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A 12-Month Open-Label Extension Study of the Safety and Tolerability of Lisdexamfetamine Dimesylate for Major Depressive Disorder in Adults

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Abstract:

Purpose/Background: Psychostimulant augmentation is considered a potential treatment strategy for individuals with major depressive disorder who do not adequately respond to antidepressant monotherapy. The primary objective of this 12-month open-label extension study was to evaluate the safety and tolerability of lisdexamfetamine dimesylate (LDX) as augmentation therapy to an antidepressant in adults with major depressive disorder.

Methods/Procedures: Eligible adults who completed 1 of 3 short-term antecedent LDX augmentation of antidepressant monotherapy studies were treated with dose-optimized LDX (20–70 mg) for up to 52 weeks while continuing on the index antidepressant (escitalopram, sertraline, venlafaxine extended-release, or duloxetine) assigned during the antecedent short-term studies. Safety and tolerability assessments included the occurrence of treatment-emergent adverse events and vital sign changes.

Findings/Results: All 3 antecedent studies failed to meet the prespecified primary efficacy endpoint, so this open-label study was terminated early. Headache (15.5% [241/1559]), dry mouth (13.6% [212/1559]), insomnia (13.1% [204/1559]), and decreased appetite (12.1% [189/1559]) were the most frequently reported treatment-emergent adverse events. The greatest mean ± SD increases observed for systolic and diastolic blood pressure and for pulse were 2.6 ± 10.85 and 1.7 ± 7.94 mm Hg and 6.9 ± 10.27 bpm, respectively. Monitoring determined that less than 1% of participants experienced potentially clinically important changes in systolic blood pressure (10 [0.6%]), diastolic blood pressure (8 [0.5%]), or pulse (6 [0.4%]).

Implications/Conclusions: The overall safety and tolerability of long-term LDX augmentation of antidepressant monotherapy was consistent with the profiles of the short-term antecedent studies, with no evidence of new safety signals.

M ajor depressive disorder (MDD) is characterized by episodes of low mood and self-esteem and markedly diminished interest or pleasure, along with cognitive and social impairments and vegetative symptoms (*Diagnostic and Statistical Manual*, American Psychiatric Association, 2013). Major depressive disorder is a highly recurrent disorder that typically increases in severity with each subsequent episode, particularly in untreated individuals.[1–3] The etiology of MDD has not been fully elucidated, but it is thought to be multifactorial, resulting from a combination of genetic, psychological, social, and biological factors.[4,5]

Many individuals with MDD fail to adequately respond to current antidepressant monotherapies or to current augmentation therapies,[6–8] which highlights the need to explore alternate treatment strategies. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study reported low remission rates with citalopram monotherapy[6] and second-step augmentation therapy.[8] Further emphasizing the need to alternative therapies, some agents approved for use as augmentation therapy for MDD in the United States are associated with safety and tolerability issues including weight gain, metabolic syndrome, and extrapyramidal adverse effects.[9–12] Psychostimulants are a possible treatment option for MDD, in part because of the putative role dopamine plays in the pathophysiology of depression and depressive symptomatology,[13,14] but limited data are available on the antidepressant effects of psychostimulant augmentation in MDD from large phase 3, randomized, placebo-controlled trials.[15]

Lisdexamfetamine dimesylate (LDX) has been investigated for its potential utility as augmentation therapy in individuals with MDD. In 2 phase 2 short-term efficacy studies, LDX augmentation of antidepressant monotherapy produced greater reductions in Montgomery-Åsberg Depression Rating Scale (MADRS) total score than placebo.[16,17] However, in 2 phase 3 short-term efficacy studies of LDX augmentation, treatment differences between LDX and placebo for the change from augmentation baseline in MADRS total score were not statistically significant[18] and, in a phase 2 dose-finding study LDX (10–70 mg), augmentation of antidepressant monotherapy did not demonstrate a significant dose response for MADRS total score changes from augmentation baseline.[19]

Across the short-term efficacy studies of LDX augmentation for MDD,[16–19] the safety and tolerability of LDX were consistent with previous studies of LDX in adults with attention deficit hyperactivity disorder (ADHD)[20] and binge eating disorder (BED).[21,22] Treatment-emergent adverse events (TEAEs) reported by greater than or equal to 5% of participants and at twice the rate of placebo across LDX augmentation studies were dry mouth, decreased appetite, insomnia, nasopharyngitis, and hyperhidrosis.[16–19] In addition,

LDX augmentation increased pulse and blood pressure and decreased weight and body mass index (BMI).[16–19]

This report describes a 12-month open-label extension study of LDX augmentation of antidepressant monotherapy in adults with MDD who completed 1 of 3 antecedent short-term studies.[18,19] The primary objective was to evaluate the long-term safety and tolerability of LDX as measured by the occurrence of TEAEs, responses on the Columbia-Suicide Severity Rating Scale (C-SSRS), and evaluation of vital signs and electrocardiograms (ECGs). Secondary objectives included evaluation of clinical outcomes based on the Clinical Global Impressions—Improvement (CGI-I) scale, the Sheehan Disability Scale (SDS), and the Quick Inventory of Depressive Symptomatology (QIDS-SR). It was hypothesized that the long-term safety and tolerability of LDX would be similar to observations from the short-term efficacy studies of LDX augmentation in MDD[16–19] and the long-term open-label safety studies of LDX in ADHD and BED.[23,24] Because the aforementioned antecedent studies failed to meet the primary efficacy endpoint,[18,19] this extension study was terminated early. However, the data from this large study, which includes 1559 individuals who were evaluated for safety and tolerability (1142 of whom completed ≥3 months of treatment and 300 of whom completed the year-long study), are clinically relevant because the use of psychostimulant augmentation in MDD continues to be of clinical interest[25–27] and because these data provide additional insight into the long-term safety and tolerability profile of LDX in individuals who are concomitantly using antidepressants.

MATERIALS AND METHODS

Study Design

This 52-week open-label extension study (ClinicalTrials. gov: NCT01436175) was conducted at 207 sites in 17 countries (February 27, 2012, to March 27, 2014) and enrolled adults who completed 1 of 3 short-term antecedent studies (ClinicalTrials. gov: NCT01435759, NCT01436149, NCT01436162).[18,19] The study consisted of a 4-week dose-optimization phase, a 48-week dose-maintenance phase, and a follow-up visit (7–9 days after the final dose).

The study protocol, final approved informed consent document, and relevant supporting information were submitted by the investigator and approved by the ethics committee and the appropriate regulatory agencies before study initiation. The study was conducted in accordance with guidelines of the International Conference on Harmonisation Good Clinical Practice, the principles of the Declaration of Helsinki, and all applicable local ethical and legal requirements. All participants provided written informed consent before performance of the study procedures.

Participants

This study included adults (men or nonpregnant women aged 18–65 years, with a primary diagnosis of nonpsychotic MDD) who completed 1 of 3 antecedent studies,[18,19] had been randomized to receive placebo or LDX during the antecedent study or entered a nonrandomized placebo treatment arm and continued to exhibit depressive symptoms (MADRS total score ≥5) at the end of the antecedent study; who did not experience clinically significant adverse events (AEs) during the antecedent study precluding LDX treatment; who had a satisfactory medical assessment with no clinically significant or relevant abnormalities based on physical examinations, clinical laboratory tests, ECGs, or vital sign assessments precluding LDX treatment; and who had the ability to understand and comply with all study-related procedures and

restrictions. Female participants of childbearing age were required to screen negative on blood pregnancy tests and be willing to use acceptable contraceptive methods.

Key exclusion criteria included current comorbid psychiatric disorders controlled with prohibited medications or uncontrolled and associated with significant symptoms; symptoms that contraindicated LDX treatment or could confound study assessments; medical conditions that might confound safety assessments or increase participant risk; hospitalization for an MDD episode since entering the antecedent study or receipt of electroconvulsive therapy for the current MDD episode; a suicide attempt within the past 3 years, identification as a suicide risk, or current demonstration of active suicidal ideation; histories of symptomatic cardiovascular disease or serious cardiac problems; moderate to severe hypertension; resting sitting systolic blood pressure (SBP) greater than 139 mm Hg or diastolic blood pressure (DBP) greater than 89 mm Hg; a family history of sudden cardiac death or ventricular arrhythmia; a clinically significant ECG or laboratory abnormality at screening; an average Fridericia-corrected QT (QTcF) or Bazett-corrected QT interval greater than 450 milliseconds if male or greater than 470 milliseconds if female; new onset or histories of seizures (other than infantile febrile seizures) or any tic disorder; current diagnosis and/or family history of Tourette disorder or serious neurologic disease; histories of significant head trauma, dementia, cerebrovascular disease, Parkinson disease, or intracranial lesions; use of medications with central nervous system effects that could affect MDD symptoms or alter the action, absorption, or disposition of LDX since antecedent study completion; use of an investigational product other than LDX within 30 days of the first visit of the current study; and participation in a previous LDX study other than the respective antecedent study or commercial use of LDX.

Treatment

Participants entering the study continued on the background antidepressant at the same dose used at the end of the antecedent study. Changes to the background antidepressant were not permitted, except for dose adjustments related to blood pressure and pulse issues that are described below. Background antidepressants were the selective serotonin reuptake inhibitors (SSRI) escitalopram (10 or 20 mg) or sertraline hydrochloride (50–200 mg) or the serotonin-norepinephrine reuptake inhibitors (SNRI) venlafaxine extended-release (37.5–375 mg) or duloxetine hydrochloride (30–120 mg). Package inserts were consulted during the study for guidance on antidepressant dosing.

During the dose-optimization phase, all participants were titrated to an individualized LDX dose, reflecting the manner in which medications are administered in clinical practice. Participants who had been treated with placebo, or those who ended the antecedent studies being treated with 10 mg LDX (in the phase 2 dose-finding antecedent study only) or 20 mg LDX, received 20 mg LDX during week 1, 30 mg LDX during week 2, and were then titrated weekly in 20-mg increments to 50 and 70 mg LDX. All other participants received 30 mg LDX during week 1 and were titrated weekly in 20-mg increments to 50 and 70 mg LDX. All titrations were done as tolerated and clinically indicated; participant safety, tolerability, and clinical response were considered when deciding if a dose increase was warranted. Dose reductions could take place at any time for safety and tolerability issues. All dose reductions were accompanied by assessments of vital signs, AEs, and C-SSRS responses. Lisdexamfetamine dimesylate (or the background antidepressant) could be down-titrated to manage blood pressure or pulse increases at any time during the dose-optimization period. If 30 mg LDX was not tolerated, participants

were down-titrated to 20 mg LDX; participants not tolerating 20 mg LDX were discontinued. Doses were not to be titrated (increased or decreased) by greater than 1 dose level at any visit.

During the 48-week dose-maintenance phase, participants continued on their dose-optimized LDX dose. Lisdexamfetamine dimesylate dose adjustments were allowed based on tolerability and clinical response at any time during this phase. Vital sign, AE, and C-SSRS assessments were to be performed in conjunction with a down-titration. Dose adjustments to the background antidepressant therapy could be considered, but changes to the assigned background antidepressant were not permitted.

Participants were discontinued during either study phase if average blood pressure or pulse (based on 3 measurements separated by approximately 2 minutes) met any of the following criteria (on 2 consecutive visits during dose optimization or at any visit during dose maintenance): resting SBP increase of greater than or equal to 10 mm Hg from antecedent study lead-in baseline and SBP of greater than or equal to 140 mm Hg, DBP increase of greater than or equal to 10 mm Hg from antecedent study lead-in baseline and DBP of greater than or equal to 90 mm Hg, or pulse increase of greater than or equal to 20 bpm from antecedent study lead-in baseline and pulse of greater than or equal to 100 bpm.

Study Endpoints

Safety and tolerability endpoints included the occurrence of TEAEs, evaluation of vital signs and weight, ECGs, clinical laboratory tests, and assessment of responses on the C-SSRS and Amphetamine Cessation Symptom Assessment (ACSA). Reports of AEs were collected during the study from the time of informed consent and were classified according to their relationship to treatment, severity, and seriousness. Specific psychiatric (aggression and violent behavior, psychosis/mania, and suicidal ideation and behavior) and nonpsychiatric (including events related to clinical laboratory tests, weight, and vital signs) events of interest were categorized as AEs of special interest. Vital signs (SBP, DBP, and pulse) and weight were assessed at week 0 (the follow-up visit from the antecedent study) and all subsequent visits. Vital signs were assessed after the participant was seated for at least 5 minutes and were based on the average of 3 measurements separated by approximately 2 minutes using automated cuffs. Clinical laboratory tests (biochemistry, hematology, urinalysis) were performed at weeks 0 (antecedent study end-of-study visit), 24, and 52/early termination (ET). A 12-lead ECG (performed in triplicate separated by approximately 2 minutes between readings) was assessed at weeks 0 (antecedent study end-of-study visit), 12, 24, 36, 48, 52/ET, and at follow-up. The C-SSRS, a semistructured interview assessing suicidal ideation and behavior,[28] was assessed at week 0 (the follow-up visit from the antecedent study) and at all visits through follow-up. The ACSA was assessed in all participants at the follow-up visit to evaluate amphetamine withdrawal symptoms after termination of LDX treatment. The ACSA[29] is a self-reported assessment containing 16 items rated on 5-point scales (0, not at all, to 4, extremely). Amphetamine Cessation Symptom Assessment items can be used to generate an aggregate score (sum of all items; range, 0–64) and 3 subscale scores (anxiety and mood [sum of items 1, 3–5, 7, 8, and 10–14; range, 0–44], fatigue [sum of items 2, 6, and 9; range, 0–12], and craving [sum of items 15 and 16; range, 0–8]).

Secondary endpoints that assessed clinical outcome were the CGI-I, SDS, and QIDS-SR. The CGI-I was assessed at all on-treatment visits through week 52/ET in all participants who completed the CGI—Severity (CGI-S) scale as part of the antecedent study at week 0 (antecedent study end-of-study visit). The CGI-I rated improvement on a 7-point scale (1, very much improved, to 7, very much worse) relative to the CGI-S at augmentation baseline of the antecedent study. The SDS, a validated measure of functional impairment in daily life,[30] was administered at week 0 (antecedent study end-of-study visit) and all on-treatment visits from week 4 through week 52/ET. The SDS measures the impact of an illness on an individual's life across multiple domains (work/school, social life, and family life/home responsibilities) using an 11-point scale (0, no impairment to 10, most severe); SDS total score ranges from 0 to 30.[31] The QIDS-SR, a 16-item validated self-administered questionnaire that rates depressive symptoms,[32] was administered at week 0 (antecedent study end-of-study visit) and all on-treatment visits from week 1 through week 52/ET. Each item is scored on a 4-point scale (0, most favorable, to 3, least favorable); total score ranges from 0 (no depression) to 27 (very severe depression).[32] The QIDS-SR was included as an endpoint in only 1 of the phase 3 studies.

Data Presentation

Data analyses were performed using SAS version 9.1 (or newer). Safety and tolerability in the safety analysis set (participants taking ≥1 study drug dose and having ≥1 postdose safety assessment in the current study) are presented descriptively. Categorical variables are summarized by number of observations and percentages; continuous variables are summarized with means and standard deviations (SD). For safety and tolerability assessments, baseline was defined as the antecedent study augmentation baseline value; ET values were defined as the last valid assessment collected after week 0.

Data from the full analysis set (FAS; safety analysis participants set having ≥1 postdose clinical outcome assessment) are presented descriptively for the CGI-I, SDS, and QIDS-SR. The number of participants included for each endpoint differed because these endpoints were not assessed in all of the antecedent studies and because participants may not have had an assessment at augmentation baseline of the antecedent study. For the CGI-I, scores were dichotomized as improved (scores of 1 [very much improved] or 2 [much improved]) or not improved (scores of 3 [minimally improved] to 7 [very much worse]). The percentages of participants categorized as improved on the CGI-I at week 52 and week 52/ET are presented. For the SDS and QIDS-SR, mean ± SD scores and changes from antecedent study augmentation baseline are summarized at week 52 and week 52/ET.

RESULTS

Participant Disposition and Demographics

Of 1570 enrolled participants, 1559 were included in the safety analysis set and 1556 were included in the FAS (Figure S1, Supplemental Digital Content 1, http://links.lww.com/JCP/A503). Among enrolled participants, more individuals received placebo (n = 1025) than LDX (n = 545) during the antecedent studies because the antecedent studies included a randomized treatment arm, in which some participants meeting randomization criteria were allocated to placebo, and a nonrandomized arm, in which participants not meeting randomization criteria were maintained on their background antidepressant and single-blind placebo. Reasons for study discontinuation are reported in Figure S1, Supplemental Digital Content 1, http://links.lww.com/JCP/A503. A total of 1270 participants (80.9%) did not complete the study, most of whom (n = 771) were discontinued because of study termination; 63 participants (antecedent study treatment: placebo [n = 40], LDX [n = 23]) were discontinued for meeting prespecified blood pressure or pulse discontinuation criteria.

Table 1 summarizes baseline characteristics of the safety analysis set. Most participants were female, white, and had a

TABLE 1. Baseline Characteristics, Safety Analysis Set

	All Participants (N = 1559)
Age, mean ± SD, y	41.9 ± 11.89
Sex, n (%)	
Male	503 (32.3)
Female	1056 (67.7)
Race/ethnicity, n (%)	
White	1273 (81.7)
Black/African American	245 (15.7)
Native Hawaiian/Pacific Islander	4 (0.3)
Asian	25 (1.6)
American Indian/Alaska native	6 (0.4)
Other	6 (0.4)
Weight, mean ± SD, kg	81.9 ± 18.31
BMI, mean ± SD, kg/m^2	28.6 ± 5.49
BMI category, n (%)	
Underweight (<18.5 kg/m^2)	4 (0.3)
Normal weight (18.5–<25.0 kg/m^2)	456 (29.2)
Overweight (25.0–<30.0 kg/m^2)	513 (32.9)
Obese (≥30.0 kg/m^2)	586 (37.6)
Antidepressant type, n (%)	
SSRI	935 (60.0)
Escitalopram oxalate	710 (45.5)
Sertraline HCl	225 (14.4)
SNRI	624 (40.0)
Venlafaxine HCl extended-release	356 (22.8)
Duloxetine HCl	268 (17.2)

HCl indicates hydrochloride.

BMI of greater than or equal to 25 kg/m^2. During the antecedent studies, more participants had been allocated to receive an SSRI than an SNRI as the background antidepressant.

LDX Exposure

Table 2 summarizes LDX exposure in the safety analysis set. The mean and median lengths of LDX exposure exceeded 160 days but the exposure range was large, owing in part to termination of the study. Most participants were treated for greater than or equal to 3 months; few participants continued treatment for greater than or equal to 12 months. The daily LDX dose over the course of the study was 49.9 ± 16.72 mg. The maximum LDX dose taken by a majority of participants was 70 mg. Compliance was in the 80% to 120% range in a majority of participants.

Safety and Tolerability

Treatment-Emergent AEs

Most participants reported TEAEs (Table 3), and most TEAEs were of mild or moderate intensity. Listings of serious TEAEs, TEAEs leading to discontinuation, and severe TEAEs reported by greater than or equal to 2 participants are summarized in the footnotes to Table 3. Among these TEAE categories, the most frequently reported serious TEAEs included suicide attempt and suicidal ideation (n = 3 for each); the most frequently reported TEAEs leading to discontinuation included blood pressure increased (n = 17; 14 and 3, respectively, with SSRI or SNRI as background antidepressant), heart rate increased (n = 10; 2 and 8, respectively, with SSRI or SNRI as background antidepressant), and QT prolongation (n = 10; 4 and 6,

respectively, with SSRI or SNRI as background antidepressant); and the most frequently reported severe TEAE was insomnia (n = 11). A majority of serious TEAEs, TEAEs leading to discontinuation, and severe TEAEs had resolved or were resolving at study termination.

Most serious TEAEs were moderate to severe in intensity, were not considered by the investigator to be related to study drug, and recovered/resolved. The serious TEAEs that were considered to be related to study drug included suicidal ideation (n = 1; severe intensity resulting in study drug discontinuation; resolved), auditory hallucination with suicidal ideations (n = 1; moderate intensity resulting in study drug discontinuation; resolved), deep vein thrombosis (n = 1; severe intensity; resolved without study drug dose change), depression (n = 1; moderate intensity resulting in study drug discontinuation; resolved), major depression (n = 1; severe depression resulting in study drug discontinuation; ongoing), and psychosis (n = 1; severe intensity resulting in study drug discontinuation; resolved). There was 1 TEAE of craving for amphetamines reported (mild severity; not considered a serious TEAE; resolved), which was deemed related to treatment by the investigator.

Treatment-emergent AEs reported by greater than or equal to 5% of participants are summarized in Table 3; the most frequently reported TEAEs were headache, dry mouth, insomnia, and decreased appetite. Psychiatric AEs of special interest were reported by 40.3% (628/1559) of participants. Psychiatric AEs of special interest reported in greater than or equal to 5% of participants were insomnia, bruxism, and anxiety (Table 3). Suicide-related TEAEs were reported by 10 participants (suicide attempts, n = 3 [0.2%]; suicidal ideation, n = 7 [0.4%]). All treatment-emergent suicide attempts were considered severe and serious; 3 instances of treatment-emergent suicidal ideation were

TABLE 2. LDX Exposure, Safety Analysis Set

	All Participants (N = 1559)
Duration of exposure*	
Mean ± SD, d	192.6 ± 118.14
Median (range), d	168.0 (2–385)
≥3 mo, n (%)	1142 (73.3)
≥6 mo, n (%)	737 (47.3)
≥9 mo, n (%)	478 (30.7)
≥12 mo, n (%)	128 (8.2)
Average daily dose*	
Mean ± SD, mg/d	49.9 ± 16.72
Median (range), mg/d	49.9 (13–167)
Total exposure (person-time), d*[†]	294,786
Maximum dose during the study, n (%)*	
20 mg/d	10 (0.6)
30 mg/d	292 (18.7)
50 mg/d	411 (26.4)
70 mg/d	846 (54.3)
Compliance, n (%)*[‡]	
<80%	67 (4.3)
80%–120%	1468 (94.2)
>120%	24 (1.5)

*Summaries over entire study.

[†]Total number of days in which lisdexamfetamine was taken summed over all participants.

[‡]The number of capsules taken × 100/the total planned days of dosing.

TABLE 3. TEAEs and Vital Sign Outliers, Safety Analysis Set

	All Participants (N = 1559)
Any TEAE, n (%)	1255 (80.5)
Serious TEAEs*	33 (2.1)
TEAEs related to study drug	945 (60.6)
TEAEs leading to discontinuation†	107 (6.9)
Severe TEAEs‡	108 (6.9)
TEAEs occurring in ≥5% of participants, n (%)	
Headache	241 (15.5)
Dry mouth	212 (13.6)
Insomnia	204 (13.1)
Decreased appetite	189 (12.1)
Nasopharyngitis	137 (8.8)
Nausea	116 (7.4)
Upper respiratory tract infection	100 (6.4)
Dizziness	91 (5.8)
Bruxism	89 (5.7)
Anxiety	83 (5.3)
Feeling jittery	82 (5.3)
Fatigue	80 (5.1)
Irritability	79 (5.1)
Vital signs	
Change from baseline at week 52/ET, mean ± SD	
SBP, mm Hg	2.4 ± 10.37
DBP, mm Hg	1.2 ± 7.94
Pulse, bpm	5.2 ± 10.58
Outlier analysis, n (%)	
Concurrent SBP ≥140 mm Hg and SBP increases ≥10 mm Hg from baseline on 2 consecutive on-treatment visits	10 (0.6)
Concurrent DBP ≥90 mm Hg and DBP increases ≥10 mm Hg from baseline on 2 consecutive on-treatment visits	8 (0.5)
Concurrent pulse ≥100 bpm and increases ≥20 bpm from baseline on 2 consecutive on-treatment visits	6 (0.4)
ECG change from baseline at week 52/ET, mean ± SD¥	
Heart rate change from baseline at week 52/ET, bpm	6.81 ± 10.472
QTcF change from baseline at week 52/ET, ms	−3.49 ± 13.090
Weight§	
Change from baseline at week 52/ET, mean ± SD	−0.88 ± 4.956
≥7% increase from antecedent study augmentation baseline, n (%)	310 (19.9)
≥7% decrease from antecedent study augmentation baseline, n(%)	154 (9.9)
BMI¶	
Change from baseline at week 52/ET, mean ± SD	−0.32 ± 1.725

*Reported by ≥2 participants: suicide attempt and suicidal ideation (n = 3 each); deep vein thrombosis, depression, and noncardiac chest pain (n = 2 each).

†Reported by ≥2 participants: blood pressure increased (n = 17); ECG QT prolonged and heart rate increased (n = 10 each); hypertension (n = 5); insomnia (n = 4); anxiety, suicidal ideation, and tachycardia (n = 3 each); auditory hallucinations, chest pain, depression, nervousness, and weight decreased (n = 2 each).

‡Reported by ≥2 participants: insomnia (n = 11); headache (n = 10); dry mouth (n = 5); back pain and influenza (n = 4 each); agitation, abdominal pain, depression, diarrhea, fatigue, viral gastroenteritis, migraine, nausea, somnolence, and suicide attempt (n = 3 each); anxiety, chest pain, decreased appetite, musculoskeletal pain, nasopharyngitis, neck pain, nephrolithiasis, suicidal ideation, upper respiratory tract infection, urticaria, and vomiting (n = 2 each).

¥n = 1476.

§n = 1558.

¶n = 1557.

considered serious and severe. All suicide-related TEAEs resolved. A serious TEAE of psychotic disorder (which resulted in study discontinuation and subsequently resolved [described above] in a participant who also reported a suicide attempt) was reported. A severe TEAE of mania (which resulted in study discontinuation and was resolving at the time of study termination) was reported in 1 participant. No aggression events were reported. Nonpsychiatric AEs of special interest were reported by 29.4%

(458/1559) of participants The only nonpsychiatric AE of special interest occurring in greater than or equal to 5% of participants was decreased appetite (Table 3). There were no deaths during the study.

Vital Signs

Increases from augmentation baseline of the antecedent studies were observed for SBP and DBP and for pulse over the course

of the study (Figure S2A and S2B, Supplemental Digital Content 2, http://links.lww.com/JCP/A504). Mean changes in blood pressure and pulse at week 52/ET and outlier analyses of vital sign changes are summarized in Table 3. Less than 1% of participants reported potentially clinically important changes in SBP, DBP, or pulse. The greatest mean ± SD increases were observed at weeks 48 and 52 for SBP (2.6 ± 10.49 mm Hg [n = 385] and 2.6 ± 10.85 mm Hg [n = 334], respectively), at week 52 for DBP (1.7 ± 7.94 mm Hg [n = 334]), and at week 3 for pulse (6.9 ± 10.27 bpm [n = 1524]).

When vital sign changes were analyzed based on background antidepressant, the greatest mean ± SD increases from augmentation baseline of the antecedent studies in participants who received SSRIs were observed at week 44 for SBP (3.6 ± 11.23 [n = 261]); weeks 24, 28, and 44 for DBP (2.3 ± 7.76 [n = 516], 2.3 ± 7.90 [n = 452], and 2.3 ± 8.45 [n = 261], respectively); and week 32 for pulse (8.2 ± 10.44 [n = 394]). At week 52/ET (n = 934), the observed mean ± SD increases in SBP, DBP, and pulse in those who received SSRIs were 2.4 ± 10.71 mm Hg, 1.6 ± 8.14 mm Hg, and 6.4 ± 10.60 bpm. The greatest mean ± SD increases from augmentation baseline of the antecedent studies in participants who received SNRIs were observed at week 52/ET for SBP (2.3 ± 9.85 [n = 624]), week 52 for DBP (0.9 ± 7.99 [n = 139]), and week 3 for pulse (5.5 ± 9.40 [n = 617]). At week 52/ET, the observed mean ± SD increases in DBP and pulse in those who received an SNRI (n = 624) were 0.6 ± 7.61 mm Hg and 3.3 ± 10.29 bpm.

Body Weight and BMI

Mean ± SD decreases from antecedent study augmentation baseline were observed for body weight and BMI (Figure S2C, Supplemental Digital Content 2, http://links.lww.com/JCP/A504). The greatest mean ± SD decreases in weight and BMI were observed at week 24 (−1.52 ± 5.311 kg [n = 870] and −0.54 ± 1.793 kg/m^2 [n = 869], respectively). Changes in weight and BMI at week 52/ET are summarized in Table 3.

Electrocardiograms

The mean heart rate change and QTcF change from antecedent study augmentation baseline at week 52/ET is reported in Table 3. The greatest mean ± SD increase in ECG-based heart rate was observed at week 36 (7.77 ± 10.255 [n = 725]). No participant had a QTcF interval of greater than or equal to 500 milliseconds or

an increase from antecedent study augmentation baseline QTcF interval of greater than or equal to 60 milliseconds.

Other Safety and Tolerability Measures

Mean changes in clinical laboratory assessments from augmentation baseline of the antecedent studies were generally of small magnitude and not considered clinically relevant. No single clinical laboratory-related TEAE occurred in greater than 1% of participants, and none were considered serious or resulted in study discontinuation. The most frequently occurring clinical laboratory-related TEAEs reported were increased alanine aminotransferase and anemia (n = 6 [0.4%] for each). Outlier analyses indicated that clinical laboratory test values considered of potential clinical relevance occurred infrequently; there was no apparent pattern of changes observed.

On the C-SSRS, greater than or equal to 1 suicide attempt was identified in 4 participants (0.3%) (3 were considered treatment-emergent; 1 was not considered treatment-emergent). Three of these instances were in relation to the suicide attempts described as TEAEs (all considered serious, severe, and not related to treatment); 1 instance resulted in study withdrawal. The remaining suicide attempt was not considered treatment-emergent but was considered serious and severe. At least 1 instance of suicidal ideation was identified in 68 participants (4.4%), with 7 of these participants having suicidal ideation reported as a TEAE by a study investigator. The TEAEs of suicidal ideation varied in intensity (mild [n = 2], moderate [n = 2], severe, [n = 3]); 3 were considered serious, 3 resulted in study discontinuation, and 3 were considered to be treatment related by the investigator.

At follow-up, mean ± SD aggregate ACSA scores (14.3 ± 10.59 [n = 1349]) and subscale scores (anxiety and mood, 9.4 ± 7.78 [n = 1351]; fatigue, 4.3 ± 3.01 [n = 1360]; craving, 0.5 ± 1.31 [n = 1357]) were low and not indicative of amphetamine withdrawal.

Clinical Outcomes

Findings at week 52/ET for the clinical outcome assessments are summarized in Table 4. On the CGI-I, the percentage of participants categorized as improved relative to antecedent study augmentation baseline was numerically higher at week 52 and week 52/ET than at week 0. On the SDS and QIDS-SR, total scores were numerically lower at weeks 0, 52, and 52/ET than at antecedent study augmentation baseline.

TABLE 4. Summary of Secondary Endpoints, Full Analysis Set

	Antecedent Study Augmentation Baseline	Week 0*	Week 52	Week 52/ET
Participants improved[†] on CGI-I, n/N (%)	—	762/1343 (56.7)	209/244 (85.7)	1021/1345 (75.9)
SDS				
Mean ± SD total score[‡]	12.7 ± 7.06 (n = 1548)	10.4 ± 6.85 (n = 1554)	7.8 ± 6.84 (n = 333)	8.4 ± 7.32 (n = 1536)
Mean ± SD change from augmentation baseline of the antecedent studies	—	−2.4 ± 7.07 (n = 1547)	−5.2 ± 7.55 (n = 331)	−4.3 ± 7.77 (n = 1530)
QIDS-SR				
Mean ± SD total score[‡]	9.7 ± 4.42 (n = 502)	8.8 ± 4.28 (n = 504)	5.9 ± 4.29 (n = 104)	6.9 ± 4.48 (n = 506)
Mean ± SD change from augmentation baseline of the antecedent study	—	−1.0 ± 4.36 (n = 500)	−3.6 ± 4.65 (n = 104)	−2.9 ± 4.92 (n = 502)

*Week 0 is the end-of-study visit from the antecedent study.

[†]Scores of 1 (very much improved) or 2 (much improved); not all participants from the antecedent phase 2 study[19] had a CGI—Severity assessment at augmentation baseline and are excluded from the data set.

[‡]Higher scores represent more severe impairment/symptoms; the QIDS-SR was only assessed in 1 antecedent study.

DISCUSSION

The primary objective of this 12-month open-label extension study was to evaluate the long-term safety and tolerability of LDX augmentation of antidepressant therapy in adults with MDD. These safety and tolerability findings are relevant because they provide additional insight into the long-term safety and tolerability of LDX in combination with SSRI and SNRI antidepressants and because there are limited long-term data available from large phase 3 studies of psychostimulant augmentation for MDD. The key findings indicate that the safety and tolerability of LDX augmentation in individuals with MDD are consistent with the known profile observed in long-term studies of LDX in adults with ADHD or BED.[23,24] Although data on the time course of TEAEs in this study are not available, the frequency of TEAEs associated with LDX treatment was reported to decrease over time in adults with ADHD during long-term LDX treatment.[24] In that study, the frequency of TEAEs after 1 month of treatment was greater than after 3, 6, 9, and 12 months of treatment.[24] Given that the majority of participants in this study were treated for greater than or equal to 3 months, the overall similarity in TEAE frequency between this study and the ADHD study (headache, 17.2%; dry mouth, 16.6%; insomnia, 19.5%; decreased appetite, 14.3%)[24] suggests that ET of this study did not result in an underestimation of the frequency of TEAEs.

The safety and tolerability of LDX observed in this study were also similar to the profiles reported in short-term studies of LDX in individuals with MDD, with the most frequently reported TEAEs in this long-term extension (headache, dry mouth, insomnia, and decreased appetite) being among the most frequently reported TEAEs in the short-term LDX studies.[16–19] Lastly, it should be noted that, in the current study, 10 participants reported suicide-related TEAEs (suicide attempts, n = 3 [0.2%]; suicidal ideation, n = 7 [0.4%]). All of these TEAEs resolved.

Treatment with LDX increased SBP, DBP, and pulse. Blood pressure and pulse were also elevated with LDX in the previously reported short-term studies of LDX augmentation of antidepressant monotherapy.[16–19] The magnitude of changes in vital sign measures in the current study is similar to that reported at study endpoint in adults with ADHD treated with LDX in a 12-month open-label extension study (SBP, 3.1 ± 10.7 mm Hg; DBP, 1.3 ± 7.6 mm Hg; pulse, 3.2 ± 11.6 bpm).[24] The vital sign increases observed throughout the on-treatment period were shifting back toward baseline at follow-up. Although outlier analyses indicated that less than 1% of participants exhibited vital sign changes that were considered by investigators to be of potential clinical relevance, the highest number of TEAE-related study discontinuations was associated with increased blood pressure (17 participants, most of which occurred in participants allocated to a background SSRI) and increased heart rate (10 participants, most of which occurred in participants allocated to a background SNRI). Furthermore, an additional 63 participants were discontinued because they met prespecified blood pressure and pulse criteria. Electrocardiogram assessments did not reveal consistent patterns of changes, but 10 participants were discontinued by a study investigator because of QT prolongation.

There were no significant differences in the treatment effects of LDX versus placebo in the short-term antecedent studies from which study participants were enrolled,[18,19] and it was concluded that LDX augmentation was not superior to placebo in reducing the depressive symptoms of MDD in individuals with inadequate responses to antidepressant monotherapy. As such, apparent improvement in clinical outcome in this open-label safety study should not be interpreted as being indicative of the long-term effectiveness or efficacy of LDX augmentation. Although it is possible that LDX may be efficacious in addressing certain dimensions of MDD psychopathology in populations of individuals exhibiting specific symptoms, such as executive dysfunction[17] or possibly anhedonia or lethargy, future studies are needed to examine this possibility.

The findings of the current study should also be considered in light of potential limitations. First, only 300 participants completed the study because it was terminated early. Therefore, data at week 52 should be interpreted with caution because of the sample size. Early study termination also resulted in high variability in the duration of LDX exposure. Second, the antecedent studies from which participants were enrolled excluded individuals with ADHD.[18,19] Additional studies would be required to determine the effects of LDX in individuals with comorbid MDD and ADHD. Lastly, the safety and tolerability findings should be considered in light of the fact that the study excluded individuals who experienced clinically significant AEs in the antecedent study that precluded further LDX exposure.

CONCLUSIONS

After up to 12 months of treatment, the safety and tolerability of LDX as augmentation therapy in adults with MDD were consistent with observations from the short-term antecedent studies[16–19] and from adults with ADHD or BED.[23,24] Most TEAEs were mild or moderate in severity, and the most frequently reported TEAEs were those known to be associated with LDX or with commonly occurring intercurrent illnesses. Treatment with LDX was associated with increased blood pressure and pulse in some individuals, so it is important for clinicians to regularly monitor vital signs when treating patients with LDX, as is recommended in the product labeling for LDX.

AUTHOR DISCLOSURE INFORMATION

C. Richards, B. Geibel, and M. Dauphin are former employees of Shire and hold stock and/or stock options in Shire. D. V. Iosifescu, in the past 3 years, has consulted for Avanir, Axsome, CNS Response, INSYS Therapeutics, Lundbeck, Otsuka, and Sunovion and has received research support through the Icahn School of Medicine at Mount Sinai from Alkermes, AstraZeneca, Brainsway, Roche, and Shire. R. Mago, in the past 3 years, has received research grants through Thomas Jefferson University from Alkermes, Forest Research Institute, Genomind, Shire Development, and Takeda Pharmaceuticals USA and has done consultations for Forest Laboratories, Jina Pharmaceuticals, GuidePoint Global, Lundbeck LLC, Nestle Health Science, Otsuka America Pharmaceuticals, and Sunovion. E. Sarkis, in the past 3 years, has conducted clinical trials with Alkermes, Allergan, AstraZeneca, Auspex, Daiichi-Sankyo, Eli Lilly, Forest, GlaxoSmithKline, Lundbeck, Neurim, Otsuka, Pfizer, Purdue, Shire, Sunovion, and Tonix. R.S. McIntyre is a consultant and has received speakers fees from Shire, Eli Lilly, Purdue, Takeda, AstraZeneca, Johnson &

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