This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

• All named persons associated with the study
• Patient identifiers within text, tables, or figures
• By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.
STUDY SYNOPSIS

Name of sponsor/company: Shire
Name of finished product: VYVANSE®, VENVANSE®
Name of active ingredient: Lisdexamfetamine dimesylate
Title of the study: A Phase 4, Open-label, Multicentre, 2-Year Safety Study of Lisdexamfetamine Dimesylate in Children and Adolescents Aged 6-17 Years with Attention-Deficit/Hyperactivity Disorder (ADHD)
Investigator(s): Coordinating Principal Investigator:
Dr. [redacted]
United Kingdom
Study center(s): This was a multicenter study conducted at 35 sites in Europe.
Publications (references): None
Study period: 07 Jul 2011 to 30 Sep 2014
Phase of development: Phase 4
Objectives:
The primary objective of this study was to evaluate the long-term safety of SPD489 administered as a daily morning dose (30, 50, and 70 mg) in the treatment of children and adolescents (6-17 years of age, inclusive, at the time of consent in this study or a previous SPD489 study [SPD489-317, SPD489-325, or SPD489-326] diagnosed with moderate to severely symptomatic ADHD.

The evaluation of safety was based on the occurrence of treatment-emergent adverse events (TEAEs), evaluation of vital signs, and electrocardiogram (ECG) results. Additionally, the effects on growth, sexual development, and neurocognition were assessed and psychiatric adverse events (AEs) including psychosis and suicidality were monitored.

The secondary objectives of this study were:
1. To assess the long-term efficacy of SPD489 using the clinician-administered ADHD-rating scale-IV (ADHD-RS-IV) total score and hyperactivity/impulsivity and inattention (“inattentiveness”) subscale scores.
2. To assess the long-term efficacy of SPD489 using global clinical measures of severity and improvement as measured by the Clinical Global Impressions–Severity of Illness (CGI-S) and Clinical Global Impressions–Global Improvement (CGI-I).
Name of sponsor/company: Shire

Name of finished product: VYVANSE®, VENVANSE®

Name of active ingredient: Lisdexamfetamine dimesylate

Methodology: This study was a Phase 4, multicenter, open-label study designed to evaluate the safety of SPD489 administered as a daily morning dose (30, 50, or 70 mg) for up to 104 weeks (2 years). Children and adolescents (6-17 years of age, inclusive, at time of consent in this study or a previous SPD489 study [SPD489-317, SPD489-325, or SPD489-326]) who had been diagnosed with ADHD were enrolled and treated for up to 104 weeks to evaluate the long-term safety and efficacy of SPD489. The study had 3 phases: (1) screening and washout; (2) a 104-week treatment phase inclusive of a 4-week Dose Optimization Period and a 100-week Maintenance Period; and (3) a safety follow-up visit (28-30 days after the last dose of investigational product). Subjects were required to visit the site up to 16 times over a 109- to 114-week period.

Subjects were screened to establish eligibility for study participation. Those who met eligibility requirements were required to undergo medication washout, if applicable. The length of the screening and washout phase ranged from 3-42 days as specified in the protocol.

Eligible subjects who were new to treatment with SPD489 (eg, had not participated in a previous SPD489 study) with a baseline ADHD-RS-IV total score \( \geq 28 \) were enrolled to receive treatment with SPD489. Subjects who participated in a previous SPD489 study (SPD489-317, SPD489-325, or SPD489-326) who had a gap in participation (>7 days) between exiting the previous study and entering this study were required to have a baseline ADHD-RS-IV total score \( \geq 28 \) in order to be enrolled to receive continued treatment with SPD489. This criterion did not apply to subjects who entered the study directly from the previous SPD489 study without any gap in participation (\( \leq 7 \) days).

During the first 4 weeks of treatment, visits were scheduled every 7 days (±3 days) to assess safety and tolerability, and to allow clinicians to titrate subjects to their optimal dose of SPD489 based on TEAEs and clinical judgment. All subjects were started at 30 mg and were titrated in weekly increments of 20 mg until an optimal dose was reached (up to a maximum of 70 mg/day). Titration to a lower dose level was permitted in decrements of 20 mg to a minimum dose of 30 mg. The investigator categorized subject response into 1 of the 3 conditions (Intolerable, Ineffective, and Acceptable Response).

Following titration to an optimal dose of SPD489, subjects continued daily morning treatment with SPD489 for the next 100 weeks. During the Maintenance Period, the investigator was permitted to make further dose adjustments based upon TEAEs and the investigator’s clinical judgment of effectiveness and tolerability.

Four weeks (+2 days) following the last dose of investigational product, subjects returned to the site for a follow-up visit (Visit 14). Visit 14 served as the safety follow-up for all subjects.

Number of subjects (planned and analyzed): At least 300 evaluable subjects were planned to be enrolled from sites within Europe and the US. Approximately 50% of the subjects enrolled could have participated in a prior SPD489 study (SPD489-317, SPD489-325 or SPD489-326).

In total, 314 children and adolescents were enrolled, including 124 rollover subjects from an antecedent study (SPD489-317, SPD489-325, or SPD489-326) and 190 subjects not previously enrolled in studies with SPD489. All of the 314 enrolled subjects were included in the Safety Population (ie, received at least 1 dose of SPD489 in this study). Of the 314 enrolled subjects, 299 (95.2%) subjects were included in the full analysis set (FAS) (ie, took at least 1 dose of SPD489 and had at least 1 on-treatment post baseline efficacy assessment). The FAS excluded 1 subject who was without post baseline efficacy data and 14 additional subjects from Site [ ] due to a serious breach of GCP identified during a site monitoring visit for another Shire study and reported to applicable regulatory authorities.
Name of sponsor/company: Shire

Name of finished product: *VYVANSE®, ENVANSE®*

Name of active ingredient: Lisdexamfetamine dimesylate

**Diagnosis and main criteria for inclusion:**

**Main inclusion criteria:**

- Subject was a male or female aged 6-17 years inclusive at the time of consent for the previous SPD489 study.
- Subject participated in SPD489-317, completed 9 weeks of treatment, and completed the 1-week post-treatment safety follow-up visit.

- Subject was a male or female aged 6-17 years inclusive at the time of consent.
- Subject met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision* (DSM IV TR™) criteria for a primary diagnosis of ADHD based on a detailed psychiatric evaluation.

- Subject had a baseline (Visit 0) ADHD-RS-IV total score $\geq 28$.
- Subjects who were females of childbearing potential had a negative serum beta human chorionic gonadotropin pregnancy test at screening (Visit –1) and a negative urine pregnancy test at baseline (Visit 0), were non-lactating, and agreed to comply with any applicable contraceptive requirements of the protocol.
- Subject’s parent or legally authorized representative (LAR) provided signature of informed consent, and there was documentation of assent (if applicable) by the subject indicating that the subject was aware of the investigational nature of the study and the required procedures and restrictions in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 and applicable regulations, before completing any study-related procedures.
- Subject and parent/LAR were willing and able to comply with all the testing and requirements defined in this protocol, including oversight of morning dosing. Specifically, the parent/LAR was to be available upon awakening, at approximately 7:00AM, to dispense the dose of investigational product for the duration of the study.
- Subjects aged 6-17 years had blood pressure measurements within the 95th percentile for age, sex, and height at screening (Visit –1) and baseline (Visit 0). Subjects aged $\geq 18$ years had a systolic blood pressure (SBP) $\leq 139$ mmHg and a diastolic blood pressure (DBP) $\leq 89$ mmHg at screening (Visit –1) and baseline (Visit 0).
- Subject was functioning at an age-appropriate level intellectually, as deemed by the study investigator.
- Subject was able to swallow a capsule.

**Main exclusion criteria:**

- Subject was terminated from a previous SPD489 study (SPD489-325 or SPD489-326) for protocol non-adherence and/or subject non-compliance and/or experienced a medication-related serious adverse event (SAE) or AE resulting in termination from the previous study.
- Subject experienced any clinically significant AEs in a prior SPD489 study (SPD489-317, SPD489-325, or SPD489-326) that, in the opinion of the investigator, would preclude further exposure to SPD489.
For all subjects:

- Subject’s symptoms were well-controlled on their currently prescribed ADHD medication with acceptable tolerability.
- Subject had a positive urine drug result at screening (Visit –1), with the exception of the subject’s current ADHD therapy.
- Subject had a current, controlled (requiring a restricted medication) or uncontrolled, comorbid psychiatric diagnosis with significant symptoms such as any severe comorbid Axis II disorder or severe Axis I disorder (such as post-traumatic stress disorder, psychosis, bipolar illness, pervasive developmental disorder, severe obsessive compulsive disorder, severe depressive or severe anxiety disorder) or other symptomatic manifestations, such as agitated states, marked anxiety, or tension that, in the opinion of the examining clinician, would contraindicate treatment with SPD489 or confound efficacy or safety assessments. Comorbid psychiatric diagnoses were established using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-age Children–Present and Lifetime Version–Diagnostic Interview (K-SADS-PL) and additional modules if warranted by the results of the initial interview. Participation in behavioral therapy was permitted.
- Subject had taken another investigational product or taken part in a clinical study with the exception of a prior SPD489 study (SPD489-317, SPD489-325, or SPD489-326) within 30 days prior to screening (Visit -1).
- Subject weighed <22.7 kg (50 lbs) or was significantly underweight based on World Health Organization Body Mass Index (BMI)-for-age sex-specific charts at screening (Visit –1). Significantly underweight was defined as a BMI <3rd percentile for this study.
- Subject was significantly overweight based on World Health Organization BMI-for-age sex-specific charts at screening (Visit –1). Significantly overweight was defined as a BMI >97th percentile for this study.
- Subject had a conduct disorder. Oppositional defiant disorder was not exclusionary.
- Subject had a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition that might confound the results of safety assessments conducted in the study or that might increase risk to the subject. Similarly, the subject was excluded if he or she had any additional condition(s) that, in the investigator’s opinion, would prohibit the subject from completing the study or would not be in the best interest of the subject. The additional condition(s) included any significant illness or unstable medical condition that could lead to difficulty complying with the protocol. Mild, stable asthma was not exclusionary.
- Subject was currently considered a suicide risk in the opinion of the investigator, had previously made a suicide attempt, or had a prior history of, or is currently demonstrating active suicidal ideation. Subjects with intermittent passive suicidal ideation were not necessarily excluded based on the assessment of the investigator.
- Subject had glaucoma.
- Subject had current abnormal thyroid function, defined as abnormal thyroid-stimulating hormone and thyroxine at screening (Visit –1). Treatment with a stable dose of thyroid medication for at least 3 months was permitted.
- Subject had any clinically significant ECG abnormality at screening (Visit –1) or baseline (Visit 0).
- Subject had any clinically significant laboratory abnormalities at screening (Visit –1) or baseline (Visit 0) if repeated.
- Subject had a documented allergy, hypersensitivity or intolerance to any active ingredient or excipients in SPD489.
- Subject had a recent history (within the past 6 months) of suspected substance abuse or dependence disorder (excluding nicotine) in accordance with DSM-IV-TR criteria.
- Subject had a history of seizures (other than infantile febrile seizures), a chronic or current tic disorder, a current diagnosis of Tourette’s Disorder, or a known family history of Tourette’s Disorder. Subject had a history of tics that was judged by the investigator to be exclusionary.
- Subject had a known history of symptomatic cardiovascular or cerebrovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may have placed them at increased vulnerability to the sympathomimetic effects of a stimulant drug.
- Subject had a known family history of sudden cardiac death or ventricular arrhythmia.
- Subject was taking any medication that was excluded.
- Subject had a medical condition, other than ADHD, that required treatment with medications that have central nervous system effects and/or affect performance. Stable use of anticholinergic or theophylline bronchodilators was not exclusionary.

Investigational product, dose, mode of administration, and batch number(s):
Lisdexamfetamine dimesylate (SPD489), VYVANSE®, VENVANSE®
Subjects were instructed to take 1 capsule daily at approximately 7:00AM

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Reference product(s), dose, mode of administration, and batch number(s): Not applicable. This was an open-label study.

Duration of treatment:
- Screening and Washout Phase: 3-42 days
- Treatment Phase: 104 weeks inclusive of:
  - Dose Optimization Period: 4 weeks
  - Maintenance Period: 100 weeks
- Follow-up Visit: 28-30 days after the last dose of investigational product
Name of sponsor/company: Shire

Name of finished product: Vyvanse®, Venvanse®

Name of active ingredient: Lisdexamfetamine dimesylate

Criteria for evaluation:

Efficacy:
- ADHD-RS-IV
- Clinical Global Impressions (CGI)

Safety
- Medical and medication history
- Physical examination
- 12-Lead ECG
- Cambridge Neuropsychological Test Automated Battery (CANTAB)
- Tanner Staging
- Brief Psychiatric Rating Scale for Children (BPRS-C)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Adverse events
- Clinical laboratory evaluations (biochemistry, hematology, urinalysis)
- Vital signs

Statistical methods:

Study populations were defined as follows:
The **Enrolled Population** included all subjects who were dispensed SPD489 product at baseline (Visit 0).
The **Safety Population** included all subjects who took at least 1 dose of SPD489 during this study. This was the population used for assessing safety information (including effects on growth, sexual development, neurocognition and psychiatric AEs).
The **FAS** included all subjects who took at least 1 dose of SPD489 during this study and had at least 1 on-treatment, post-baseline assessment for any efficacy variable. This was the population used for assessing efficacy information.

Categorical variables were summarized using number of observations and percentages, and continuous variables were summarized using descriptive statistics.

All AEs, including TEAEs, were summarized by system organ class and preferred term for number of subjects and proportion reporting the event. A similar summary was produced for prior to treatment AEs, SAEs, AEs leading to termination, severe AEs, and AEs with at least a possible relationship to the investigational product. The intensity of AEs and the relationship to investigational product and withdrawals due to AEs were summarized for each system organ class and preferred term.

Summary statistics were presented for the ADHD-RS-IV total score and hyperactivity/impulsivity and inattention subscale scores, and changes from baseline (Visit 0), at each visit for both observed data, and applying the last observation carried forward (LOCF) technique.

The CGI-S and CGI-I were summarized (n, %) for each visit using both observed data, and applying the LOCF technique.
Name of sponsor/company: Shire

Name of finished product: **VYVANSE**, **VENVANSE**

Name of active ingredient: Lisdexamfetamine dimesylate

Results:

Safety results:
The majority of subjects (89.8%) had at least 1 TEAE during the study and most TEAEs were mild or moderate in intensity; severe TEAEs occurred in 37 (11.8%) subjects.

Decreased appetite (54.1%), nasopharyngitis (23.2%), headache (21.7%), and weight decreased (20.1%) were the most frequently reported TEAEs.

The majority of subjects (73.9%) had at least 1 TEAE that was considered by the investigator to be related to investigational product and those reported by more than 10.0% of subjects included decreased appetite (49.4%), weight decreased (18.2%), and insomnia (13.1%).

A similar percentage of children (6-12 years of age) and adolescents (13-17 years of age) experienced TEAEs (89.6% and 90.2%, respectively) and a similar percentage of males and females experienced TEAEs (88.8% and 93.8%, respectively).

No deaths were reported during this study.

Overall, 28 (8.9%) subjects experienced 36 serious TEAEs. Syncope, required to be reported per protocol as an SAE, was experienced by 6 (1.9%) subjects, appendicitis was experienced by 3 (1.0%) subjects, and pyelonephritis was experienced by 2 (0.6%) subjects. All other SAEs occurred in 1 subject each.

A total of 39 (12.4%) subjects discontinued investigational product and were terminated from the study due to at least 1 TEAE. The most common TEAEs leading to discontinuation of investigational product were decreased appetite (2.2%), drug ineffective (1.9%), irritability (1.3%), depressed mood (1.3%), and insomnia and tic (1.0% each). All but 5 of the 59 TEAEs leading to premature discontinuation were considered by the investigator to be related to investigational product.

Psychiatric TEAEs of special interest included psychosis/mania events (experienced by 1 subject), suicidal events (ideation in 2 subjects and attempt in 1 subject), aggression events (experienced by 17 subjects), and other events (experienced by no subjects).

SPD489 was generally associated with mean increases from baseline in pulse, SBP, and DBP, consistent with the known effects of stimulant treatment. The boxplots of change from baseline by visit for vital signs show that the following vital signs reach a plateau around Week 36 for pulse, Week 60 for SBP and Week 24 for DBP.

Initial small decreases from baseline in mean body weight and BMI were noted, consistent with the known effect of stimulant treatment. The z-scores for body weight and BMI tended to shift lower over the course of the first 36 weeks, and then to remain relatively stable.

No clinically concerning trends in ECG interval data were observed and no ECG-related TEAEs were reported for any subject.

Based on the CSSR-S, 7 subjects had suicidal ideation or behavior while on treatment; 1 subject had an actual suicide attempt reported as a TEAE.

Results of Tanner staging were consistent with physical/sexual maturation of the subjects over time (up to 2 years). Based on the CANTAB, there was no evidence of untoward cognitive safety signals associated with SPD489.
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**Safety results:**
The safety results over the first and second years of this study were generally consistent with the well documented safety profile associated with SPD489. Overall, SPD489 was generally well tolerated with no new trends or patterns in safety findings noted.

**Efficacy results:**
Improvements from baseline on ADHD RS IV total score and subscales were observed at all study visits, including at the last on-treatment assessment (LOTA).

On the CGI-I at LOTA, SPD489 treatment was associated with improvement for 77.9% of subjects. Greater than 80% or more of the subjects were “improved” from Week 4 onward.

Overall, age group and sex did not appear to modify the treatment effect for either the ADHD -RS-IV or the CGI-I results. Subgroup results were consistent with those determined using the FAS.

Although at baseline, no subjects were considered “normal, not at all ill” or “borderline mentally ill,” at LOTA, the majority of subjects were in these 2 categories (24.4% and 32.4%, respectively), and the overall pattern of CGI-S severity had shifted to less severe.

At LOTA, most of the subjects who received SPD489 were responders (30% responders: 77.3%; 50% responders: 69.2%).

**Conclusions:**
This section contained Summary and Conclusion information which could be considered promotional in nature. This section has been removed to allow the reader to draw their own conclusions.

**Date of report:** 26 Mar 2015