Maintenance of Efficacy of Lisdexamfetamine Dimesylate in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Randomized-Withdrawal Study Design

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Objective: In this phase 3 extension study, the long-term maintenance of efficacy of lisdexamfetamine dimesylate (LDX) in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) was evaluated using a randomized-withdrawal study design. **Method:** European and US patients (6–17 years; N = 276) with ADHD were entered into a 26-week open-label trial of LDX treatment. Those who completed the open-label period (n = 157) were randomized 1:1 to their optimized dose of LDX (30, 50, or 70 mg per day) or placebo for a 6-week randomized-withdrawal period (RWP). The primary efficacy measure was the proportion of patients meeting treatment failure criteria (≥50% increase in ADHD Rating Scale IV total score and ≥2-point increase in Clinical Global Impressions–Severity of Illness [CGI-S] score, compared with RWP start point). Safety and tolerability were also evaluated. **Results:** During the RWP (LDX, n = 78; placebo, n = 79), significantly fewer patients receiving LDX met treatment failure criteria (15.8%) compared with those receiving placebo (67.5%; difference = –51.7%; 95% confidence interval = –65.0, –38.5; $p < .001$). Most treatment failures occurred at or before the week 2 visit after randomization. Treatment-emergent adverse events were reported in 39.7% and 25.3% of patients receiving LDX and placebo, respectively, during the RWP. **Conclusions:** These data demonstrate the maintenance of efficacy of LDX during long-term treatment in children and adolescents with ADHD. The rapid return of symptoms on LDX withdrawal demonstrates the need for continuing treatment. The safety profile of LDX was consistent with that of other stimulants. Clinical trial registration information—Double-Blind, Placebo-Controlled, Randomized Withdrawal, Extension, Safety and Efficacy Study of LDX in Children and Adolescents Aged 6-17; http://clinicaltrials.gov; NCT00784654. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(6): 647–657. **Key Words:** attention-deficit/hyperactivity disorder, randomized controlled trial, central nervous system stimulants, lisdexamfetamine dimesylate, maintenance of efficacy

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in childhood, with an estimated worldwide prevalence of approximately 5%.[1,2] Pharmacological treatments for ADHD include amphetamine- and methylphenidate-based stimulant drugs, the nonstimulant norepinephrine reuptake inhibitor atomoxetine, and the α_2-adrenergic agonists clonidine and guanfacine.[1,3-6]

Supplemental material cited in this article is available online.

Lisdexamfetamine dimesylate (LDX) is the first prodrug stimulant[7] and is currently indicated for the treatment of ADHD in the USA, Canada, Brazil and certain European countries. After oral administration, LDX is rapidly absorbed from the gastrointestinal tract and is enzymatically hydrolyzed, primarily in the blood, resulting in the gradual release of therapeutically active *d*-amphetamine and the naturally occurring amino acid L-lysine.[8] The prodrug properties of LDX provide a long duration of action and low intra- and inter-patient variability in systemic exposure to *d*-amphetamine.[7,9]

The short-term efficacy of LDX has been established in a series of pivotal randomized, double-blind, placebo-controlled trials in the USA; significant improvements in ADHD Rating Scale IV (ADHD-RS-IV) scores were seen in children (aged 6–12 years), adolescents (aged 13–17 years) and adults (aged 18–55 years) with ADHD.[10-15] In addition, a laboratory school study in children and a simulated workplace study in adults showed that the effects of LDX were ongoing at 13 and 14 hours (these being the last time points evaluated), respectively.[15,16] The present investigation (SPD489-326; ClinicalTrials.gov Identifier NCT00784654) was preceded by a 7-week, phase 3 European trial (SPD489-325; ClinicalTrials.gov Identifier: NCT00763971) in 336 children and adolescents with ADHD, which found that both LDX and the reference treatment OROS-MPH produced significantly greater improvements than placebo in symptoms and global improvement, as assessed using the ADHD-RS-IV and Clinical Global Impressions–Improvement (CGI-I), respectively.[13] Adverse events associated with LDX treatment were consistent with the known effects of long-acting stimulant use.

Although ADHD is a chronic condition, studies investigating the long-term maintenance of effect of therapeutic agents are limited and are generally not of randomized and controlled design.[17-19] In long-term, open-label studies of LDX in children and adults with ADHD, improvements in core symptoms were maintained for up to 12 months, with most treatment-emergent adverse events (TEAEs) being mild or moderate in severity.[20,21] Only 1 randomized controlled trial has been reported that monitored the efficacy of LDX treatment over a period of more than 7 weeks; this study enrolled adults with ADHD who had received commercially available LDX for at least 6 months, and included a 3-week open-label period (OLP) followed by a 6-week randomized-withdrawal period (RWP).[17] The present study (SPD489-326) was designed to evaluate the long-term maintenance of efficacy of LDX in children and adolescents with ADHD, and consisted of 2 phases. The first phase assessed the efficacy and safety of LDX treatment throughout an OLP of at least 26 weeks. The second phase was a RWP that investigated the need for continued LDX treatment in order to maintain efficacy.

METHOD

Study Design and Population

SPD489-326 was originally designed as a 52-week, open-label extension of study SPD489-325. However, as agreed with regulatory agencies within the European Union, the protocol was amended to include a fixed-dose OLP and a double-blind, 2-arm, parallel-group, placebo-controlled RWP (Figure 1); as part of the amendment, the planned duration of the study was reduced from 52 weeks to 33 weeks. The antecedent study (SPD489-325) enrolled children and adolescents

FIGURE 1 Study design. Note: ET = early termination; R = revised protocol. [a]Patients enrolled from SPD489-325 before the protocol amendment could have attended maintenance period visits for up to 52 weeks (visits 10–17) before the revised protocol was approved.