.6)	0.47 (0.22, 0.72)	<0.001
Visit 3 (Day 21)	-20.9	-15.3	-5.6 (-8.4, -2.8)	0.49 (0.24, 0.74)	<0.001
Visit 4 (Day 28)	-23.2	-17.7	-5.5 (-8.3, -2.8)	0.49 (0.25, 0.74)	<0.001
Visit 5 (Day 35)	-24.0	-18.1	-6.0 (-8.7, -3.2)	0.54 (0.29, 0.78)	<0.001
Visit 6 (Day 42)	-24.8	-18.7	-6.2 (-8.9, -3.4)	0.55 (0.30, 0.80)	<0.001
Visit 7 (Day 49)	-25.4	-19.0	-6.4 (-9.2, -3.7)	0.58 (0.33, 0.83)	<0.001
Visit 8 (Day 56)	-25.7	-19.5	-6.2 (-9.1, -3.4)	0.54 (0.30, 0.79)	<0.001
Visit 9 (Day 63)	-26.1	-19.7	-6.5 (-9.3, -3.6)	0.56 (0.31, 0.80)	<0.001

^a Least square 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 country group as fixed effects, and baseline value as a covariate.

Note: A negative difference in LS Mean (SPD489 – STRATTERA) indicates a positive effect of SPD489 over STRATTERA.

Note: Visit 9 LOCF is equivalent to Observed Values Endpoint

ADHD-RS-IV=Attention-deficit/Hyperactivity Disorder Rating Scale – IV; ANCOVA=analysis of covariance; CI=confidence interval; LOCF=last observation carried forward; LS=least square

Figure 5: Mean ADHD-RS-IV Total Scores Presented Over Time by Treatment Group - LOCF (Full Analysis Set)

Statistically and clinically significant superiority of Elvanse over Strattera has been demonstrated on change from baseline to endpoint (Visit 9, LOCF).

Conclusions on efficacy demonstrated in Study SPD489-317

Study SPD489 -317 provides clear evidence that Elvanse achieves more rapid control of ADHD symptoms compared to Strattera in this patient population and more importantly produces a greater reduction in core symptoms over a 9-week treatment period.

Clinical safety

The MAH reports that no new safety signals were observed in Study SPD489-317 and that the safety results presented in this study were generally consistent with the well-documented safety profiles associated with lisdexamfetamine and atomoxetine.

The majority of subjects in both treatment groups had at least one treatment-emergent adverse event (TEAE) during the study and the majority of all TEAEs were mild or moderate in intensity.

Decreased appetite (25.8%) and weight decreased (21.9%) were the most frequently reported TEAEs among lisdexamfetamine subjects. Among atomoxetine subjects, headache (16.4%) and nausea (15.7%) were the most frequently reported TEAEs.

There were no serious adverse events or deaths reported during the study.

Eighteen subjects (lisdexamfetamine, eight subjects and atomoxetine, ten subjects) were discontinued from investigational product due to at least one TEAE. All TEAEs leading to premature discontinuation were considered by the investigator to be related to investigational product.

Specifically with regard to lisdexamfetamine, adverse events were consistent with the previously established adverse event profile for lisdexamfetamine. The majority of TEAEs were mild or moderate, resolved prior to the end of study participation, did not impact dosing with investigational product, and either required no treatment or were managed with nonpharmacologic treatment.

Mean increases from baseline in pulse and blood pressure (systolic and diastolic) were noted among lisdexamfetamine subjects, which were not clinically significant, and are consistent with the known effects of stimulant treatment. Moderate mean decreases from baseline in body weight were noted among lisdexamfetamine subjects, which are consistent with the known effects of stimulant treatment.

Both atomoxetine and stimulants including Elvanse are well known to cause increases in heart rate and blood pressure. This study provides a very useful opportunity to compare the magnitude of the changes produced by each drug. The key findings are presented below.

Pulse

The mean (standard deviation [SD]) changes from baseline at endpoint (and associated minimum and maximum values) are presented below for pulse (bpm):

Lisdexamfetamine 3.6 (10.49) (-20 to 35)

Strattera 3.7 (10.75) (-34 to 37).

Sitting Systolic Blood Pressure

The mean (SD) changes from baseline at endpoint (and associated minimum and maximum values) are presented below for sitting systolic blood pressure (mmHg):

Lisdexamfetamine 0.7 (9.08) (-20 to 25)

Strattera 0.6 (7.96) (-20 to 20).

Sitting Diastolic Blood Pressure

The mean (SD) changes from baseline at endpoint (and associated minimum and maximum values) are presented below for sitting diastolic blood pressure (mmHg):

Lisdexamfetamine 0.1 (8.33) (-25 to 24).

Strattera 1.3 (8.24) (-23 to 24)

Elvanse and Strattera seemed to cause similar increases in heart rate and systolic blood pressure that are consistent with the well-known data from previous studies. Elvanse seemed in the simple analysis presented here to have less effect than Strattera on diastolic blood pressure, but the more comprehensive presentations of the data indicate that the difference is not statistically significant and that both products appear to have a very modest effect on increasing diastolic blood pressure.

Conclusions

Study SPD489 -317 provides clear evidence that Elvanse achieves more rapid control of ADHD symptoms compared to Strattera in this patient population and more importantly produces a greater reduction in core symptoms over a 9-week treatment period.

SmPCs and a PIL have been updated satisfactorily.

The grant of this variation is recommended.

Decision	-	Granted
Date	-	31 March 2014

Annex II

Reference:	PL 08081/0050-0011 (UK/H/3326/001/II/006); PL 08081/0051-0012 (UK/H/3326/002/II/006); PL 08081/0052-0012 (UK/H/3326/003/II/006);
Product:	Elvanse 30, 50 & 70mg Capsules, hard
Marketing Authorisation Holder:	Shire Pharmaceuticals Contracts Limited.
Active Ingredients:	Lisdexamfetamine dimesylate
Reason:	To update section 4.2 (Posology and administration) of the SPC to add alternative methods of administration. Consequently, the PIL has been updated.

Background

Two alternative options for administering SPD489 have been investigated. In bioavailability Study SPD489-123, the contents of a SPD489 capsule were emptied into a soft food (vanilla yogurt) or into orange juice. The resulting pharmacokinetic profiles of lisdexamfetamine and d-amphetamine were then compared with the pharmacokinetic profiles when SPD489 is administered as an intact capsule.

The relative bioavailability for each of the two test means of administration was evaluated by calculating the point estimate and 90% confidence intervals (CIs) for comparisons of C_{max} , AUC_{last} , and AUC_{0-inf} for SPD489 70mg mixed in orange juice with intact SPD489 70mg capsule (the reference treatment), and SPD489 70mg mixed in vanilla yogurt with the reference treatment. Equivalence was assumed if the 90% CI of the geometric least-squares mean ratios for the pharmacokinetic parameter fell within the interval (0.80, 1.25).

The study is stated to have been conducted in compliance with the Declaration of Helsinki and in compliance with the International Conference on Harmonisation Good Clinical Practice Guidelines (1996), and European Guidelines.

Supporting Evidence

Bioequivalence study SPD489-123

The study was an open-label, randomised, three-treatment, six-sequence, three-period crossover, single-dose bioavailability study comparing three methods of administration.

After an overnight fast subjects were administered one of the following in each treatment period:

Treatment A: One SPD489 70mg capsule emptied into orange juice

Treatment B: One SPD489 70mg capsule emptied into vanilla yogurt

Treatment C: One SPD489 70mg intact capsule administered with a glass of water

Study SPD489-123 utilised the current US 70mg capsule formulation, which differs from the EU capsule formulation only in the composition of the capsule shell (the US capsule shell contains E110 [sunset yellow]). This dye is not included in the EU capsule shell, however, all other capsule shell constituents are identical. This dye difference is considered insignificant, and will not affect the physical properties (apart from the appearance) or performance of the capsule, nor the delivery of active substance.

Blood samples were taken for plasma levels pre-dose and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hours after drug administration. There was a washout period of 7 days between study treatment administrations.

Population studied

Thirty healthy adult subjects were recruited into the study. All 30 subjects were checked-in for periods 1, 2 and 3 and received trial medication for all three periods. One subject discontinued from the study; this subject requested to be withdrawn from the Day 1 of Treatment Period 3, after receiving SPD489 70mg in orange juice (Treatment A). No treatment-emergent adverse events (TEAEs) were reported for this subject. All 30 subjects were included in the analyses. This is satisfactory as the withdrawn subject had sufficient evaluable data to be included as specified in the protocol.

Pharmacokinetic Variables

The primary variables were AUC_{0-t} , AUC_{0-inf} and C_{max} . T_{max} was also calculated.

Criteria for conclusion of bioequivalence were that the 90% confidence interval of the relative mean test/reference ratios of AUC_{0-t} and C_{max} for the test and reference formulation should be within 80–125 %.

Statistical methods

ANOVA was performed on the ln-transformed C_{max} , AUC_{0-t} and AUC_{0-inf} . T_{max} was analysed non-parametrically.

Results

Pharmacokinetic parameters for the pro-drug lisdexamfetamine

Table 2: Comparisons of Log-transformed Pharmacokinetic Parameters for Lisdexamfetamine (Study SPD489-123; Pharmacokinetic Set)			
Parameter	SPD489 70mg in Orange Juice (Trt A)	SPD489 70mg in Yogurt (Trt B)	SPD489 70mg Intact Capsule (Trt C)
$AUC_{0-\infty}$ (ng·h/mL)			
Geometric least squares means	30.33	42.38	42.39
Ratio of geometric least squares means (Trt A or Trt B:Trt C)	0.716	1.000	NA
90% CI	0.647, 0.792	0.896, 1.116	NA
p-value	<0.0001	0.9973	NA
AUC_{last} (ng·h/mL)			
Geometric least squares means	25.88	33.54	36.55
Ratio of geometric least squares means (Trt A or Trt B:Trt C)	0.708	0.918	NA
90% CI	0.655, 0.766	0.849, 0.992	NA
p-value	<0.0001	0.0716	NA
C_{max} (ng/mL)			
Geometric least squares means	23.46	30.30	36.59
Ratio of geometric least squares means (Trt A or Trt B:Trt C)	0.641	0.828	NA
90% CI	0.582, 0.707	0.752, 0.912	NA
p-value	<0.0001	0.0019	NA

Note: Exponentiated least squares means and CIs are from an analysis of variance on natural log-transformed data. AUC_{last} =area under the curve from the time of dosing to the last measurable concentration; $AUC_{0-\infty}$ =area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration; CI=confidence interval; C_{max} =maximum concentration occurring at t_{max} where t_{max} =time of maximum observed concentration sampled during a dosing interval; NA=not applicable; Trt=Treatment.
Source: SPD489-123 CSR, Table 8.

Comparisons (orange juice to intact capsule, and yogurt to intact capsule) of log-transformed pharmacokinetic parameters for lisdexamfetamine are presented in Table 2. For lisdexamfetamine in orange juice, the ratios of geometric means (comparison to intact

capsule) for $AUC_{0-\infty}$, AUC_{last} , and C_{max} and the associated 90% CIs were below the pre-specified range of 0.80-1.25. For lisdexamfetamine in yogurt, the ratios of geometric least squares means (comparison to intact capsule) for $AUC_{0-\infty}$ and AUC_{last} and the associated 90% CIs fell within the range of 0.80-1.25. The ratio of geometric means for C_{max} fell within the pre-specified range of 0.80-1.25; however, the lower 90% CI fell below the range. It is noted that lisdexamfetamine is an inactive prodrug; and, therefore, lisdexamfetamine levels do not determine pharmacological activity.

It is agreed that for the parent drug bioequivalence to administration of the intact capsule is shown for administration in yoghurt, but not for administration in orange juice. It is also agreed that lisdexamfetamine is an inactive prodrug; and, therefore, lisdexamfetamine levels do not determine pharmacological activity. The significance of these findings is discussed below.

Pharmacokinetic parameters for the active dexamfetamine

Table 3: Summary of Selected <i>d</i>-amphetamine Pharmacokinetic Parameters by Treatment (SPD489-123; Pharmacokinetic Set)				
		Treatment Group		
Pharmacokinetic Parameter	Statistic	SPD489 70mg in Orange Juice (Trt A)	SPD489 70mg in Yogurt (Trt B)	SPD489 70mg Intact Capsule (Trt C)
C_{max} (ng/mL)	n	30	30	30
	Mean (SD)	59.1 (9.47)	59.0 (9.28)	61.0 (10.81)
	Min-max	34.8-78.7	36.5-80.1	38.8-79.7
AUC_{last} (ng·h/mL)	n	30	30	30
	Mean (SD)	1140.9 (274.1)	1110.1 (252.9)	1180.2 (295.1)
	Min-max	699-2114	592-1885	729-2152
$AUC_{0-\infty}$ (ng·h/mL)	n	30	30	30
	Mean (SD)	1230.9 (291.7)	1180.4 (275.6)	1252.4 (315.3)
	Min-max	740-2179	613-1978	761-2250
$t_{1/2}$ (hr)	n	30	30	30
	Mean (SD)	11.6 (2.4)	11.7 (2.2)	11.6 (2.2)
	Min-max	6.98-19.16	7.21-16.97	7.44-15.35
t_{max} (hr)	n	30	30	30
	Mean (SD)	4.8 (1.1)	4.2 (0.6)	3.8 (1.1)
	Min-max	4-8	4-6	2-6
CL/F (L/hr)	n	30	30	30
	Mean (SD)	59.9 (13.86)	62.7 (15.86)	59.3 (14.52)
	Min-max	32.1-94.6	35.4-114.1	31.1-92.0

AUC_{last} =area under the curve from the time of dosing to the last measurable concentration; $AUC_{0-\infty}$ =area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration; CL/F=total body clearance for extravascular administration divided by the fraction of dose absorbed; C_{max} =maximum concentration occurring at t_{max} ; max=maximum; min=minimum; SD=standard deviation; t_{max} =time of maximum observed concentration sampled during a dosing interval; Trt=treatment; $t_{1/2}$ =terminal half-life.

Source: SPD489-123 CSR, Table 9.

Table 4: Summary of Statistical Comparisons of Log-transformed Pharmacokinetic Parameters for *d*-amphetamine (SPD489-123; Pharmacokinetic Set)

Parameter	SPD489 70mg in Orange Juice (Trt A)	SPD489 70mg in Yogurt (Trt B)	SPD489 70mg Intact Capsule (Trt C)
AUC_{0-∞} (ng·h/mL)			
Geometric least squares means	1200	1149	1216
Ratio of geometric least squares means (Trt A or Trt B:Trt C)	0.986	0.945	NA
90% CI	0.955, 1.019	0.915, 0.976	NA
p-value	0.4867	0.0054	NA
AUC_{last} (ng·h/mL)			
Geometric least squares means	1112	1083	1147
Ratio of geometric least squares means (Trt A or Trt B:Trt C)	0.970	0.944	NA
90% CI	0.937, 1.004	0.912, 0.977	NA
p-value	0.1425	0.0069	NA
C_{max} (ng/mL)			
Geometric least squares means	58.33	58.26	60.06
Ratio of geometric least squares means (Trt A or Trt B:Trt C)	0.971	0.970	NA
90% CI	0.945, 0.998	0.944, 0.997	NA
p-value	0.0792	0.0680	NA

Note: Exponentiated least squares means and CIs are from an analysis of variance on natural log-transformed data.

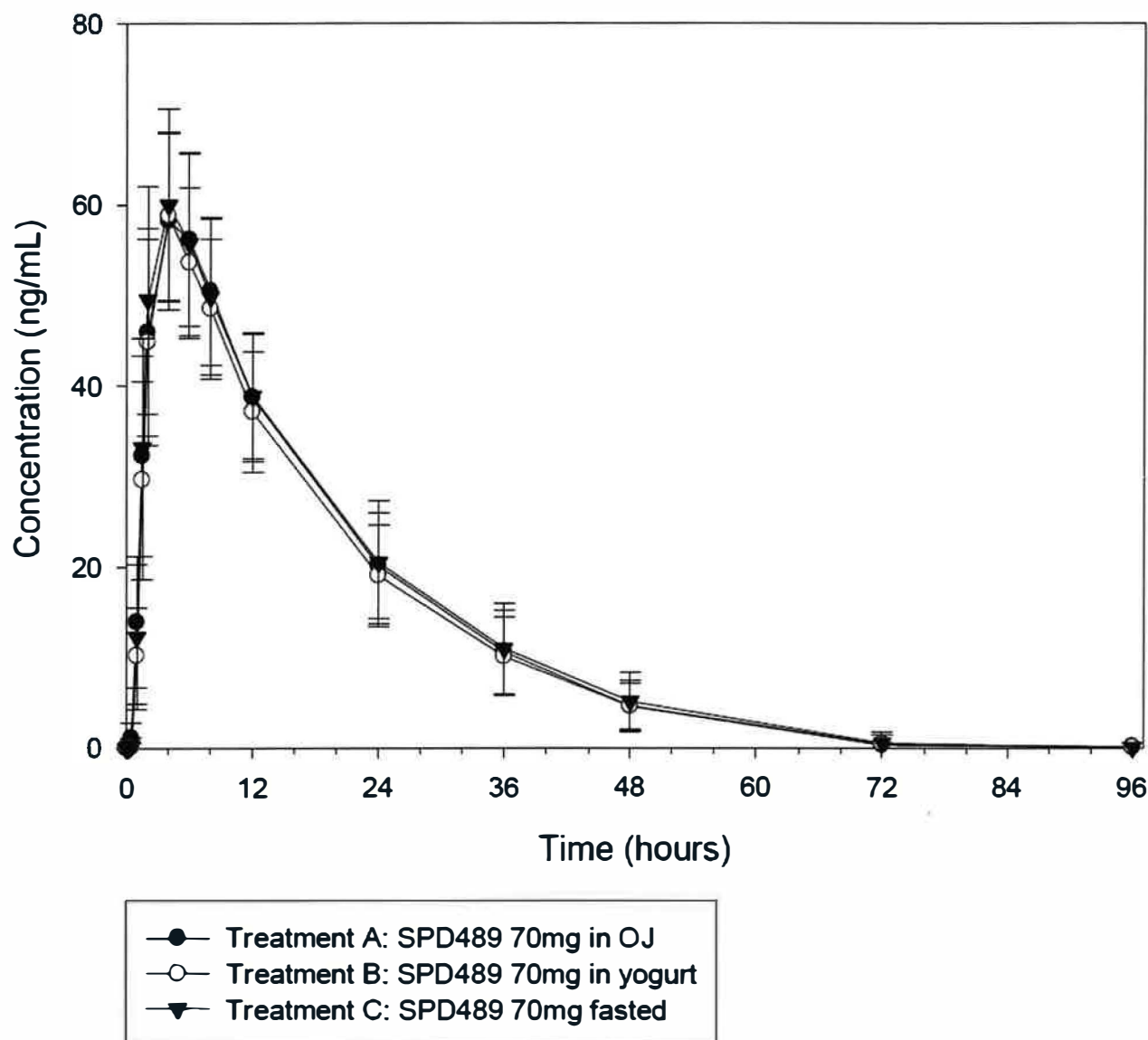
AUC_{last}=area under the curve from the time of dosing to the last measurable concentration; AUC_{0-∞}=area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration; CI=confidence interval; C_{max}=maximum concentration occurring at t_{max} where t_{max}=time of maximum observed concentration sampled during a dosing interval; NA=not applicable; Trt=Treatment.

Source: SPD489-123 CSR, Table 10.

A summary of selected pharmacokinetic parameters for *d*-amphetamine is presented by treatment group in Table 3. The means for C_{max}, AUC_{last}, AUC_{0-∞}, and C_{L/F} were generally similar for all three treatments; as were the mean t_½ and t_{max} (refer to SPD489-123 CSR). Comparisons (orange juice to intact capsule, and yogurt to intact capsule) of log-transformed pharmacokinetic parameters for *d*-amphetamine are presented in Table 4. For *d*-amphetamine in orange juice or in yogurt, the ratios of geometric least squares means (comparison to intact capsule) for AUC_{0-∞}, AUC_{last}, and C_{max} and the associated 90% CIs were within the pre-specified range of 0.80-1.25.

For the active *d*-amphetamine, the pharmacokinetic results are similar for the three methods of administration and the test/reference geometric ratios comfortably meet the 80-125% standard criteria. According to the CHMP guideline, bioequivalence is based on the data for the parent compound; so strictly speaking bioequivalence is not concluded here for administration with orange juice. However, for this application we are interested in the demonstration of therapeutic equivalence based on pharmacokinetic data. As lisdexamfetamine is an inactive prodrug; it is dexamfetamine levels that determine pharmacological activity and form the basis for a conclusion of therapeutic equivalence (see further justification in the overall conclusions below).

Figure 3: Mean ($\pm$ SD) *d*-amphetamine Plasma Concentrations versus Time (SPD489-123; Pharmacokinetic Set)



The individual patient data are generally reassuring, showing mostly good superimposability of the plots and an appropriate degree of inter-individual and intra-individual variation.

Applicant's summary on pharmacokinetics

For the prodrug lisdexamfetamine, in comparison to the intact capsule, the 90% CIs for $AUC_{0-\infty}$ and AUC_{last} fell within the pre-specified range of 0.80-1.25; but the 90% CI was below the range for C_{max} when SPD489 was administered in yogurt. All 90% CIs fell below the pre-specified range when SPD489 was administered in orange juice (Table 2).

Lisdexamfetamine is however pharmacologically inactive, and therefore the assessment of bioequivalence is based on the *d*-amphetamine pharmacokinetic parameters.

For the pharmacologically active substance *d*-amphetamine, the 90% CIs for $AUC_{0-\infty}$, AUC_{last} , and C_{max} were all within the pre-specified range of 0.80-1.25 for both administration of SPD489 in yogurt and orange juice compared to intact capsule (Table 4). The results of this study support the administration of SPD489 in orange juice or yogurt as an alternative to

the intact capsule. Based on *d*-amphetamine $AUC_{0-\infty}$ and C_{max} comparisons, intra-subject variability was low.

For the active *d*-amphetamine the pharmacokinetic results are similar for the three methods of administration and the test/reference geometric ratios comfortably meet the 80-125% standard criteria. According to the CHMP guideline, bioequivalence is based on the data for the parent compound so strictly speaking bioequivalence is not concluded here for administration with orange juice. However, for this application we are interested in the demonstration of therapeutic equivalence based on pharmacokinetic data. As lisdexamfetamine is an inactive prodrug; it is dexamfetamine levels that determine pharmacological activity. The inequivalence for the parent lisdexamfetamine does not imply any concerns regarding therapeutic equivalence.

Safety

No unexpected safety or tolerability issues were identified. SPD489 70mg was generally well-tolerated when administered as an intact capsule in orange juice or in yoghurt. There were no serious or severe TEAEs during the study and no discontinuations from the study due to TEAEs. All TEAEs were considered mild in severity.

Conclusion

For administration in yoghurt, the 90% confidence intervals for the primary variables AUC_{0-t} , AUC_{0-inf} and C_{max} are well within the acceptance range of 80-125% for both the inactive prodrug lisdexamfetamine and the active *d*-amphetamine. Bioequivalence to administration of the intact capsule may be concluded.

For administration in orange juice, both AUC and C_{max} for lisdexamfetamine are reduced relative to administration of the intact capsule. However, this is not reflected in the data for the active *d*-amphetamine, where there is no difference for either AUC or C_{max} . There are various possible explanations for this, relating to both the rate and extent of absorption and the rate of clearance from the circulation. Activation in red blood cells of lisdexamfetamine to dexamfetamine is the rate-limiting step that determines the rate of input of the active substance into the circulation.

As it is dexamfetamine levels that determine pharmacological activity, clinical equivalence may be concluded from the data presented. There are no new safety issues.

SmPCs and a PIL have been updated satisfactorily.

The grant of this variation is recommended.

Decision	-	Granted
Date	-	07 January 2015

Annex III

Reference:	PL 08081/0050-0012 (UK/H/3326/001/II/007); PL 08081/0051-0013 (UK/H/3326/002/II/007); PL 08081/0052-0013 (UK/H/3326/003/II/007);
Product:	Elvanse 30, 50 & 70mg Capsules, hard
Marketing Authorisation Holder:	Shire Pharmaceuticals Contracts Limited.
Active Ingredients:	Lisdexamfetamine dimesylate
Reason:	To update sections 4.2 (Posology and method of administration) and 5.2 (Pharmacokinetic properties) of the SmPC (and consequentially the leaflet) with the recently completed Phase 1 Study SPD489-120, which characterises the pharmacokinetics, safety, and tolerability of SPD489 in subjects with varying degrees of impaired renal function compared to subjects with normal renal function.

Background

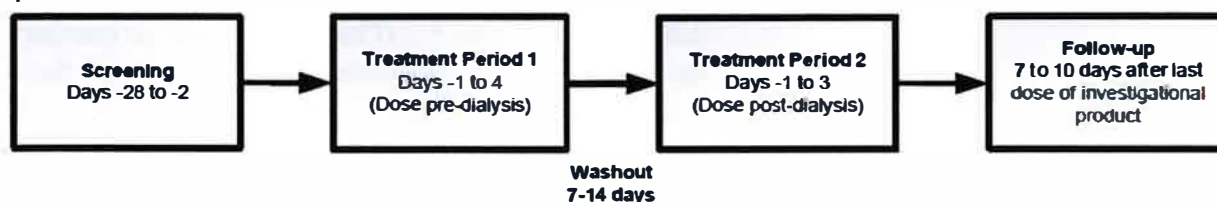
This submission presents the results of one Phase I study (SPD489-120) characterising the pharmacokinetics, safety, and tolerability of SPD489 in subjects with varying degrees of impaired renal function compared to subjects with normal renal function. Prior to this study, pharmacokinetic results were obtained primarily in those with normal renal function. Study SPD489-120 assessed the impact of renal impairment on the pharmacokinetics of both the prodrug lisdexamfetamine and the active metabolite *d*-amphetamine following administration of a single 30mg dose of SPD489. The need for dose modification in renally impaired patients was also assessed.

The study is stated to have been conducted in compliance with the Declaration of Helsinki and in compliance with the International Conference on Harmonisation GCP guidelines (1996), and European Guidelines.

Supporting Evidence

Study SPD120

This was a single-dose, open-label study conducted in the United States in adult subjects age 18-85 years. The primary objective of this study was to assess the pharmacokinetics of lisdexamfetamine and *d*-amphetamine following a single dose of SPD489 30mg in subjects with normal renal function and varying degrees of impaired renal function including End Stage Renal Disease (ESRD). The two secondary objectives were to evaluate the dialyzability of lisdexamfetamine and *d*-amphetamine, and to assess the safety and tolerability of SPD489. The study design diagram is presented in Figure 2. Subjects with ESRD (Group 5) were evaluated both pre-dialysis (Treatment Period 1) and post-dialysis (Treatment Period 2).

Figure 2: Study Design Diagram**Groups 1 to 4****Group 5**

Subjects were enrolled into 1 of 5 renal function groups (see Table 2) based on creatinine clearance at the Screening Visit as calculated by the Modification of Diet in Renal Disease (MDRD) equation. For subjects with ESRD, creatinine clearance was also calculated prior to the start of Period 2.

Table 2: Definition of Renal Function Groups

Group	Description	Estimated GFR
1	Normal renal function	$\geq 90 \text{ mL/min/1.73m}^2$
2	Mild renal impairment	≥ 60 to $\leq 89 \text{ mL/min/1.73m}^2$
3	Moderate renal impairment	≥ 30 to $\leq 59 \text{ mL/min/1.73m}^2$
4	Severe renal impairment. OR ESRD not requiring hemodialysis	≥ 15 to $\leq 29 \text{ mL/min/1.73m}^2$. OR $< 15 \text{ mL/min/1.73m}^2$
5	ESRD requiring hemodialysis	Not applicable

ESRD=end-stage renal disease; GFR=glomerular filtration rate; min=minute

On dosing day (Day 1), subjects in Groups 1-4 received a single SPD489 30mg dose. Subjects in Group 5 received a single SPD489 30mg dose on Day 1 of Treatment Period 1 and a second single SPD489 30mg dose on Day 1 of Treatment Period 2 with a 7- to 14-day washout between the two treatment periods. Pharmacokinetic blood sampling occurred pre-dose and at ½, 1, 1½, 2, 3, 4, 6, 8, 12, 24, 30, 48, 72, and 96 hours post dose for Groups 1-4. Group 5 subjects were also assessed at 9 and 10 hours post dose. Paired arterio-venous plasma, regular plasma, and dialysate concentrations of lisdexamfetamine and *d*-amphetamine were measured using validated liquid chromatography, with tandem mass spectrometry methods.

All the pharmacokinetic analyses were performed using the Pharmacokinetic Analysis Set, defined as all subjects in the Safety Analysis Set for whom the primary pharmacokinetic data were considered sufficient and interpretable. The Safety Analysis Set is defined as all subjects who took at least one dose of investigational product and had at least one post dose safety assessment.

Safety was evaluated by collecting reported adverse events (AEs) at regular intervals throughout the study and by the assessment of clinical laboratory evaluations, vital signs

measurements, and 12-lead electrocardiograms (ECGs). Serial blood pressure and pulse measurements were obtained prior to dosing through 96 hours post dose in each period.

Study Population

The study enrolled 40 adults, with eight subjects in each of the five renal function groups. Potential subjects were excluded if they had a history of uncontrolled moderate to severe hypertension or had a resting sitting systolic blood pressure >149mmHg or diastolic blood pressure >90mmHg at the Screening Visit or on the day prior to dosing; had any clinically significant ECG or clinical laboratory abnormalities; or clinically significant cardiovascular disease.

All 40 subjects completed the study and were included in both the Safety Analysis Set and the Pharmacokinetic Analysis Set. Subjects in the Safety Analysis Set consisted of 23 male and 17 female subjects with a mean age of 61.6 years (range 40-76 years). Subjects in the normal and mild renal impairment group were primarily female (75% in both groups), while subjects in the moderate renal impairment group (87.5% male), severe renal impairment group (62.5% male), and ESRD group (87.5% male) were primarily male. The majority of subjects were white (62.5%) and identified themselves as not Hispanic or Latino (57.5%). The mean body mass index for subjects in the study was 28.928 kg/m².

Bioanalytical Measurements

For the prodrug lisdexamfetamine:

- In samples from subjects with ESRD requiring dialysis (Group 5), variations in lisdexamfetamine concentrations were observed during sample re-assay and incurred sample reproducibility evaluation. After a thorough investigation, it was determined that these variations resulted from factor(s) in the plasma of Group 5 subjects. The plasma used in the pre-study validation was from subjects whose renal function impairment was not as severe as that of Group 5 subjects in this study.
- Lisdexamfetamine concentration data for samples from subjects in Groups 1-4 were determined to be accurate. The analytical methods for quantitation of lisdexamfetamine concentrations in human plasma and human dialysate were demonstrated to be acceptable.

For the active metabolite *d*-amphetamine:

- *d*-amphetamine concentration data were determined to be accurate for all renal function groups (Groups 1-5). The analytical methods for quantitation of *d*-amphetamine concentrations in human plasma and human dialysate were demonstrated to be acceptable.

In summary, variations in lisdexamfetamine quantitation were observed only for samples from Group 5 subjects. There was no effect on *d*-amphetamine quantitation in samples from any renal function group.

Lisdexamfetamine Results

For subjects with mild, moderate, or severe renal impairment (Groups 2-4), plasma lisdexamfetamine concentrations versus time curves were generally similar to those for subjects with normal renal function. Mean plasma lisdexamfetamine concentrations peaked at 1 hour post-dose and returned to pre-dose levels at 4-6 hours post-dose. A summary of selected lisdexamfetamine pharmacokinetic parameters following administration of SPD489 30mg is presented in Table 3. For subjects with mild, moderate, and severe renal impairment, the lisdexamfetamine mean C_{max} and mean AUC_{last} were not substantially different from normal subjects. Mean weight-corrected CL_F for subjects with mild and moderate renal impairment (19.3-20.4L/hr/kg) was similar to that for subjects with normal renal function (17.0L/hr/kg). The mean weight-corrected CL_F for subjects with severe renal impairment (13.0L/hr/kg) was somewhat less compared to subjects with normal renal function.

Generally, in subjects with ESRD requiring dialysis (Group 5), the mean plasma lisdexamfetamine concentrations peaked at 1.5 hours post-dose. These subjects had higher means for C_{max} and AUC_{last} compared to subjects with normal renal function. For all renal function groups (Groups 1-5), the median lisdexamfetamine t_{max} (range 1.0-1.3hrs), and $t_{1/2}$ (range 0.5-0.7hrs) were generally similar.

Table 3: Summary of Selected Lisdexamfetamine Pharmacokinetic Parameters in Plasma by Renal Function Group (Pharmacokinetic Analysis Set)							
Parameter	Statistic	Renal Function Group					
		Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe ^a Renal Impairment	ESRD	
						Period 1 (Dose Pre-dialysis)	Period 2 (Dose Post-dialysis)
C_{max} (ng/mL)	n	8	8	8	8	8	8
	Mean	15.7	16.0	12.8	13.9	60.7	37.7
	(SD)	(3.3)	(10.5)	(3.7)	(9)	(120.3)	(71)
	Median	15.1	14.1	11.9	13.1	19.7	12.8
	%CV	21.2	66	29.0	65.2	198.2	188.6
	Min-max	11.7-21.2	7.9-40.8	7.7-17.5	3.8-30.7	7.6-358	5.3-213
AUC_{last} (ng·h/mL)	n	8	8	8	8	8	8
	Mean	17.5	16.7	15.5	19.2	1244.3	864.5
	(SD)	(4.5)	(12.6)	(5.9)	(10)	(2768.9)	(2094.1)
	Median	18.4	13.0	14.9	17.3	323.3	149
	%CV	25.6	75.3	38.2	51.9	222.5	242.2
	Min-max	12.5-25.8	8.3-47.4	6.5-27.3	5.1-33.5	7.2-8064.7	5.1-6038.8
CL_F (L/hr/kg)	n	2	2	5	4	2	0
	Mean	17.0	19.3	20.4	13.0	13.1	Statistics not calculable with the available data
	(SD)	(2.6)	(16.1)	(4.7)	(2.9)	(1.7)	
	Median	17.0	19.3	19.7	11.8	13.1	
	%CV	15.5	83.4	23.2	22.2	12.6	
	Min-max	15.1-18.8	7.9-30.7	14.5-25.5	11.0-17.3	11.9-14.2	

^a Severe includes subjects with ESRD not requiring hemodialysis.

AUC_{last} =area under the curve from the time of dosing to the last measurable concentration; CL_F =total body clearance for extravascular administration divided by the fraction of dose absorbed (weight-corrected); C_{max} =maximum concentration occurring at t_{max} ; CV=coefficient of variation; ESRD=end-stage renal disease; max=maximum; min=minimum; SD=standard deviation

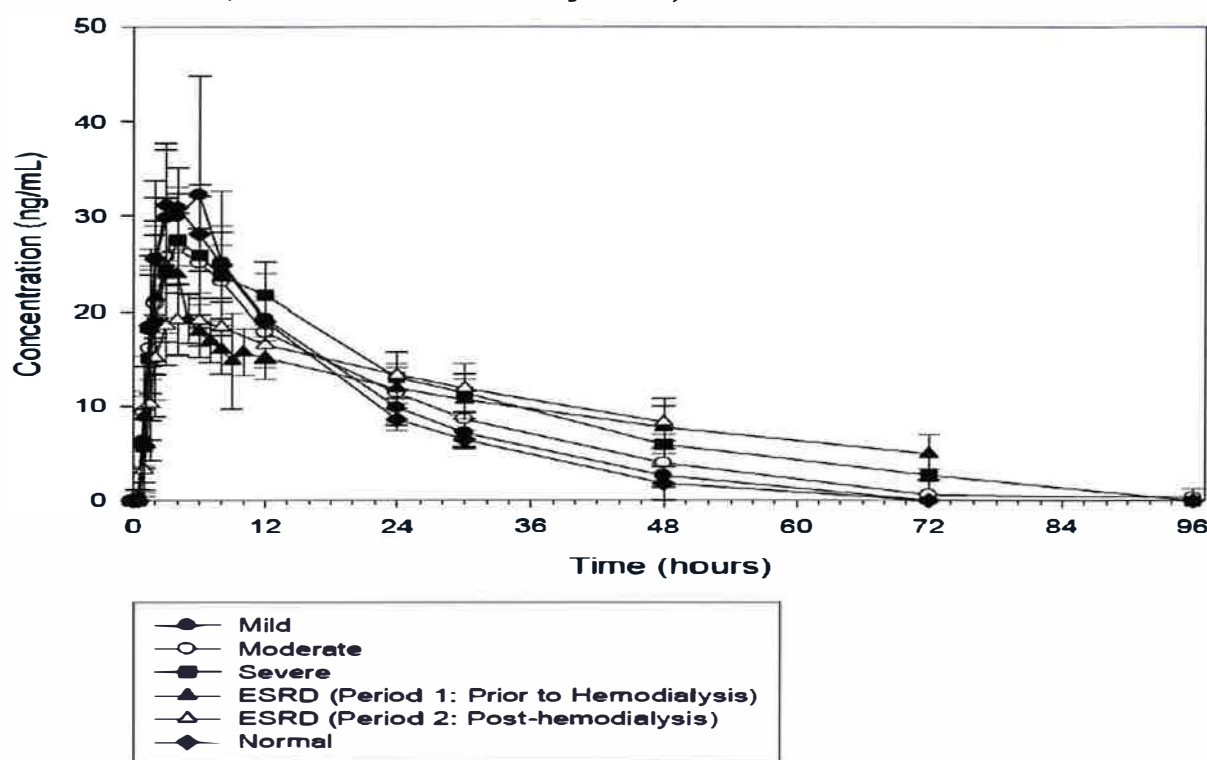
In order to examine the relationship between lisdexamfetamine pharmacokinetic parameters and renal function (estimated by both the Cockcroft-Gault and the MDRD equations), a regression analysis was performed across the range of renal function groups. There were no strong correlations between renal function and pharmacokinetic parameters.

For the eight ESRD subjects requiring dialysis (Group 5), lisdexamfetamine concentrations in dialysate were measured following SPD489 administration. Almost no lisdexamfetamine was recovered in the dialysate; the mean percent recovered was 0% (range 0%-0.1%).

d-amphetamine Results

Plasma concentrations versus time curves for d-amphetamine were generally similar for all renal function groups (see Figure 3); however, peak concentrations were slightly lower in subjects with ESRD.

Figure 3: Mean ($\pm$ SD) d-amphetamine Plasma Concentrations versus Time (Linear Scale, Pharmacokinetic Analysis Set)



Note: Severe includes ESRD subjects not requiring hemodialysis.

d-amphetamine=dextroamphetamine; ESRD=end-stage renal disease; SD=standard deviation

Following the administration of SPD489 30mg, the mean d-amphetamine AUC_{last} increased, whereas the mean C_{max} decreased with increasing renal impairment relative to subjects with normal renal function (see Table 4).

The mean weight-corrected CL/F value among subjects with renal impairment was lowest in subjects with ESRD (0.3L/hr/kg in both periods) compared with 0.7L/hr/kg in subjects with normal renal function; this represents an approximately 50% decrease.

Median t_{max} was similar in all the groups, ranging from 3-4 hours. Median $t_{1/2}$ increased with increasing renal impairment. The shortest median $t_{1/2}$ was observed in subjects with normal renal function (11.4 hours), and the longest median time observed in subjects with ESRD (34.6-37.0 hours).

Table 4: Summary of Selected *d*-amphetamine Pharmacokinetic Parameters in Plasma by Renal Function Group (Pharmacokinetic Analysis Set)

		Renal Function Group					
		Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe ^a Renal Impairment	ESRD	
						Period 1 (Dose Pre-dialysis)	Period 2 (Dose Post-dialysis)
Parameter	Statistic	n=8	n=8	n=8	n=8	n=8	n=8
C_{max} (ng/mL)	Mean	32.2	35.1	27.5	28.4	25.5	20.1
	(SD)	(5.3)	(11.1)	(4.9)	(5.9)	(8)	(3.3)
	Median	34.2	32.2	26.9	27.6	23.1	20
	%CV	16.3	31.7	17.7	20.6	31.3	16.4
	Min-max	21.9-38.5	24.1-56.6	21.5-36.6	19.9-35.8	18-43.3	14.8-24
AUC_{last} (ng·h/mL)	Mean	527.9	577.1	610.6	779.5	741.8	623.8
	(SD)	(69.9)	(117.9)	(170.7)	(146.1)	(134.8)	(102)
	Median	535.2	550.4	612.3	750.2	751.6	626.2
	%CV	13.2	20.4	27.9	18.7	18.2	16.4
	Min-max	431.1-616.6	436.6-781.7	321.3-920.8	601.7-1001.3	528.2-968.8	459.3-743.4
CL/F (L/hr/kg)	Mean	0.7	0.7	0.5	0.4	0.3	0.3
	(SD)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.2)
	Median	0.7	0.7	0.6	0.4	0.3	0.3
	%CV	8.9	18.5	25.7	14.1	36.8	54
	Min-max	0.6-0.8	0.5-0.9	0.3-0.8	0.3-0.5	0.2-0.6	0.2-0.7
$t_{1/2}$ (hr)	Mean	12.1	12.8	16.8	19.8	40.9	38.2
	(SD)	(2.5)	(2)	(5.2)	(1.9)	(16.3)	(16.5)
	Median	11.4	12.5	15.7	19.8	34.6	37.0
	%CV	20.4	15.6	30.8	9.4	39.9	43.3
	Min-max	9.9-17.6	9.7-15.8	12-28	16.6-22.4	23.5-67.7	18.3-73.9

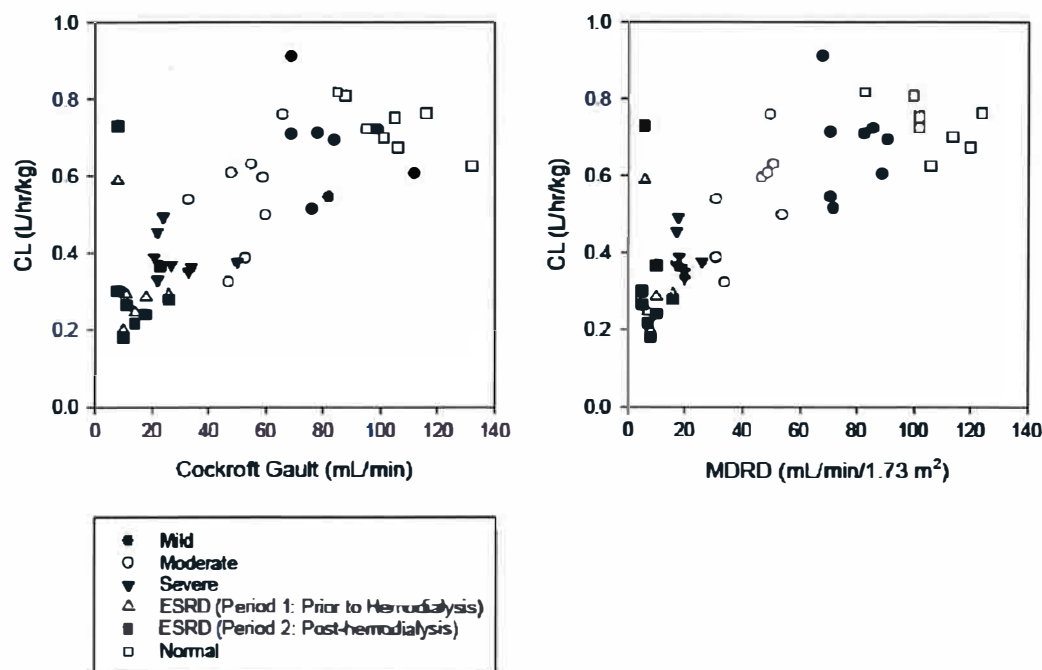
^a Severe includes subjects with ESRD not requiring hemodialysis.

AUC_{last} =area under the curve from the time of dosing to the last measurable concentration; $AUC_{0-\infty}$ =area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration; CL/F =total body clearance for extravascular administration divided by the fraction of dose absorbed; C_{max} =maximum concentration occurring at t_{max} ; CV=coefficient of variation; *d*-amphetamine=dextroamphetamine; ESRD=end-stage renal disease; max=maximum; min=minimum; SD=standard deviation $t_{1/2}$ =terminal half-life.

In order to examine the relationship between *d*-amphetamine pharmacokinetic parameters and renal function (estimated by both the Cockcroft-Gault and the MDRD equations), a regression analysis was performed across the range of renal function groups. Data from subjects with ESRD during Period 2 (post-dialysis) were excluded from the analysis.

As renal impairment increased, *d*-amphetamine exposure (AUC) increased, and weight-corrected *d*-amphetamine clearance (see Figure 4) decreased. There were relatively strong correlations between renal function and AUC_{inf} as well as weight-adjusted CL/F . When renal function was estimated using the Cockcroft-Gault equation, the R_2 for AUC_{inf} was 0.404, and the R_2 for CL/F was 0.593. Similar results were obtained when renal function was estimated using the MDRD equation.

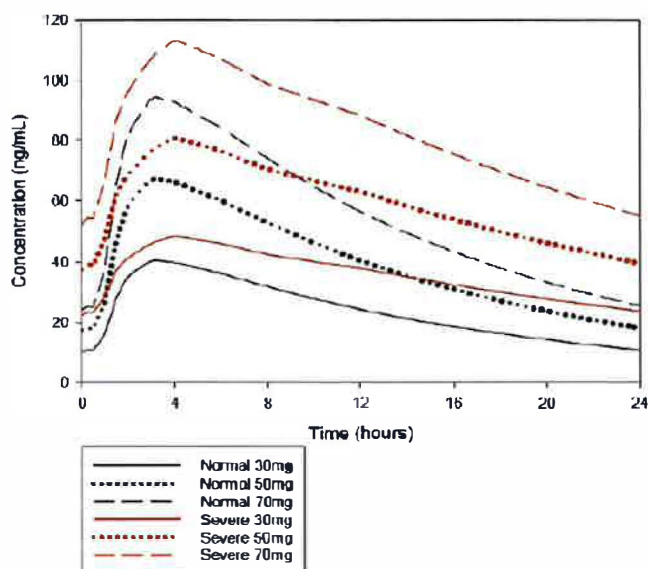
No apparent trends were noted between renal function and other *d*-amphetamine pharmacokinetic parameters.

Figure 4: Individual *d*-amphetamine Weight-corrected Clearance Versus Renal Function (Pharmacokinetic Analysis Set)

Note: Severe includes subjects with ESRD not requiring hemodialysis.

CL=clearance; *d*-amphetamine=dextroamphetamine; ESRD=end-stage renal disease; MDRD=Modification of Diet in Renal Disease

For the eight ESRD subjects requiring dialysis (Group 5), *d*-amphetamine concentrations in dialysate were measured following SPD489 administration. Very little *d*-amphetamine was recovered in the dialysate; the mean percent recovered was 2.63% (range, 2.18-3.30%). Simulations were performed in order to better assess the impact of severe renal function on the plasma concentration of *d*-amphetamine over time. Steady-state *d*-amphetamine plasma concentrations (see Figure 5) and pharmacokinetic parameters (see Table 5) have been simulated for subjects with normal renal function and for subjects with severe renal impairment (Group 4 subjects) at three SPD489 dose strengths (30, 50, and 70mg). These dose-based simulations suggest that in patients with severe renal insufficiency (Glomerular Filtration Rate [GFR] between 15 to <30mL/min/1.73m²) the maximum daily dose should not exceed 50mg.

Figure 5: Simulated Steady-state *d*-amphetamine Plasma Concentrations for Subjects with Normal Renal Function and Severe Renal Impairment

d-amphetamine=dextroamphetamine

Table 5: Simulated Steady-state *d*-amphetamine Pharmacokinetic Parameters for Subjects with Normal Renal Function and Severe Renal Impairment

Renal Function Group		C_{max} (ng/mL)	AUC_{tau} (ng.h/mL)
Normal Renal Function	30mg	40.38	572.0
	50mg	67.30	953.3
	70mg	94.22	1334.6
Severe Renal Impairment	30mg	48.40	856.6
	50mg	80.66	1427.7
	70mg	112.92	1998.8

AUC_{tau} =area under the curve for the defined interval between doses; C_{max} =maximum concentration occurring at t_{max} ;
d-amphetamine=dextroamphetamine

Pharmacokinetic Summary

The results of this study demonstrate that exposure to the pharmacologically active metabolite *d*-amphetamine increases as renal impairment increases due to an increase in the $t_{1/2}$ of *d*-amphetamine. Based on the data obtained in the study and simulations performed to assess the impact of severe renal function on the plasma concentration of *d*-amphetamine over time, it is recommended that in patients with severe renal insufficiency (GFR between 15 to <30mL/min/1.73m²), the maximum daily dose of SPD489 should not exceed 50mg. Further dosage reduction should be considered in patients undergoing dialysis.

Neither lisdexamfetamine nor *d*-amphetamine is dialyzable.

Safety

Treatment-emergent adverse events (TEAEs) were reported by 14 (35.0%) of the 40 subjects in the study. There were no serious AEs and no discontinuations due to an AE during the conduct of this study. There were no severe AEs; all AEs were of mild or moderate intensity (primarily mild).

TEAEs considered treatment related were those typically associated with stimulant therapy, including dizziness, dry mouth, insomnia, headache, and blood pressure increased. The frequencies of TEAEs did not appear to increase with increasing renal impairment.

Table 6: Treatment-emergent Adverse Events by Preferred Term and Renal Function Group (Safety Analysis Set)

Preferred Term	Normal Renal Function (N=8)			Mild Renal Impairment (N=8)			Moderate Renal Impairment (N=8)			Severe ^a Renal Impairment (N=8)			ESRD (N=8)			Total (N=40)		
	n	(%)	m	n	(%)	m	n	(%)	m	n	(%)	m	n	(%)	m	n	(%)	m
Any TEAE	3	(37.5)	4	4	(50.0)	6	3	(37.5)	3	2	(25.0)	2	2	(25.0)	3	14	(35.0)	18
Dizziness	1	(12.5)	1	0			1	(12.5)	1	0			0			2	(5.0)	2
Feeling of relaxation	0			2	(25.0)	2	0			0			0			2	(5.0)	2
Blood pressure increased	0			1	(12.5)	1	1	(12.5)	1	0			0			2	(5.0)	2
Nausea	1	(12.5)	1	0			0			0			0			1	(2.5)	1
Vomiting	1	(12.5)	1	0			0			0			0			1	(2.5)	1
Dry mouth	0			1	(12.5)	1	0			0			0			1	(2.5)	1
Eructation	0			1	(12.5)	1	0			0			0			1	(2.5)	1
Headache	0			0			0			1	(12.5)	1	0			1	(2.5)	1
Somnolence	0			0			1	(12.5)	1	0			0			1	(2.5)	1
Insomnia	1	(12.5)	1	0			0			0			0			1	(2.5)	1
Musculoskeletal pain	0			0			0			0			1	(12.5)	1	1	(2.5)	1
Pain in extremity	0			0			0			0			1	(12.5)	1	1	(2.5)	1
Oropharyngeal pain	0			0			0			1	(12.5)	1	0			1	(2.5)	1
Pruritus generalised	0			1	(12.5)	1	0			0			0			1	(2.5)	1
Hypotension	0			0			0			0			1	(12.5)	1	1	(2.5)	1

^a Severe includes ESRD patients not requiring hemodialysis.

Note: Subjects were counted once per preferred term, per renal function group. Percentages were based on all subjects in the Safety Analysis Set. Adverse events were classified into preferred term using Version 16.0 of MedDRA.

ESRD=end-stage renal disease; m=number of events; TEAE=treatment-emergent adverse event

Pulse rate and blood pressure (BP) were measured across the dosing day. Increases in pulse rate and BP occurred in all groups after administration of investigational product, consistent with the changes expected in subjects receiving stimulant therapy. For subjects with normal renal function groups as well as subjects with mild, moderate, and severe renal impairment, pulse rates gradually increased from baseline with a peak mean maximum increase from baseline occurring between approximately 6-12 hours post dose.

In conclusion, SPD489 was well-tolerated by normal subjects and subjects with varying degrees of impaired renal function. There were no apparent differences in safety profile among subjects in the various groups. The frequencies of TEAEs did not increase with increasing renal impairment. Blood pressure and pulse rates increases were generally consistent with the changes observed in previous studies of SPD489 enrolling healthy normal volunteers. For subjects with ESRD requiring dialysis, there were no apparent differences in the safety profiles between Period 1 (pre-dialysis) and Period 2 (post dialysis).

Conclusions

A decrease in the glomerular filtration of excreted substances is a hallmark of renal dysfunction, and the results of this study demonstrate that median $t_{1/2}$ of *d*-amphetamine (the pharmacologically active metabolite) increases with the severity of renal impairment. The mean weight-corrected C_{LF} was approximately 50% lower in subjects with ESRD compared to subjects with normal renal function. Further, the relatively alkaline urine associated with renal impairment may also reduce urinary *d*-amphetamine excretion.

Based on the results of simulations of the steady state *d*-amphetamine plasma concentrations, as well as a comparison of pharmacokinetic parameters in subjects with severe renal impairment to those with normal renal function, it is recommended that the prescribing information be updated to limit the maximum daily dose of SPD489 to 50mg in patients with severe renal insufficiency (GFR 15-30mL/min/1.73m²). Further dosage reduction should be considered in patients undergoing dialysis. It is agreed that there is no need for dose adjustment in patients with moderate renal impairment.

Additionally, the prescribing information will be updated to state that lisdexamfetamine and *d*-amphetamine are not dialyzable.

No clear relationship to degree of renal impairment was seen for the known cardiovascular effects of SPD489. It is agreed that there are no new safety issues identified in relation to renal impairment, subject to the maximum dose of 50mg in severe renal impairment.

SmPCs and a PIL have been updated satisfactorily.

The grant of this variation is recommended.

Decision	-	Granted
Date	-	07 January 2015