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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 ($\geq 50\%$ 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 neuro-behavioral 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}

Lisdexamfetamine dimesylate (LDX) is the first prodrug stimulant⁷ 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}



Supplemental material cited in this article is available online.

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,

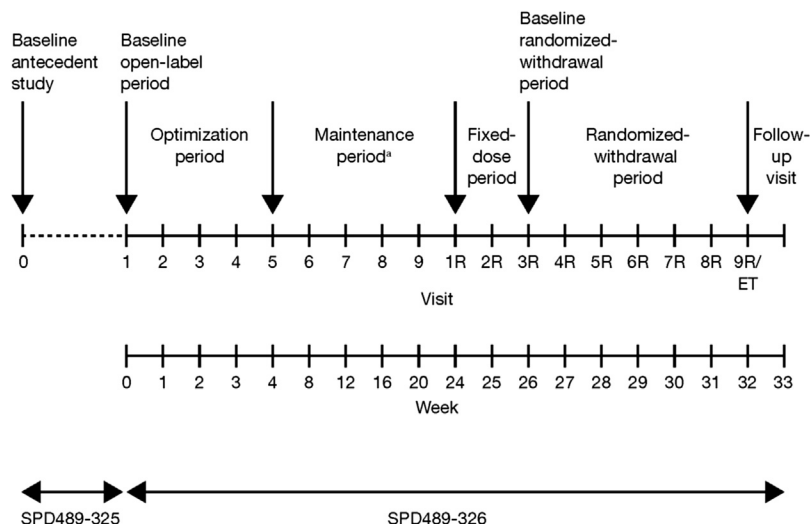
improvements in core symptoms were maintained for up to 12 months, with most treatment-emergent adverse events (TEAEs) being mild or moderate in severity.^{20,21} Only 1 randomized controlled trial has been reported that monitored the efficacy of LDX treatment over a period of more than 7 weeks; this 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. ^aPatients 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.



(aged 6–17 years) in Europe with a primary diagnosis of ADHD. To ensure a sample size sufficient for assessment of the primary efficacy measure (treatment failure), the protocol was also amended to allow patients (aged 6–17 years) with a primary diagnosis of ADHD from US sites to be evaluated for direct entry into SPD489-326.

European patients eligible for SPD489-326 had to have completed at least 4 weeks of double-blind treatment, reached visit 4 (week 4) and completed the 1-week post-treatment washout in the antecedent study, without experiencing any clinically significant adverse events that would preclude exposure to LDX. All patients had ADHD of at least moderate severity, defined as an ADHD-RS-IV total score of 28 or higher at baseline of the antecedent study (European patients) or at visit 1 (US patients). ADHD was diagnosed according to the criteria of *DSM-IV-TR*. Failure to respond to OROS-MPH therapy was a key exclusion criterion for both SPD489-326 (US patients) and the antecedent study, SPD489-325. US patients who had failed to respond to more than 1 adequate course of amphetamine therapy were also excluded from SPD489-326. Individuals whose current ADHD medication provided effective control of symptoms with acceptable tolerability were excluded, as were patients with comorbid psychiatric diagnoses with significant symptoms.

Baseline was defined as the baseline of SPD489-325, or, for directly enrolled US patients, visit 1 of SPD489-326. The OLP comprised 4 weeks of dose optimization followed by at least 20 weeks of dose maintenance, and then a 2-week fixed-dose period (Figure 1). Individuals enrolled from SPD489-325 before the protocol amendment could have attended maintenance period visits for up to 52 weeks (visits 10–17).

During dose optimization, all patients were started at LDX 30 mg per day on the morning after visit 1; if necessary, the dose was adjusted at subsequent visits in weekly 20-mg increment(s) to LDX 50 mg per day and then 70 mg per day until an acceptable response was achieved (defined as a 30% or greater reduction in ADHD-RS-IV total score from baseline and a CGI-I score of 1 or 2, with tolerable side effects). Patients then continued treatment with LDX during the dose-maintenance and fixed-dose periods. Further dose adjustments based on effectiveness and tolerability were permitted during the dose-maintenance period but not during the fixed-dose period that immediately preceded the randomized withdrawal. Patients were withdrawn from the study if, during the fixed-dose period, they required dose adjustments, experienced unacceptable side effects, or had an ADHD-RS-IV total score above 22 or a CGI-S score of 3 or more.

At the start of the RWP, eligible patients were randomized in a 1:1 ratio either to continue receiving their optimal dose of LDX or to switch to placebo for up to 6 weeks (Figure 1). An automated, interactive response system (accessible by telephone or the Internet) was

used to generate the random (concealed) allocation sequence, enroll patients, and assign individuals to study treatments. During the RWP, LDX and placebo products were overencapsulated and had an identical appearance; patients, caregivers, and investigators were blinded to the treatment allocation. Treatment was administered orally to patients once daily at approximately 7 AM.

The study was conducted in accordance with International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki. Written informed consent was provided by each patient's parent or legally authorized representative, and documentation of assent (if applicable) by the patient was required to confirm that he or she was aware of the investigational nature of the study and the required procedures and restrictions in accordance with the ICH GCP Guideline E6 and applicable regulations. The study protocol and amendments (<http://clinicaltrials.gov/ct2/show/NCT00784654>) were approved by the institutional review board or independent ethics committee of each center.

Study Measures

The primary efficacy outcome was the proportion of patients meeting treatment failure criteria by the end of the RWP. Treatment failure was defined as a 50% or greater increase in ADHD-RS-IV total score and a 2-point or greater increase in CGI-S score at any double-blind visit relative to the start of the RWP (visit 3R). Visits during the RWP were weekly (Figure 1). Individuals who met the treatment failure criteria during the RWP were immediately withdrawn from the study. Secondary efficacy outcomes included the maintenance of effect of LDX treatment during the OLP, as assessed using ADHD-RS-IV and CGI-I scores relative to baseline.

The ADHD-RS-IV, CGI-S, and CGI-I assessments were conducted by a physician experienced in the evaluation of children and adolescents with ADHD, based on information from the patient and their parent. Patients who were withdrawn from the study were asked to attend an early termination visit, which included the same assessments as scheduled for the last on-treatment study visit (visit 9R).

Adverse events, weight, height, and vital signs were recorded at all visits. Electrocardiography (ECG) was performed at screening and at visits 1 (US patients only), 7, 3R, and 9R/early termination. TEAEs were defined as such if they started or worsened during the period between the day of a patient's first dose of study treatment and the 3 days after cessation of treatment.

Statistical Analysis

The primary efficacy analysis was performed on the percentage of patients meeting treatment failure criteria by the end of the RWP using the Cochran-Mantel-Haenszel (CMH) test stratified by country.

RWP endpoint was the last on-treatment visit after randomization (visit 3R) with a nonmissing assessment. Patients who withdrew from the study during the RWP and did not provide efficacy data at the early termination visit were classed as treatment failures, as were those without an endpoint value. Treatment failure rates during the RWP were also assessed using the CMH test at each double-blind visit. The difference between groups in time to treatment failure (days) was assessed using the Wilcoxon test, stratified by country. Mean changes from baseline in ADHD-RS-IV scores during the OLP were assessed using a 1-sample t test. OLP endpoint was the last on-treatment visit after visit 1 with a nonmissing assessment, up to and including visit 3R (or up to and including visit 17 for patients who, before the protocol amendment, continued past visit 9 but did not enter the fixed-dose period). During the OLP, the CGI-I was analyzed categorically by calculating the percentage of individuals showing an improvement (CGI-I score of 1 [very much improved] or 2 [much improved]).

The open-label safety population and open-label full analysis set (FAS) included all patients who received at least 1 dose of study drug during the study. The randomized safety population and randomized FAS included all patients who were randomized and received at least 1 dose of any study treatment during the RWP. Efficacy outcomes during the OLP and RWP were assessed in the open-label FAS and randomized FAS, respectively. The sample size for this study was sufficient to detect treatment failure rates of 20% and 50% in the LDX and placebo groups, respectively, at a minimum 90% power and a significance level of 0.05 (2-sided).

RESULTS

Patient Disposition and Baseline Characteristics

A total of 276 patients were enrolled in SPD489-326. Of these, 236 patients were from study SPD489-325 and were enrolled from 37 sites in Europe (Germany, $n = 95$; Sweden, $n = 49$; Hungary, $n = 28$; Italy, $n = 20$; United Kingdom, $n = 16$; France, $n = 11$; Belgium, $n = 9$; Poland, $n = 8$). The remaining 40 patients were directly enrolled from 4 US sites. At the start of the RWP, 78 patients were randomized to LDX and 79 to placebo (Figure S1, available online). The open-label safety population comprised all 276 enrolled patients, and the randomized safety population comprised all 157 randomized individuals. Baseline characteristics were similar across the open-label safety population and both groups within the randomized safety population (Table 1). During the study, a serious breach of GCP at 1 European site resulted in the data from 14 patients being excluded from the efficacy analysis. The open-label FAS therefore comprised 262 individuals and the randomized FAS comprised 153 patients (LDX, $n = 76$; placebo $n = 77$). The study was conducted from January 27, 2009, to October 26, 2011.

A total of 110 of 276 patients (39.9%) in the open-label safety population discontinued LDX treatment before finishing the open-label period (27 during dose optimization, 53 during dose

TABLE 1 Baseline Demographics and Clinical Characteristics of Study Patients

Characteristic	Open-Label Safety Population (N = 276)		Randomized Safety Population			
			LDX (n = 78)		Placebo (n = 79)	
Age, y, mean (SD)	10.9	(2.82)	11.0	(2.63)	11.3	(2.58)
Sex, male, n (%)	212	(76.8)	61	(78.2)	62	(78.5)
Age group, n (%)						
6–12 years	191	(69.2)	55	(70.5)	50	(63.3)
13–17 years	85	(30.8)	23	(29.5)	29	(36.7)
Race, white, n (%)	257	(93.1)	74	(94.9)	75	(94.9)
BMI, kg/m ² , mean (SD)	19.40	(3.461)	19.44	(3.760)	20.17	(3.645)
Baseline ADHD-RS-IV total score, mean (SD)	40.7	(6.86)	41.9	(6.77)	40.2	(6.96)
Baseline CGI-S rating, mean (SD)	4.9	(0.80)	5.1	(0.81)	5.0	(0.72)
ADHD subtype, n (%)						
Predominantly inattentive	46	(16.7)	16	(20.5)	11	(13.9)
Predominantly hyperactive/impulsive	7	(2.5)	1	(1.3)	0	
Combined	223	(80.8)	61	(78.2)	68	(86.1)
Time since ADHD diagnosis, y, mean (SD)	2.28	(2.693)	2.87	(2.870)	2.46	(2.803)

Note: Age is that at the start of SPD489-325 or, for directly enrolled patients, at the time of informed consent before entering SPD489-326. Measurements are from the screening visit of SPD489-325 or, for directly enrolled patients, the last assessment before the first dose of study drug. Percentages are based on the number of patients with data in each treatment group. ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale IV; BMI = body mass index; CGI-S = Clinical Global Impressions—Severity; LDX = lisdexamphetamine dimesylate.

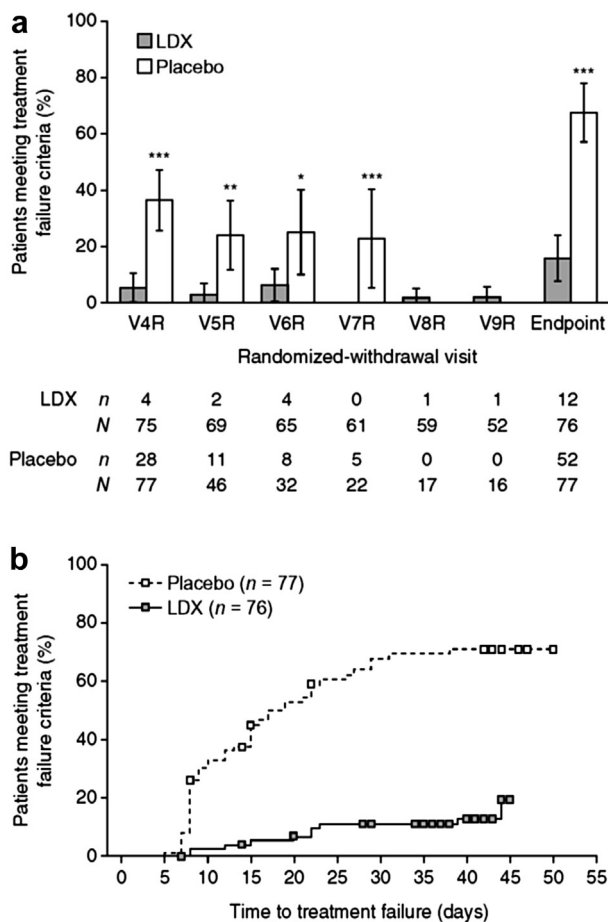
maintenance, and 30 during the fixed-dose period) (Figure S1, available online). Causes of discontinuation during the OLP were TEAEs (n = 44), refused further study participation (n = 22), lack of efficacy (n = 21), lost to follow-up (n = 11), protocol nonadherence/patient noncompliance (n = 7), and other reasons (n = 5). The final dose of LDX at OLP endpoint was 30 mg per day in 82 patients (29.7%), 50 mg per day in 98 patients (35.5%), and 70 mg per day in 96 patients (34.8%). In the LDX group of the randomized safety population (n = 78), the dose of LDX at RWP endpoint was 30 mg per day in 19 patients (24.4%), 50 mg per day in 27 patients (34.6%), and

70 mg per day in 32 patients (41.0%). In the placebo group of the randomized safety population (n = 79), the dose of LDX immediately before switching to placebo was 30 mg per day in 20 patients (25.3%), 50 mg per day in 36 patients (45.6%), and 70 mg per day in 23 patients (29.1%).

Efficacy

Primary Outcome: Randomized-Withdrawal Period. Significantly fewer patients receiving LDX met the treatment failure criteria (12/76; 15.8% [95% CI = 7.6, 24.0]) at RWP endpoint compared with those receiving placebo (52/77; 67.5% [95% CI = 57.1, 78.0]; Figure 2A). The difference between the

FIGURE 2 Treatment failure rates during the randomized-withdrawal period (randomized full analysis set). Note: LDX = lisdexamphetamine dimesylate; R = revised protocol; V = visit. (a) Treatment failure rates (95% CI) at each visit and at endpoint. **p* = .005, ***p* = .001, ****p* < .001 based on the Cochran–Mantel–Haenszel test stratified by country comparing the 2 treatment groups. Endpoint was the last on-treatment visit after visit 3R with a nonmissing assessment. Patients without an endpoint value were classed as treatment failures. Percentages are calculated as the number of treatment failures (n) divided by the number of patients with data at that visit (N) in each treatment group. (b) Kaplan–Meier plot of time to treatment failure. Day 0 = start of the randomized-withdrawal period. The difference between groups in time to treatment failure was significant (*p* < .001, Wilcoxon test stratified by country). Symbols represent censored observations.



LDX group and placebo group in patients meeting treatment failure criteria was -51.7% (95% CI = $-65.0, -38.5$; $p < .001$). The proportion of patients meeting relapse criteria was significantly lower in the LDX than in the placebo groups irrespective of age (6–12 years: LDX 10/53 [18.9%], placebo 34/50 [68.0%], $p < .001$; 13–17 years: LDX 2/23 [8.7%], placebo 18/27 [66.7%], $p < .001$), sex (males: LDX 10/59 [16.9%], placebo 42/60 [70.0%], $p < .001$); females: LDX 2/17 [11.8%], placebo 10/17 [58.8%], $p = 0.007$), and region (Europe: LDX 10/66 [15.2%], placebo 45/66 [68.2%], $p < .001$; US: LDX 2/10 [20.0%], placebo 7/11 [63.6%], $p = 0.049$).

The majority of placebo-treated patients who met treatment failure criteria did so at or before the week 2 visit after randomization. Six of 12 patients in the LDX group and 39 of 52 patients in the placebo group who met the relapse criteria did so at visits 4R or 5R (Figure 2). Figure 2B shows a Kaplan–Meier plot of time to treatment failure during the RWP. The median time to treatment failure was not calculable for the LDX group (because less than half of the patients met treatment failure criteria during the RWP) and was 17.0 days (95% CI = 12.0, 22.0) for the placebo group. The difference between groups in distribution of the time to treatment failure was significant ($p < .001$).

In supportive analyses, 2 additional definitions of treatment failure were defined separately on the basis of a 50% increase in ADHD-RS-IV total score or a 2-point change in CGI-S. When

treatment failure was defined as a 50% increase in ADHD-RS-IV total score, the proportions of treatment failures (95% CI) at RWP endpoint were 28.9% (18.8, 39.1) for LDX and 79.2% (70.2, 88.3) for placebo; the difference between the LDX and placebo groups was -50.3% ($-63.9, -36.6$). Similarly, 17.1% (8.6, 25.6) and 68.8% (58.5, 79.2) of patients receiving LDX and placebo, respectively, met a treatment failure criterion of at least a 2-point increase from baseline in CGI-S score at RWP endpoint; the difference between the LDX and placebo groups was -51.7% ($-65.1, -38.4$).

Secondary Outcome: Randomized-Withdrawal Period (ADHD-RS-IV Total Score). At RWP baseline (visit 3R), mean (SD) ADHD-RS total scores in the LDX and placebo groups were 10.2 (5.92) and 9.5 (6.45), respectively (randomized FAS). Using the last-observation-carried-forward method, the mean (SD) change from randomized baseline to endpoint in the LDX group was 1.9 (6.97, $n = 73$) compared with 14.5 (9.95, $n = 73$) in the placebo group, with a statistically significant ($p < .001$) least-squares mean difference (LDX – placebo) of -12.6 (95% CI = $-15.4, -9.8$).

Secondary Outcomes: Open-Label Period. At baseline, the mean (SD) ADHD-RS-IV total score was 40.6 (6.8) (open-label FAS). The mean (SD) change from baseline in ADHD-RS-IV total score at OLP endpoint was -26.6 (11.4) ($p < .001$). Significant changes in mean (SD) ADHD-RS-IV subscale scores were also seen. At baseline, the mean (SD) score for the hyperactivity/impulsivity subscale was 18.8 (5.5) and for the inattention subscale was

TABLE 2 Summary of Treatment-Emergent Adverse Events (TEAEs) During Open-Label Period (Open-Label Safety Population) and Randomized-Withdrawal Period (Randomized Safety Population)

Patients, n (%)	Open-Label Period		Randomized-Withdrawal Period			
	(N = 276)		LDX (n = 78)		Placebo (n = 79)	
Any TEAE	227	(82.2)	31	(39.7)	20	(25.3)
Any serious TEAE	12	(4.3)	0		0	
Any TEAE leading to discontinuation of study drug	45	(16.3) ^a	0		1	(1.3)
TEAEs ($\geq 10\%$ of patients in any treatment group)						
Decreased appetite	76	(27.5)	3	(3.8)	0	
Headache	58	(21.0)	6	(7.7)	5	(6.3)
Decreased weight	46	(16.7)	2	(2.6)	1	(1.3)
Nasopharyngitis	43	(15.6)	7	(9.0)	3	(3.8)
Anorexia	41	(14.9)	0		0	
Insomnia	39	(14.1)	1	(1.3)	1	(1.3)
Vomiting	32	(11.6)	2	(2.6)	1	(1.3)

Note: TEAEs are listed by decreasing frequency in the open-label safety population. LDX = lisdexamphetamine dimesylate.

^aOne patient had a TEAE leading to discontinuation that started in the open-label period but ended during the randomized-withdrawal period. In Figure S1, available online, this patient has been included as withdrawing because of an adverse event during the randomized-withdrawal period.

21.8 (3.5); at OLP endpoint, reductions of 12.5 (6.3) and 14.1 (6.4) points, respectively, were seen in these subscale scores (open-label FAS). At OLP endpoint, 205 of 257 patients (79.8%) were categorized as “improved” (CGI-I score of 1 or 2).

Safety. During the OLP, most patients had at least 1 TEAE (Table 2). Most TEAEs were mild or moderate in severity; 25 of 276 (9.1%) patients reported severe TEAEs. Serious TEAEs occurred in 12 of 276 (4.3%) patients during the OLP. Syncope, which was required to be reported as a serious TEAE, was reported in 2 individuals. The only other serious TEAE to be reported in more than 1 individual was aggression (*n* = 2). During the RWP, no TEAEs were reported in 10% or more of patients in either treatment group, all TEAEs were mild or moderate in severity, and no serious TEAEs occurred (Table 2). No deaths occurred during the study.

During the OLP, 45 of 276 patients (16.3%) experienced a total of 77 TEAEs leading to discontinuation (including 1 patient who had a TEAE leading to discontinuation that started in the OLP but continued into the RWP). The most common TEAEs leading to discontinuation were insomnia (8 patients, 2.9%), aggression (5 patients, 1.8%), and decreased appetite, headache, and depressed mood (each in 4 participants, 1.4%). Three patients reported serious TEAEs leading to discontinuation (mild syncope [*n* = 1], moderate abdominal pain [*n* = 1], and severe explosive behavior [*n* = 1]); all resolved and were considered by the investigators to be unrelated to the study treatment. During the RWP, no patient in the LDX group had a TEAE that led to discontinuation. One patient in the placebo group discontinued treatment because of 2 TEAEs (restlessness and an increase in ADHD behavior).

LDX treatment was associated with modest increases in mean pulse rate, heart rate, systolic blood pressure, and diastolic blood pressure. Decreases were observed in mean body weight from baseline to OLP endpoint, and from baseline to RWP endpoint with LDX (Table 3). From baseline to OLP endpoint, there was a mean (SD) weight loss of 2.24 (3.9) kg. During the RWP, patients who continued to receive LDX maintained a stable weight, whereas those who were randomized to placebo increased in weight (Table 3).

DISCUSSION

This study was the first to use a randomized-withdrawal design to evaluate the maintenance

TABLE 3 Summary of Changes to Vital Signs, Weight, and Electrocardiogram Parameters

	Open-Label Safety Population (N = 276)				Randomized Safety Population (N = 157)			
	Baseline, mean (SD)	Mean Change (SD):		Mean Change (SD):		Mean Change (SD):		Placebo ^a (n = 79)
		Baseline to OLP Endpoint	Baseline to OLP Endpoint	Baseline to Visit 3R	Baseline to RWP Endpoint	LDX (n = 78)	Placebo ^a (n = 79)	
Systolic blood pressure, mm Hg	107.8 (9.91)	+1.6 (10.31)	108.4 (9.73)	+1.7 (11.78)	+1.2 (9.10)	+1.5 (11.79)	-0.6 (9.66)	
Diastolic blood pressure, mm Hg	67.1 (9.37)	+2.3 (10.13)	67.1 (9.78)	+1.8 (10.91)	+2.2 (8.61)	+1.4 (11.27)	-0.1 (8.12)	
Pulse, beats/min	77.3 (10.78)	+5.9 (12.61)	77.5 (12.33)	+6.3 (14.64)	+4.7 (11.33)	+5.6 (15.52)	+4.2 (10.30)	
Weight, kg	44.66 (16.013)	-2.24 (3.866)	45.12 (16.209)	-2.30 (4.147)	-3.12 (4.364)	-2.06 (4.434)	-1.35 (3.870)	
Heart rate, beats/min	75.9 (10.34)	+7.8 (12.48)	75.1 (10.51)	+6.9 (13.00)	+6.2 (11.37)	+6.1 (12.59)	+2.3 (9.29)	
QTcF interval, ms	377.8 (15.41)	-1.1 (14.84)	378.9 (16.22)	-1.5 (14.67)	-3.9 (11.95)	-3.1 (15.31)	-2.5 (12.12)	

Note: Baseline measurements are from baseline of the antecedent study (SPD489-325) or, for directly enrolled patients, visit 1 of SPD489-326. The open-label period (OLP) endpoint was the last on-treatment visit after visit 1 with a nonmissing assessment, up to and including visit 3R (or up to and including visit 17 for patients who continued past visit 9, without entering the fixed-dose period, before protocol amendment). The randomized-withdrawal period (RWP) endpoint was the last on-treatment visit after visit 3R with a nonmissing assessment. QTcF = QT interval corrected using Fridericia's formula.
^aThe placebo group of the randomized safety population received lisdexamphetamine dimesylate (LDX) during the OLP and placebo during the RWP.

of efficacy of LDX in children and adolescents with ADHD. In patients aged 6–17 years with ADHD who had maintained responder status after at least 26 weeks of open-label LDX treatment, long-term efficacy was demonstrated. There was a significantly lower proportion of treatment failures in the group who continued LDX treatment in the double-blind RWP compared to those who stopped LDX and switched to placebo, irrespective of age, sex, or region. In the placebo group, the return of ADHD symptoms was usually rapid, with most placebo-treated patients who met treatment failure criteria doing so at or before the week 2 visit following discontinuation of LDX. In addition, during the OLP, ADHD-RS-IV total and subscale scores were significantly reduced, a high percentage of patients (79.8%) reported an improvement on the CGI-I at OLP endpoint, and a low proportion of patients (21/276, 7.6%) discontinued treatment because of lack of efficacy compared with the overall proportion of discontinuations during the OLP (110/276, 39.9%).

Compared with the primary efficacy outcome, for which treatment failure was based on there being above-threshold changes in both the ADHD-RS-IV and the CGI-S, treatment failure rates based on a 50% change in ADHD-RS-IV total score alone were higher, with 28.9% of patients in the LDX group meeting this criterion. One explanation for this may be that symptoms were overstated by individuals (or their parents) worried that they had been assigned to placebo and were seeking to return to active treatment, the so called “negative placebo effect.” However, the treatment failure rates for the 2-point shift in CGI-S alone were almost identical to the combined rates, suggesting that the changes in the CGI-S were the main driver for the primary combined outcome. The differences between the treatment groups remained constant, irrespective of whether the combined or separate outcomes were used, suggesting that a change in threshold for treatment failure did not differentially favor 1 treatment arm over the other. Furthermore, supportive analyses confirmed that symptomatology as assessed using the ADHD-RS-IV total score was stable in the LDX group during the RWP but worsened significantly in the placebo group.

The present observations in children and adolescents are supported by recently reported data from a randomized-withdrawal study of LDX in

adults with ADHD who had been receiving commercially available LDX for at least 6 months. After a further 3 weeks of open-label treatment, patients were randomized in a double-blind fashion to continue LDX or to switch to placebo for 6 weeks. Treatment failure, based on the same criteria as the present study, occurred in 75.0% of adult patients receiving placebo compared with 8.9% receiving LDX, with most failures occurring within 1 to 2 weeks of treatment withdrawal.¹⁷ Together, these results suggest that the efficacy of LDX is maintained after long-term treatment in patients of all ages with ADHD.

Other examples of the use of a randomized-withdrawal protocol to demonstrate the maintenance of efficacy of ADHD medications are limited. In children (aged 6–11 years), rates of withdrawal due to a return to pre-study symptoms during a 12-month RWP, after 3 months of single-blind amphetamine treatment, were significantly greater in the placebo group (71%) than in the amphetamine (29%) group.¹⁸ Similarly, among children and adolescents (aged 6–17 years) who responded to 6 weeks of open-label treatment with dexamethylphenidate, significantly more patients receiving placebo (61.5%) than dexamethylphenidate (17.1%) met the relapse criterion of a CGI-I score of 6 or 7 (much worse or very much worse) during a 2-week RWP.²² Also, after 12 weeks of open-label atomoxetine, significantly fewer patients (aged 6–15 years) receiving atomoxetine (22.3%) than patients receiving placebo (37.9%) relapsed during a 9-month RWP, although the small proportion of individuals who met the relapse criteria (an increased ADHD-RS-IV total score to 90% of baseline levels and an increased CGI-S score of at least 2 points) complicates the interpretation of these data.²³ Furthermore, when the atomoxetine-treated patients in this study were subsequently re-randomized to an additional 6 months of double-blind treatment with atomoxetine or placebo, relapse rates were again low in both groups (atomoxetine, 2.5%; placebo, 12.2%).²⁴ It was suggested that the low rates of relapse in this study may have been due to a reduction in the severity of symptoms at discontinuation compared with study entry, perhaps reflecting ongoing cognitive and emotional development. However, the high proportions of relapse in the present study despite similar study design and demographics suggest otherwise. Two randomized-withdrawal studies of OROS-MPH in adults with ADHD found that

the return of symptoms was numerically but not significantly greater in patients randomized to placebo compared with continued active treatment.^{25,26} It is possible that the small sample sizes and/or prominent placebo effects may have affected these results, or that the patients may have developed better coping or adaptive skills during their extended period of stimulant therapy.

In the present study, LDX was generally well tolerated, with TEAEs leading to discontinuation reported by 16.3% of patients during the OLP. The profile of TEAEs seen with LDX was consistent with that reported in previous LDX studies in children and adolescents with ADHD.^{11-13,15} No new clinically concerning or unexpected TEAEs occurred. The TEAEs most commonly reported during the RWP (decreased appetite, headache, weight decrease, nasopharyngitis, anorexia, insomnia, and vomiting) were consistent with the known effects of stimulant treatment. The lower incidence of TEAEs in the RWP than the OLP may have been related to the shorter duration of treatment or the discontinuation of patients with TEAEs during the OLP. During the RWP, the overall incidence of TEAEs was greater in the LDX group than in the placebo group; this may have been due to the higher rate of treatment failure and thus shorter duration of exposure in the placebo group than in the LDX group. Discontinuation of LDX treatment during the RWP was not associated with any safety concerns. Effects on weight and vital signs were modest and consistent with those observed with stimulant therapy.

A key strength of the randomized-withdrawal study design is that it allows the assessment of longer-term efficacy of a treatment using an experimental approach but without the ethical issues raised by asking participants to accept the possibility of long-term treatment with placebo. The randomized-withdrawal study design combines a randomized, double-blind, placebo-controlled methodology with the option of a rapid return to active treatment in patients who experience a return of symptoms when switched to placebo. In contrast, long-term, randomized, double-blind, placebo-controlled trials require patients to be assigned to placebo for extended periods, to their possible detriment; and long-term, open-label trials, which do have the advantage of approximating to real-world treatment, lack the experimental rigor of randomized, double-blind, placebo-controlled studies. The open label run-in to the randomized withdrawal

also allows the researcher to focus attention during the experimental phase on known treatment responders, who more closely resemble those individuals who, in actual clinical practice, will be most likely to remain on medication over the long term. Other strengths of SPD489-326 include a patient population of both children (aged 6–12 years) and adolescents (aged 13–17 years) enrolled from 9 different countries and the relatively long duration of at least 26 weeks. In addition, this study used a composite definition of treatment failure that required worsening on 2 different clinical assessment scales, 1 scale measuring symptoms (ADHD-RS-IV) and the other measuring function (CGI-S). Therefore, treatment failure in this study reflects a pronounced level of symptom return.

A potential limitation of the study is that the population of patients entering the RWP would have been enriched for LDX responders, as patients who did not benefit from, or could not tolerate, LDX were withdrawn during the OLP. However, it should be noted that this patient population reflects those individuals who would be taking LDX long-term in routine clinical practice. A further potential limitation concerns the requirement for patients to meet treatment failure criteria on only 1 occasion. It is possible that, for some individuals for whom relapse occurred early (i.e., within the first week after randomization), this represented a “rebound” due to withdrawal that would have settled over time. Although this is possible, we believe that a gap of 1 week between randomization and assessment was adequate to allow such withdrawal effects to wear off. Finally, it should be acknowledged that treatment failure criteria during the RWP ($\geq 50\%$ increase in ADHD-RS-IV total score and a ≥ 2 -point increase in CGI-S score) differed from that used to determine an acceptable response during dose optimization ($\geq 30\%$ reduction in ADHD-RS-IV total score and a CGI-I score of 1 or 2). However, any possible impact of this difference would be expected to apply equally to both treatment groups.

In summary, this placebo-controlled, double-blind, randomized-withdrawal study demonstrates the maintenance of efficacy of LDX after long-term treatment in children and adolescents with ADHD. There are few long-term controlled studies in children and adolescents with ADHD that have evaluated maintenance of efficacy versus placebo, and the results of this study

therefore represent an important addition to the evidence base in this field. Furthermore, this is the first long-term study of LDX that includes European patients. The rapid return of symptoms after LDX withdrawal shows the need for continuing treatment in children and adolescents with ADHD and the importance of adherence to treatment. Further studies are warranted to assess longer-term effectiveness and safety outcomes. &

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FIGURE S1 Patient disposition during the open-label and randomized-withdrawal periods. Note: FAS = full analysis set; GCP = Good Clinical Practice; LDX = lisdexamphetamine dimesylate. ^aSPD489-326 was originally designed as a 12-month open-label study; the protocol was amended to include a fixed-dose period and double-blind randomized-withdrawal period.

