

The following information concerns a use that has not been approved by the US Food and Drug Administration.

ABSTRACT

Objective: To evaluate the efficacy and safety of lisdexamfetamine dimesylate (LDX) used as augmentation to an antidepressant in adults with major depressive disorder (MDD).

Methods: This multicenter trial enrolled adults (18-55 y) with MDD; comorbid ADHD and other Axis I disorders were excluded. Following an 8-week open-label prospective escitalopram treatment (titrated to 20 mg/d), participants with persistent and residual depressive symptoms (17-item Hamilton Rating Scale for Depression [HAM-D17] score ≥ 4) were randomized to 6-week adjunctive treatment with double-blind LDX (20, 30, or 50 mg/d) or placebo. Adults were further stratified as nonremitters (Montgomery-Asberg Depression Rating Scale [MADRS] >10) or remitters at randomization to augmentation (week 8). Efficacy assessments were mean change from week 8 in MADRS total score (primary, analyzed by ANCOVA in nonremitters, with prespecified 2-sided significance level of 0.10); HAM-D17; Clinical Global Impressions-Severity and -Improvement; and Quick Inventory of Depressive Symptomatology-Self Report. Safety assessments included treatment-emergent adverse events (TEAEs), systolic (SBP) and diastolic (DBP) blood pressure, pulse, ECG, and laboratory findings.

Results: Of 246 enrolled adults, 239 received open-label treatment and 173 received randomized treatment: 129 nonremitters (65 LDX; 64 placebo) and 44 remitters (23 LDX; 21 placebo). Of 89 adults withdrawing early, 20 withdrew during randomized treatment (6 [3.4%] due to TEAEs). During randomized treatment, 61.8% (107/173) were female; 76.9% (133/173) were white. The mean (SD) MADRS total scores for nonremitters at point of randomization to augmentation (week 8) were 20.3 (7.16) and 20.8 (6.42) for LDX and placebo groups, respectively. At endpoint (week 14) of randomized treatment, least squares mean (SE) change from week 8 was significantly greater ($P=.0902$) with LDX (-7.1 [0.93]) vs placebo (-4.9 [0.94]) in nonremitters. No differences were found for remitters. For adults receiving randomized treatment, 60.2% (53/88) on LDX and 49.4% (42/85) on placebo had TEAEs; 1 serious TEAE during randomized treatment occurred in an adult receiving placebo. TEAEs with an incidence $\geq 5\%$ for LDX vs placebo, respectively, were dry mouth (11.4% vs 0%), headache (11.4% vs 4.7%), decreased appetite (6.8% vs 2.4%), nasopharyngitis (5.7% vs 3.5%), and insomnia (4.5% vs 7.1%). Mean (SD) change from week 8 to 14 in SBP, DBP, and pulse for LDX was 2.3 (9.04) mmHg, 0.9 (6.61) mmHg, and 3.3 (8.45) bpm, respectively. No clinically significant mean changes were seen in ECG and laboratory findings.

Conclusion: Augmentation with LDX for adults with MDD and residual symptoms on escitalopram met prespecified signal detection parameters. Further studies are needed. The safety profile of LDX was consistent with prior LDX ADHD studies and long-acting stimulant use.

INTRODUCTION

- Antidepressant monotherapy is effective in some patients with major depressive disorder (MDD), but most will not achieve remission with initial treatment¹
 - In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 47% of study participants achieved response and 33% achieved remission with citalopram monotherapy based on the 16-Item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR)²
- Psychostimulants have been used to augment antidepressants based on the following rationale:
 - The monoamine deficiency hypothesis of MDD suggests that depression is related to deficiency in the monoamine-based neurotransmitters serotonin, norepinephrine, and dopamine³
 - Amphetamines increase synaptic levels of dopamine and norepinephrine⁴
- Case reports have indicated that d-amphetamine may be beneficial as augmentation treatment for depression^{5,6}
- Lisdexamfetamine dimesylate (LDX) is a prodrug of d-amphetamine
 - After oral administration, LDX is converted to the amino acid l-lysine and therapeutically active d-amphetamine; conversion occurs primarily in the blood⁷
 - LDX is approved for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children (6-12 years), adolescents (13-17 years), and adults⁸

OBJECTIVE

- The primary objective of this proof-of-concept study was to evaluate the efficacy of LDX vs placebo as augmentation for treatment of MDD in adults with residual depressive symptoms following 8 weeks of escitalopram treatment by assessing mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score
 - Secondary assessments presented here include mean change in Hamilton Rating Scale of Depression (HAM-D17) QIDS-SR, Clinical Global Impressions-Severity (CGI-S) and -Improvement (CGI-I), and safety profile

METHODS

Study Design (Figure 1)

- Double-blind, multicenter (15 US sites), placebo-controlled, randomized, parallel-group, exploratory study of LDX or placebo for 6 weeks as augmentation to escitalopram oxalate in adults with MDD
 - Conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki and approved by each center's institutional review board
 - All participants provided written informed consent

Open-Label Escitalopram Treatment Phase (Weeks 0-8)

- Baseline assessments (week 0) and open-label escitalopram⁹ (Figure 1)
 - Escitalopram initiated at 10 mg/d; after 1 week, increased to 20 mg/d

Randomized Treatment Phase (Weeks 8-14)

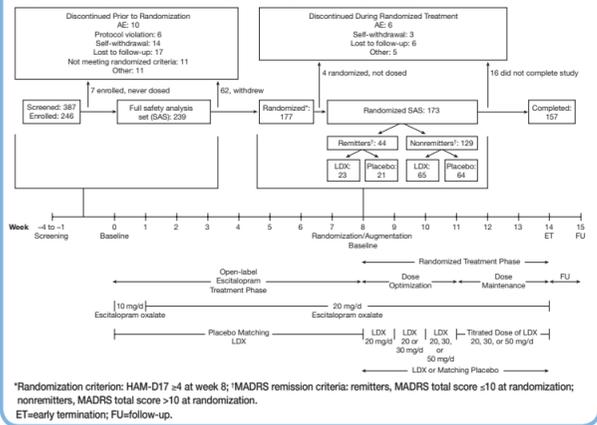
- Eligible participants were randomized in a 1:1 ratio to double-blind treatment with dose-optimized LDX or placebo as augmentation therapy to escitalopram
- Participants were eligible for randomization and entry into the double-blind augmentation treatment phase if both of the following criteria were met:
 - Residual MDD symptoms at week 8 (HAM-D17 score ≥ 4)
 - No changes in physical examination, laboratory, electrocardiogram (ECG), or vital signs during open-label escitalopram treatment phase that precluded study continuation
- LDX dosing was initiated at 20 mg/d
 - Adjusted weekly to 20, 30, or 50 mg/d based on investigator-determined clinical response and tolerability
 - If deemed appropriate by the investigator, a 1-time dose decrease was permitted
 - LDX dose at week 11 was maintained for weeks 12-14

Efficacy and Safety of Lisdexamfetamine Dimesylate as Augmentation Therapy in Adults With Major Depressive Disorder Treated With an Antidepressant

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Figure 1. Diagram of study design and disposition of participants



*Randomization criterion: HAM-D17 ≥ 4 at week 8; *MADRS remission criteria: remitters, MADRS total score ≤ 10 at randomization; nonremitters, MADRS total score >10 at randomization. ET=early termination; FU=follow-up.

Participants

- Key inclusion criteria
 - Adults (18-55 years) with nonpsychotic MDD
 - MDD diagnosis defined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and confirmed by Module A of the Mini-International Psychiatric Interview
 - Screening/baseline HAM-D17 score ≥ 10 (in participants receiving treatment for their current depressive episode) or ≥ 22 (in participants not receiving treatment for their current depressive episode)
- Key exclusion criteria
 - Current MDD episode that is unresponsive to escitalopram or 2 other antidepressants; lifetime history of MDD episodes that are unresponsive to escitalopram or ≥ 3 other antidepressants
 - Severe comorbid Axis II disorder and severe Axis I disorder (assessed by SCID-I)
 - ADHD (assessed based on historical diagnosis and a screening questionnaire)
 - History of or current suicide risk, attempts, or ideations
 - Family history of sudden cardiac death or ventricular arrhythmias or personal history of symptomatic cardiovascular disease or structural cardiac abnormalities
 - History of or current substance abuse or dependence

Efficacy Assessments and Endpoints

- MADRS total score (primary efficacy variable; weeks 0-14): a validated, semistructured clinician interview with 10 items (scored 0-6) in 7 domains; scores range from 0-60
- HAM-D17 (weeks 0-14): a validated clinician-administered 17-item checklist (8 scored 0-4; 9 scored 0-2) of depressive symptoms in 9 domains; scores range from 0-50
- QIDS-SR (weeks 0, 8, and 14): a validated self-report instrument comprising 16 items (scored 0-3); scores range from 0-27
- CGI-I (weeks 1-14) and CGI-S (weeks 0, 8, and 14): global evaluation of illness improvement and severity, respectively, over time; CGI-I scores range from 1 (very much improved) to 7 (very much worse) and CGI-S scores range from 1 (normal, not at all ill) to 7 (the most extremely ill)

Safety Assessments

- Adverse events (AEs) were assessed at all visits and classified using the *Medical Dictionary for Regulatory Activities* (MedDRA), Version 11.1
 - Treatment-emergent AEs (TEAEs) were AEs that started or deteriorated on or after the date of the first dose of study drug during the randomized treatment phase and no later than 3 days following the last dose of study drug
- Vital signs (systolic blood pressure [SBP], diastolic [DBP], and pulse) and weight were assessed at all visits
- Laboratory (screening, weeks 8, 11, and 14) and physical exams (screening, weeks 8 and 14) were assessed
- ECGs were assessed at screening, week 0, and weeks 8-14
- The Columbia Suicide Severity Rating Scale (C-SSRS) was administered at all visits
- **Statistical Analysis**
 - Primary efficacy analysis
 - Primary efficacy outcome: mean change in MADRS total score from week 8 to 14
 - Based on primary efficacy analysis set defined as all escitalopram nonremitters (participants with MADRS total score >10 at week 8) who took ≥ 1 dose of randomized augmentation treatment and who had ≥ 1 postrandomization MADRS assessment
 - Last observation carried forward: the last completed assessment prior to study discontinuation or study termination was carried over for endpoint analysis

- Analysis of covariance (ANCOVA) model, with randomized augmentation treatment group as factor and augmentation baseline MADRS as a covariate
- 2-sided significance level of 0.10
- For the primary efficacy analysis set, adjusted effect size for augmentation of LDX vs placebo was calculated post hoc based on ANCOVA model with randomized augmentation treatment group as a factor and the MADRS total score at augmentation baseline as a covariate
- Number needed to treat (NNT) was calculated as the reciprocal of the difference between LDX and placebo remitters (MADRS total score ≤ 10) at week 14
- Secondary efficacy analyses
 - Secondary efficacy outcome variables: HAM-D17, QIDS-SR, CGI-I, and CGI-S
 - Based on full analysis set defined as all randomized participants who took ≥ 1 dose of randomized medication and who had ≥ 1 postrandomization MADRS assessment
 - ANCOVA models with outcome variables, augmentation treatment, and augmentation baseline remission status (when applicable) as factors and corresponding augmentation baseline as covariate
 - 2-sided significance level of 0.10
- Proportion of participants achieving response (50% reduction) or remission was analyzed using Fisher exact tests or Cochran-Mantel-Haenszel tests stratified by augmentation baseline remission status (when applicable)
- Safety analyses
 - Safety analysis set: all participants who took ≥ 1 dose of open-label escitalopram and who had ≥ 1 posttreatment safety assessment
 - Randomized safety analysis set: all participants who took ≥ 1 dose of randomized LDX or placebo and who had ≥ 1 postrandomization safety assessment

RESULTS

Participant Disposition (Figure 1), Demographics, and Baseline Characteristics (Table 1)

- Mean (SD) time since first diagnosis with MDD was 6.2 (8.17) years, since first depressive episode was 9.8 (9.53) years, and since onset of current episode was 15.5 (28.58) months
 - 72.8% of participants had experienced 1 or more prior depressive episodes

Table 1. Baseline Demographics and Clinical Characteristics of Participants: Overall Safety Analysis Set, Escitalopram Nonremitters, and All Randomized Participants

Characteristic	Statistic	Randomized Augmentation Treatment Phase				
		SAS (n=239)	Escitalopram Nonremitters (n=65)	Placebo (n=64)	All Randomized Participants (n=129)	
Age (y)	Mean (SD)	37.9 (10.21)	41.2 (9.60)	39.5 (10.40)	39.4 (9.65)	
Sex	Male	n (%)	97 (40.6)	28 (43.1)	22 (34.4)	35 (39.8)
	Female	n (%)	142 (59.4)	37 (56.9)	42 (65.6)	53 (60.2)
Race	White	n (%)	177 (74.1)	51 (78.5)	47 (73.4)	67 (76.1)
	All others	n (%)	62 (25.9)	14 (21.5)	17 (26.6)	21 (23.9)
Ethnicity	Hispanic	n (%)	15 (6.3)	3 (4.6)	4 (6.3)	3 (3.4)
	Non-Hispanic	n (%)	224 (93.7)	62 (95.4)	60 (93.8)	85 (96.6)
Screening height (cm)	Mean (SD)	170.0 (9.51)	171.2 (9.45)	168.5 (9.78)	170.7 (9.53)	
Screening weight (kg)	Mean (SD)	83.5 (18.35)	85.9 (18.41)	81.2 (19.83)	85.0 (18.68)	
Baseline ¹ MADRS total score	Mean (SD)	32.8 (4.86)	20.3 (7.16)	20.8 (6.42)	16.6 (8.90)	
Baseline ¹ HAM-D17 score	Mean (SD)	25.1 (3.05)	15.8 (5.32)	16.3 (4.77)	13.4 (6.15)	

¹Nonremitters: MADRS total score >10 at randomization. ²Baseline scores for the SAS were at study baseline (week 0); baseline scores for the randomized double-blind phase were at randomization augmentation baseline (week 8). Percentages may not total 100% owing to rounding.

Efficacy

- MADRS (Figure 2a and Table 2)
 - Overall mean (SD) change in MADRS total scores with open-label escitalopram treatment (n=237) at week 8 was -15.6 (9.66)
 - For escitalopram nonremitters, augmentation with LDX and placebo decreased MADRS total scores (improved) from weeks 9-14 compared with week 8 (Figure 2a)
 - For escitalopram remitters, augmentation with LDX decreased MADRS total scores vs placebo significantly ($P=.0902$) at week 14 (Figure 2a and Table 2)
 - Adjusted effect size (90% confidence interval [CI]) for change in MADRS total scores with LDX vs placebo at endpoint (week 14) was -0.3 (-0.6, 0.0), indicating that LDX treatment is more favorable
 - NNT for symptom remission (MADRS total score ≤ 10) with LDX augmentation was 6.7 for escitalopram nonremitters
 - For escitalopram remitters, least squares (LS) mean (90% CI) changes in MADRS total scores at week 14 were 0.1 (-1.8, 2.0) and -1.1 (-3.1, 0.9) for those taking LDX and placebo, respectively ($P=.4726$)

Figure 2. MADRS (2a) and HAM-D17 (2b) total score change from augmentation baseline for escitalopram nonremitters.

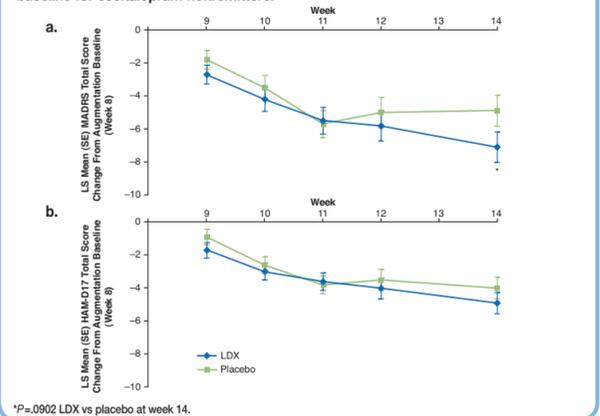


Table 2. Effects of Randomized Treatment With LDX and Placebo on Depressive Symptoms Assessed by MADRS, HAM-D17, and QIDS-SR in Escitalopram Nonremitters and All Randomized Participants

	Measure	Statistic	Escitalopram Nonremitters			All Randomized Participants		
			LDX (n=65)	Placebo (n=64)	P value	LDX (n=88)	Placebo (n=85)	P value
MADRS	Change in total score	LS mean change (90% CI)	-7.1 (-8.7, -5.6)	-4.9 (-6.4, -3.3)	.0902	-4.8 (-6.3, -3.4)	-3.5 (-4.9, -2.0)	.2101
	50% decrease at week 14	n (%)	43 (66.2)	32 (50.0)	.0754	64 (72.7)	52 (61.2)	.1038
HAM-D17	MADRS total score ≤ 10 at week 14	n (%)	32 (49.2)	22 (34.4)	.1088	52 (59.1)	40 (47.1)	.1049
	Change in total score	LS mean change (90% CI)	-4.9 (-6.0, -3.9)	-4.0 (-5.1, -2.9)	.3091	-3.9 (-5.0, -2.9)	-3.4 (-4.5, -2.4)	.5109
QIDS-SR	50% decrease at week 14	n (%)	41 (63.1)	35 (54.7)	.3736	62 (70.5)	55 (64.7)	.4376
	HAM-D17 total score ≤ 10 at week 14	n (%)	21 (32.3)	17 (26.6)	.5633	37 (42.0)	33 (38.8)	.7073
QIDS-SR	Change in total score	LS mean change (90% CI)	-2.4 (-3.1, -1.6)	-1.2 (-2.0, -0.4)	.0774	-2.5 (-3.1, -1.8)	-1.2 (-1.9, -0.6)	.0203

*For QIDS-SR, n=83 and n=82 for escitalopram nonremitters in the LDX and placebo groups, and n=85 and n=83 for all randomized LDX and placebo participants, respectively.

- HAM-D17 (Figure 2b and Table 2)
 - For escitalopram nonremitters, augmentation with LDX and placebo decreased HAM-D17 total scores from weeks 9-14 (Figure 2b) compared with week 8
 - Change in HAM-D17 scores from week 8 to 14 were numerically greater with LDX vs placebo; these changes were not statistically significant (Table 2)
- QIDS-SR
 - For escitalopram nonremitters, augmentation with LDX significantly decreased QIDS-SR total scores vs placebo at week 14 compared with week 8 ($P=.0774$) (Table 2)
 - For escitalopram remitters, LS mean (90% CI) change in QIDS-SR total scores at week 14 were -1.9 (-2.9, -0.9) and -0.4 (-1.4, -0.5) for those taking LDX and placebo, respectively ($P=.0852$)
- CGI
 - At week 14, LS mean (SE) CGI-I scores were similar in both groups (LDX, 2.4 [0.14]; placebo, 2.6 [0.14]; $P=.3199$)
 - However, CGI-S scores at week 14 showed a numerically greater proportion of patients had no to mild illness with LDX (88.9%) vs placebo (61.3%)

Safety (Table 3)

- During augmentation with LDX and placebo, 53 (60.2%) and 42 (49.4%) participants, respectively, experienced TEAEs

- No participants on LDX experienced serious TEAEs
- 1/85 (1.2%) on placebo experienced rhabdomyolysis, a serious TEAE that resolved over 20 days
- 16/88 (18.2%) and 13/85 (15.3%) on LDX and placebo, respectively, experienced psychiatric TEAEs
- 2/88 (2.3%) on LDX were discontinued owing to TEAEs (increased liver enzymes; ECG nonspecific T-wave abnormality)
- 1/85 (1.2%) on placebo was discontinued owing to TEAEs (increased gamma glutamyltransferase)
- Most TEAEs were mild or moderate in intensity
- No participants receiving LDX or placebo experienced psychosis/mania events, suicidal events, or aggression events
- C-SSRS
 - During augmentation, 1, 2, and 1 participants receiving LDX at weeks 9, 10, and 14, respectively, and 1 participant receiving placebo at weeks 9, 10, 12, and 14 reported suicidal ideations by answering "yes" to the question: "Have you wished you were dead or wished you could go to sleep and not wake up?"
 - At screening, 1 participant exhibited suicidal behavior that resulted in moderate physical damage and required medical attention
 - No participants exhibited suicidal behavior during augmentation treatment

Table 3. TEAEs Occurring in $\geq 5\%$ of Participants Receiving LDX or Placebo During Randomized Augmentation of Escitalopram Treatment

TEAE, n (%) (MedDRA Preferred Term; Version 11.1)	LDX (n=88)	Placebo (n=85)
Any TEAE	53 (60.2)	42 (49.4)
Dry mouth	10 (11.4)	0
Headache	10 (11.4)	4 (4.7)
Decreased appetite	6 (6.8)	2 (2.4)
Nasopharyngitis	5 (5.7)	3 (3.5)
Insomnia	4 (4.5)	6 (7.1)

Vital Signs and ECG (Table 4)

- Small mean increases in blood pressure and pulse were noted; no increase in QTcF was seen with LDX (Table 4)
- There were no changes over time in mean clinical laboratory values that were of clinical concern

Table 4. Mean (SD) Change From Study Baseline and Augmentation Baseline to Week 14 in Vital Signs and ECG by Randomized Treatment Group

Parameter, Mean (SD)	Randomized Augmentation Treatment Phase				
	Change From Study Baseline (Week 0)	Change From Augmentation Baseline (Week 8)	LDX	Placebo	
Vital sign	SBP (mm Hg)	1.5 (8.52)	-1.4 (10.19)	2.3 (9.04)	0.5 (8.98)
	DBP (mm Hg)	0.9 (5.83)	-1.4 (8.31)	0.9 (6.61)	-1.0 (7.19)
	Pulse (bpm)	-0.1 (9.37)	-1.2 (9.05)	3.3 (8.45)	-0.4 (7.10)
	Weight (kg)	-1.4 (3.20)	0.0 (2.93)	-1.2 (2.00)	0.3 (2.05)
ECG findings	BMI (kg/m ²)	-0.5 (1.11)	0.0 (1.00)	-0.4 (0.70)	0.1 (0.70)
	Heart rate (bpm)	-0.1 (11.02)	-2.8 (8.35)	4.8 (8.64)	-0.4 (7.39)
	QTcF (msec)	3.4 (12.32)	3.3 (11.86)	-4.9 (11.84)	-1.6 (11.23)

bpm=beats per minute.

CONCLUSIONS

- In this proof-of-concept study, augmentation with LDX for adult escitalopram nonremitters with MDD and residual symptoms while on escitalopram met prespecified signal-detection parameters, suggesting efficacy vs placebo in improving depressive symptoms
- 44 of 173 randomized participants with residual symptoms, based on HAM-D17 scores, were considered escitalopram remitters based on MADRS total scores, suggesting that many patients may continue to experience residual symptoms despite achieving overall remission criteria with treatment
- Adjusted effect size of MADRS total scores for LDX vs placebo at endpoint (-0.3) was similar to the effect size (0.228) predicted to achieve significant differences in the STAR*D analysis¹⁰ and similar to effect size (0.35) for MADRS total scores for aripiprazole vs placebo as augmentation of standard antidepressant treatment¹¹
- LDX improved MDD symptoms vs placebo as determined by both clinician-assessed and patient self-reported measures for escitalopram nonremitters
- LDX improved self-assessed MDD symptoms for escitalopram remitters
 - This may suggest that self-perceived improvement in symptoms may register changes that are not well captured by clinician-rated assessment
- Limitations in this proof-of-concept study included
 - Small sample size, limiting statistical power
 - Relatively short duration of the study precluded interpretation of long-term benefits of augmentation with LDX and limited detection of AEs occurring at later times
 - Relatively narrow range of HAM-D17 scores relative to study entry criteria and criteria for residual symptoms may have limited the ability to discern change in symptom scores
- The safety profile of LDX was consistent with prior LDX ADHD studies and long-acting stimulant use

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