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# Efficacy of Lisdexamfetamine in Adults With Moderate to Severe Binge-Eating Disorder
## A Randomized Clinical Trial

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**IMPORTANCE** The ability of pharmacotherapies to prevent relapse and maintain efficacy with long-term treatment in psychiatric conditions is important.

**OBJECTIVE** To assess lisdexamfetamine dimesylate maintenance of efficacy in adults with moderate to severe binge-eating disorder.

**DESIGN, SETTING, AND PARTICIPANTS** A multinational, phase 3, double-blind, placebo-controlled, randomized withdrawal study including 418 participants was conducted at 49 clinical research study sites from January 27, 2014, to April 8, 2015. Eligible adults met *DSM-IV-R* binge-eating disorder criteria and had moderate to severe binge eating disorder (≥3 binge-eating days per week for 14 days before open-label baseline; Clinical Global Impressions–Severity [CGI-S] scores ≥4 [moderate severity] at screening and open-label baseline). Following a 12-week, open-label phase (dose optimization, 4 weeks [lisdexamfetamine dimesylate, 50 or 70 mg]; dose maintenance, 8 weeks), lisdexamfetamine responders (≤1 binge eating day per week for 4 consecutive weeks and CGI-S scores ≤2 at week 12) were randomized to placebo or continued lisdexamfetamine during a 26-week, double-blind, randomized withdrawal phase.

**INTERVENTIONS** Lisdexamfetamine administration.

**MAIN OUTCOMES AND MEASURES** The primary outcome variable, time to relapse (≥2 binge-eating days per week for 2 consecutive weeks and ≥2-point CGI-S score increases from randomized withdrawal baseline), was analyzed using a log-rank test (primary analysis); the analysis was stratified for dichotomized 4-week cessation status. Safety assessments included treatment-emergent adverse events.

**RESULTS** Of the 418 participants enrolled in the open-label phase of the study, 411 (358 [87.1%] women; mean [SD] age, 38.3 [10.4] years) were included in the safety analysis set. Of 275 randomized lisdexamfetamine responders (placebo, n = 138; lisdexamfetamine, n = 137), the observed proportions of participants meeting relapse criteria were 3.7% (5 of 136) for lisdexamfetamine and 32.1% (42 of 131) for placebo. Lisdexamfetamine demonstrated superiority over placebo on the log-rank test ($\chi^2_1$, 40.37; $P < .001$) for time to relapse; the hazard ratio, based on a Cox proportional hazards model for lisdexamfetamine vs placebo, was 0.09 (95% CI, 0.04-0.23). The treatment-emergent adverse events observed were generally consistent with the known profile of lisdexamfetamine.

**CONCLUSIONS AND RELEVANCE** Risk of binge-eating relapse over 6 months was lower in participants continuing lisdexamfetamine than in those randomized to placebo. The hazard for relapse was lower with lisdexamfetamine than placebo.

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Supplemental content

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Lisdexamfetamine dimesylate is approved for adults with moderate to severe binge-eating disorder (BED) in the United States and Canada.[1] In 2 identically designed, randomized, double-blind, placebo-controlled trials, dose-optimized lisdexamfetamine dimesylate, 50 or 70 mg/d, produced clinically meaningful and statistically significant reductions in binge-eating days per week vs placebo in adults with protocol-defined moderate to severe BED.[2] The safety and tolerability of lisdexamfetamine in short-term clinical studies of BED[2,3] were consistent with its known profile in attention-deficit/hyperactivity disorder.[1]

The ability of pharmacotherapies to prevent relapse and maintain long-term efficacy in psychiatric conditions is important. This report describes the results of a double-blind, placebo-controlled, randomized withdrawal study that assessed the maintenance of efficacy of lisdexamfetamine in adults with protocol-defined moderate to severe BED.

### Key Points

**Question** After initial response to lisdexamfetamine in adults with moderate to severe binge-eating disorder and no other current psychiatric comorbidity, is the relapse risk for binge eating lower with continued lisdexamfetamine treatment compared with placebo?

**Findings** In this randomized clinical trial of 418 participants, continued lisdexamfetamine treatment was associated with a significantly lower relapse risk for binge eating over 6 months than placebo (3.7% vs 32.1%). The estimated hazard for relapse with lisdexamfetamine was 11 times lower than with placebo.

**Meaning** These findings extend and support previous findings of the efficacy of lisdexamfetamine for the treatment of moderate to severe binge-eating disorder.

## Methods

### Study Design and Treatment

This multinational, phase 3, double-blind, placebo-controlled, randomized withdrawal study was conducted at 49 sites between January 27, 2014, and April 8, 2015. Participant enrollment ranged from 1 to 16 across sites (United States: n = 337 [38 sites], Germany: n = 37 [6 sites], Sweden: n = 24 [2 sites], Spain: n = 15 [2 sites], and Canada: n = 5 [1 site]).

Using an enrichment strategy,[4] the study included a 12-week open-label phase (dose optimization: 4 weeks [lisdexamfetamine dimesylate, 50 or 70 mg]; dose maintenance: 8 weeks); a 26-week, double-blind, randomized withdrawal phase; and a follow-up visit (eFigure in Supplement 1). The study protocol is available in Supplement 2.

The study was conducted according to International Conference on Harmonisation of Good Clinical Practice guidelines, the Declaration of Helsinki,[5] and applicable ethical and legal requirements. The protocol and supporting information were approved by ethics committees and regulatory agencies from participating countries. In the United States, a central ethics committee (Copernicus) and local ethics committee (University of Cincinnati and McLean Hospital/Partners HealthCare) were used. Ethics committees in Europe varied by site and country. The regulatory agencies providing approval for the study included the US Food and Drug Administration, the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte) for Germany, the Medical Products Agency for Sweden, the Agencia Española de Medicamentos y Productos Sanitarios for Spain, and the Therapeutic Products Directorate for Canada. Participants provided written informed consent before study-specific procedures were conducted and received financial compensation (approximately $40 per visit to cover travel, child care, or other incidental expenses).

At open-label baseline, participants began 12 weeks of open-label lisdexamfetamine. Participants received their once-daily dose at approximately 7 AM. During week 1, treatment started with lisdexamfetamine dimesylate, 30 mg/d. During weeks 2 and 3, respectively, the lisdexamfetamine dimesylate daily dosage was titrated to 50 mg and then, as clinically indicated and tolerated, to 70 mg. Down-titration to 50 mg was allowed if 70 mg was not tolerated. Dose changes were not permitted after week 3. After a dose reduction, further changes were not allowed. If 50 mg of lisdexamfetamine was not tolerated, participants were discontinued. The lisdexamfetamine dose established during dose optimization was maintained for the entire study.

After the open-label phase, lisdexamfetamine responders (participants reporting ≤1 binge-eating day per week for 4 consecutive weeks and having Clinical Global Impressions-Severity [CGI-S][6] scores ≤2 [borderline ill or less] at randomization) entered the double-blind, randomized withdrawal phase and were randomized 1:1 to placebo or continued dose-optimized lisdexamfetamine. Randomization was accomplished using an interactive web response system. For blinding, treatments were identical in appearance.

### Participants

Eligible adults (18-55 years) met *DSM-IV-TR* BED criteria (confirmed by the eating disorders module of the Structured Clinical Interview for the *DSM-IV-TR* Axis I Disorders and the Eating Disorder Examination Questionnaire) and had protocol-defined moderate to severe BED (≥3 binge-eating days per week for 14 days before open-label baseline based on participant-reported binge-eating diaries and CGI-S scores ≥4 [at least moderate severity] at screening and open-label baseline). Participants were also required to have a body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 18 to 45 at screening and open-label baseline. Women of childbearing age were required to have a negative serum pregnancy test at screening, a negative urine pregnancy test at open-label baseline, and to use acceptable contraceptive methods. Serum pregnancy and urine pregnancy tests, respectively, were also obtained at the last on-treatment visit or early termination (ET) and at 4-week intervals through treatment week 36.

Study exclusion criteria (eMethods in Supplement 1) included current anorexia nervosa or bulimia nervosa, comorbid psychiatric disorders (uncontrolled and associated with significant symptoms), psychotherapy or weight loss support for

BED (initiated <3 months before screening), psychostimulant use for BED (≤6 months before screening), screening Montgomery-Åsberg Depression Rating Scale[7] score of 18 or higher, past suicide attempt or current active suicidal ideation, history of cardiovascular health problems, clinically significant electrocardiogram (ECG) abnormalities at screening, moderate or severe hypertension, a history of stimulant abuse or dependence, recent (within the past 6 months) substance abuse or dependence, or use of prohibited medications.

## Outcomes

### Efficacy

The primary efficacy outcome was time to relapse (the occurrence of ≥2 binge-eating days per week for 2 consecutive weeks and a ≥2-point CGI-S score increase from randomized withdrawal baseline) from randomization. The number of binge-eating days per week (confirmed binge-eating days between visits multiplied by 7 and divided by the number of nonmissing diary days during the period) was based on clinical interviews conducted by trained investigators. The inclusion of nonmissing diary days ensured that the number of binge-eating days per week was not artificially reduced. Qualified clinicians were trained to ensure standardization. Between-site reliability was not evaluated, but personnel at all sites received extensive training (by J.I.H. and S.L.M.) on *DSM-IV-TR* BED criteria, core BED symptoms, the definition of binge episodes, and binge diary content, completion instructions, and interpretation.

Secondary outcomes included binge-eating days per week, CGI-S scores, and Yale-Brown Obsessive Compulsive Scale modified for Binge Eating (Y-BOCS-BE) scores.[8] Binge-eating days per week information was collected at open-label baseline, all visits, and follow-up. The CGI-S, which rated BED severity on a 7-point scale (1, normal, not at all ill; to 7, among the most extremely ill), was assessed at screening, all visits, and follow-up. The Y-BOCS-BE, a validated 10-item clinician-rated scale used in other studies[9-11] to assess the obsessiveness of binge-eating thoughts and compulsiveness of binge-eating behaviors (0, no symptoms, to 4, extreme symptoms; total score range, 0-40), was assessed at open-label baseline, week 4, randomization baseline, and weeks 16, 20, 24, 28, 32, and 38 or ET.

### Safety and Tolerability

Safety and tolerability assessments included adverse events (AEs), vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse) and weight, ECG, clinical laboratory values, and Columbia-Suicide Severity Rating Scale (C-SSRS)[12] and Amphetamine Cessation Symptom Assessment (ACSA)[13] responses. Adverse events were collected from the time of informed consent through follow-up. Vital signs and weight were assessed at screening and each visit; vital signs were also assessed at follow-up. A 12-lead ECG was performed at screening, open-label baseline, and weeks 4, 12, 14, 20, 28, and 38 or ET. The C-SSRS, a semistructured interview examining suicidal ideation and behavior, was assessed at screening and all visits through follow-up. The ACSA, a 16-item self-completed questionnaire rated on 5-point scales (0, not at all, to 4, extremely; total score range, 0-64), was evaluated at open-label baseline, randomized withdrawal baseline, week 38 or ET, and each day until follow-up.

## Statistical Analysis

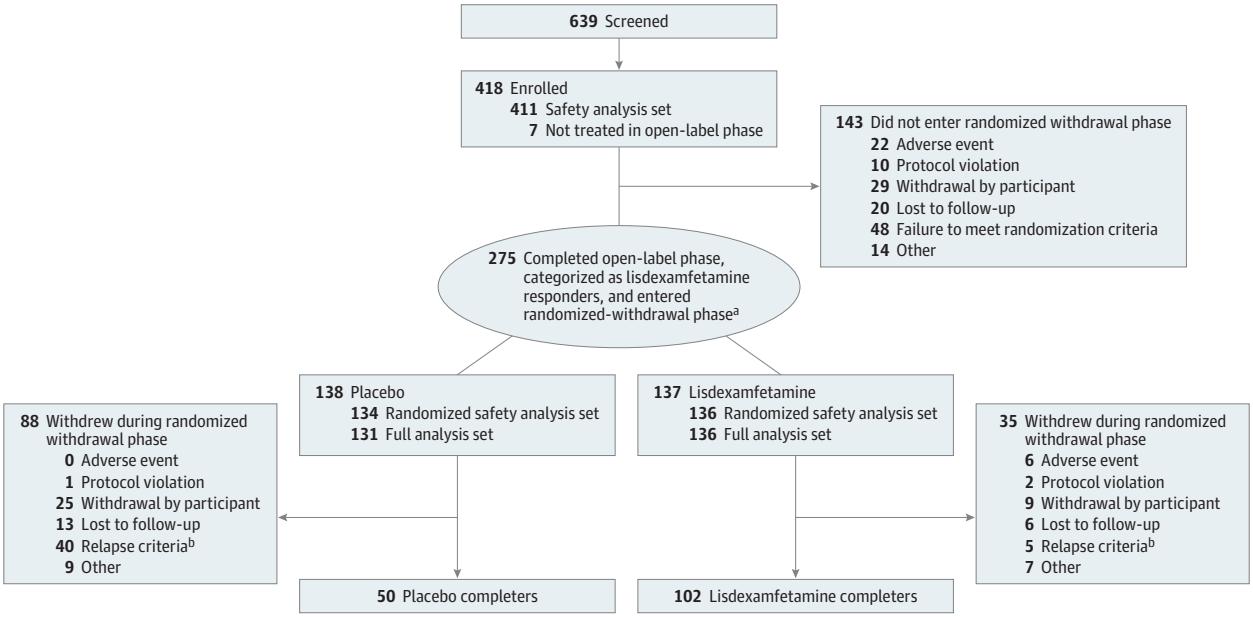
Sample size was determined for the primary outcome using nQuery Advisor, version 6.0 (Statistical Solutions). Assuming true cumulative relapse rates of 30% and 55%, respectively, for lisdexamfetamine and placebo (hazard ratio for lisdexamfetamine vs placebo, 0.447), 72 participants needed to relapse to provide 90% power for the 2-sided log-rank test (significance level, 5%). Assuming a 20% open-label dropout rate and 65% response rate for participants completing open-label treatment, 214 participants (107 receiving treatment) were to be randomized. Assuming a 20% discontinuation rate for randomized participants before relapse, 72 participants experiencing relapse would be observed based on the assumed true relapse rates.

The primary efficacy analysis of time to relapse (in days) from randomization was conducted in the full analysis set (randomized participants receiving ≥1 study drug dose during the randomized withdrawal phase and having ≥1 postrandomization CGI-S assessment). The primary statistical analysis used a stratified log-rank test, stratifying for 4-week cessation status (yes/no [no binge-eating days in the 4 weeks preceding randomization]). Statistical significance was set at a 2-sided $P < .05$. A secondary analysis of time to relapse used a Cox proportional hazards model (2-sided $P < .05$) stratified by 4-week cessation status. Time to relapse is presented using the Kaplan-Meier method. A life-table estimation for the proportion of participants relapsing was generated using the Kaplan-Meier method, with 95% CI estimates calculated by the Greenwood formula.

Two types of time to relapse sensitivity analyses (based on alternative relapse criteria or alternative responder criteria) were conducted. Analyses using alternative relapse criteria examined relapse (1) based on the occurrence of 2 or more binge-eating days per week for 2 consecutive weeks (binge-eating days per week analysis [excluding CGI-S]) and (2) using prespecified primary relapse criteria but excluding relapses within 18 days of randomization (18-day exclusion analysis). The 18-day exclusion criteria encompassed the first postbaseline visit, allowing for exclusion of participants whose relapse might be related to abrupt treatment discontinuation. Analyses using alternative response criteria included lisdexamfetamine responders meeting 8-week cessation criteria (8-week responder analysis [≤1 binge-eating day per week for 8 consecutive weeks before randomization and a CGI-S score of ≤2 at weeks 8-12]), which represented a more stable response than the prespecified criteria. Statistical assessment of these analyses employed the model used for the primary efficacy analysis.

Treatment differences in the change from randomized withdrawal baseline for binge-eating days per week and Y-BOCS-BE total score were assessed in the full analysis set using mixed-effects models for repeated-measures analysis over all postrandomization visits, with treatment, visit, and their interaction as factors; baseline score as a covariate; and

Figure 1. CONSORT Diagram




[a] Only protocol-defined lisdexamfetamine dimesylate responders (those reporting ≤1 binge-eating day per week for the past 4 consecutive weeks [28 days] with a Clinical Global Impressions-Severity score ≤2) were randomized.

[b] The occurrence of 2 or more binge-eating days per week for 2 consecutive weeks and a 2-point or more CGI-S score increase from randomized withdrawal baseline.

the interaction of baseline score with visit included in the model. The CGI-S score distribution differences at week 38 or ET were assessed in the full analysis set using a covariate-adjusted Cochran-Mantel-Haenszel test with a modified ridit score, adjusting for randomized withdrawal baseline score as a covariate. Secondary outcome analyses were not adjusted for multiplicity, so all *P* values are nominal and descriptive.

Safety and tolerability are described in the safety analysis set (participants receiving ≥1 open-label study drug dose) for the open-label phase and the randomized safety analysis set (randomized participants receiving ≥1 blinded randomized withdrawal study drug dose) for the randomized withdrawal phase.

## Results

### Participant Disposition and Demographics

Of the 418 participants enrolled in the study, 411 (358 [87.1%] women; mean [SD] age, 38.3 [10.4] years) were included in the safety analysis set. Participant disposition is summarized in **Figure 1**; demographic and clinical characteristics are reported in **Table 1**. Most participants were white, female, and obese. The mean (SD) open-label baseline number of binge-eating days per week in the safety analysis set (n = 411) was 4.86 (1.24).

### Open-Label Phase

#### Exposure

The mean (SD) daily lisdexamfetamine dose and exposure duration, respectively, in the safety analysis set was 57.13 (9.74) mg and 73.6 (22.7) days. Adherence (taking 80%-120% of study medication based on the number of capsules taken ×100 / total dosing days) was 99.3% (408 of 411) in the safety analysis set.

#### Binge-Eating Days per Week and CGI-S Scores

The mean number of binge-eating days per week decreased from 4.76 (1.21) at open-label baseline to 0.13 (0.27) at randomized withdrawal baseline in the full analysis set. Participants in the full analysis set (n = 267) were categorized as moderately (142 [53.2%]), markedly (96 [36.0%]), severely (28 [10.5%]), and among the most extremely (1 [0.4%]) ill on the CGI-S at open-label baseline and as normal, not at all ill (212 [79.4%]) or borderline mentally ill (55 [20.6%]) at randomized withdrawal baseline.

#### Safety and Tolerability

Many participants reported treatment-emergent AEs (TEAEs) (**Table 2**); most were mild or moderate in severity. Three serious TEAEs were reported (congenital anomaly in offspring, pneumonia, and convulsion; 1 each). The TEAEs reported by more than 5% of participants were dry mouth, headache, insomnia, decreased appetite, nausea, constipation, anxiety, hyperhidrosis, feeling jittery, and diarrhea. No deaths were reported.

Mean increases in blood pressure and pulse and decreases in weight from open-label baseline at week 12 or ET were observed with lisdexamfetamine (Table 2). Electrocardiographic-assessed heart rate increases at week 12 or ET were also observed (Table 2). Mean changes from open-label baseline in clinical laboratory values were small; no clinically meaningful changes were noted.

Table 1. Baseline[a] Demographic and Clinical Characteristics, Full Analysis Set[b]

| Characteristic | Placebo (n = 131) | Lisdexamfetamine Dimesylate (n = 136) |
|---|---|---|
| Age, mean (SD), y | 40.1 (9.9) | 37.3 (10.0) |
| Sex, No. (%) | | |
| Female | 112 (85.5) | 122 (89.7) |
| Race, No. (%) | | |
| White | 113 (86.3) | 112 (82.4) |
| Nonwhite | 18 (13.7) | 24 (17.6) |
| Weight, mean (SD), kg | 97.66 (21.06) | 92.42 (18.42) |
| BMI, mean (SD) | 34.76 (6.37) | 33.06 (5.63) |
| BMI category, No. (%) | | |
| Normal, ≥18.5 to <25.0 | 9 (6.9) | 11 (8.1) |
| Preobesity, ≥25.0 to <30.0 | 22 (16.8) | 33 (24.3) |
| Obesity class I, ≥30.0 to <35.0 | 35 (26.7) | 43 (31.6) |
| Obesity class II, ≥35.0 to <40.0 | 35 (26.7) | 37 (27.2) |
| Obesity class III, ≥40.0 | 30 (22.9) | 12 (8.8) |
| 4-wk Cessation status, yes, No. (%)[c] | 86 (65.6) | 89 (65.4) |
| Binge eating, mean (SD), d/wk | 4.71 (1.23) | 4.80 (1.19) |
| CGI-S score, mean (SD) | 4.6 (0.7) | 4.5 (0.7) |
| CGI-S, No. (%)[d] | | |
| Moderately ill | 63 (48.1) | 79 (58.1) |
| Markedly ill | 52 (39.7) | 44 (32.4) |
| Severely ill | 15 (11.5) | 13 (9.6) |
| Among the most extremely ill | 1 (0.8) | 0 |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CGI-S, Clinical Global Impressions–Severity.

[a] All values are for open-label baseline except for 4-week cessation status, which applies to the randomized withdrawal baseline.

[b] Randomized participants taking 1 or more study drug dose during the randomized withdrawal phase and having 1 or more postrandomization CGI-S assessment; data are for participants subsequently randomized to placebo or lisdexamfetamine during the randomized withdrawal phase.

[c] Four-week cessation status at randomized withdrawal baseline defined as having no binge days during the previous 4 weeks before randomization (based on case report form).

[d] A CGI-S score of 4 or higher (at least moderately ill) was required for study eligibility (score range, 1 to 7).

On the C-SSRS, positive responses for "wish to be dead" (n = 3) and nonsuicidal self-injurious behavior (n = 2) were reported. No suicide attempts were reported.

## Double-blind, Randomized Withdrawal Phase

### Exposure

The mean daily lisdexamfetamine dimesylate dose in the randomized safety analysis set was 64.05 (8.91) mg; the duration of exposure was 98.9 (72.8) days with placebo and 157.6 (51.6) days with lisdexamfetamine. Adherence was 96.3% (129 of 134) and 100% (136 of 136) with placebo and lisdexamfetamine, respectively.

### Time to Binge-Eating Relapse

The observed percentage of participants meeting relapse criteria was 32.1% (42 of 131) with placebo and 3.7% (5 of 136) with lisdexamfetamine. **Figure 2** shows the time course of relapse (eTable 1 in Supplement 1 provides time to relapse life-table). For the primary analysis, time to relapse statistically favored lisdexamfetamine ($\chi^2_1$, 40.37; $P < .001$). The secondary Cox proportional hazards analysis was also statistically significant (hazard ratio, 0.09; 95% CI, 0.04-0.23; $P < .001$) and in favor of lisdexamfetamine. Sensitivity analyses supported the primary analysis (**Table 3**).

### Other Efficacy

eTable 2 in Supplement 1 summarizes secondary outcomes. At weeks 37 to 38, the least-squares mean treatment difference for the change from randomized withdrawal baseline in binge-eating days per week indicated that there was an increase for placebo compared with lisdexamfetamine (−0.61; 95% CI, −0.81 to −0.42; nominal $P < .001$). At week 38 or ET, CGI-S score distributions differed between treatment groups (nominal $P < .001$), with placebo scores skewed toward more severe illness than lisdexamfetamine scores. At week 38, the least-squares mean treatment difference for the change from randomized withdrawal baseline indicated that there were total score increases for placebo compared with lisdexamfetamine on the Y-BOCS-BE (−5.6; 95% CI, −7.2 to −3.9; nominal $P < .001$).

### Safety and Tolerability

A higher percentage of lisdexamfetamine participants reported TEAEs (Table 2); most were of mild or moderate intensity. Two serious TEAEs were reported during the randomized withdrawal phase for lisdexamfetamine (breast cancer and nerve root compression; 1 each). The TEAEs reported by 5% or more of participants in any treatment group were nasopharyngitis and headache (lisdexamfetamine and placebo), upper respiratory tract infection, and dry mouth (lisdexamfetamine), and fatigue (placebo). No deaths of enrolled participants were reported. The death of an infant born to a participant randomized to lisdexamfetamine was reported. The lisdexamfetamine dimesylate dose was titrated to 70 mg before the participant had a positive serum pregnancy test, at which time treatment was discontinued. At birth, the infant had 3 serious TEAEs (exomphalos, limb malformation, and congenital diaphragmatic hernia), which resulted in death.

Mean decreases in SBP and weight and increases in DBP and pulse were observed with placebo at week 38 or ET; SBP, DBP, and pulse increased and weight decreased with lisdexamfetamine (Table 2). Electrocardiographic-assessed heart rate increases were observed at week 38 or ET (Table 2). Mean changes from baseline in clinical laboratory values were small; no clinically meaningful mean changes were noted.

On the C-SSRS, positive responses for "wish to be dead" (placebo, n = 1; lisdexamfetamine, n = 1) and for nonsuicidal self-injurious behavior (lisdexamfetamine, n = 1) were reported. No suicide attempts were reported.

On the day of last dose at week 38 or ET, mean (SD) aggregate ACSA scores were 4.8 (6.7) with placebo (n = 44) and 4.7 (7.8) with lisdexamfetamine (n = 85). The mean (SD) aggregate ACSA score increased to 6.1 (7.6) on day 2 after the last lisdexamfetamine dose (n = 78) and to 5.1 (7.0) on day 1 after the last placebo dose (n = 40) and was 5.2 (7.9) and 3.9 (5.8),

Table 2. TEAEs and Changes in Vital Signs and ECG From Open-Label Baseline

| Characteristic | Open-Label[a] | Randomized Withdrawal[b] | |
|---|---|---|---|
| | All Participants (n = 411) | Placebo (n = 134) | Lisdexamfetamine Dimesylate (n = 136) |
| Any TEAE, No. (%) | 338 (82.2) | 62 (46.3) | 82 (60.3) |
| Serious TEAE | 3 (0.7) | 0 | 2 (1.5) |
| TEAE related to study drug | 287 (69.8) | 19 (14.2) | 32 (23.5) |
| Severe TEAE[c] | 12 (2.9) | 0 | 4 (2.9) |
| TEAEs leading to discontinuation[d] | 22 (5.4) | 0 | 6 (4.4) |
| TEAEs occurring in ≥5% of participants, No. (%) | | | |
| Dry mouth | 139 (33.8) | 2 (1.5) | 7 (5.1) |
| Headache | 66 (16.1) | 9 (6.7) | 12 (8.8) |
| Insomnia | 46 (11.2) | 2 (1.5) | 1 (0.7) |
| Decreased appetite | 38 (9.2) | 0 | 0 |
| Nausea | 35 (8.5) | 3 (2.2) | 6 (4.4) |
| Anxiety | 29 (7.1) | 2 (1.5) | 2 (1.5) |
| Constipation | 28 (6.8) | 1 (0.7) | 4 (2.9) |
| Hyperhidrosis | 23 (5.6) | 0 | 3 (2.2) |
| Feeling jittery | 21 (5.1) | 0 | 0 |
| Diarrhea | 21 (5.1) | 3 (2.2) | 2 (1.5) |
| Nasopharyngitis | 20 (4.9) | 9 (6.7) | 13 (9.6) |
| Fatigue | 18 (4.4) | 7 (5.2) | 4 (2.9) |
| Upper respiratory tract infection | 11 (2.7) | 5 (3.7) | 11 (8.1) |
| Vital sign and weight changes, mean (SD) | Week 12/ET[e,f] | Week 38/ET[f] | |
| SBP, mm Hg | 1.14 (9.94) | -0.28 (9.64) | 2.07 (9.96) |
| DBP, mm Hg | 1.79 (7.53) | 0.38 (7.88) | 0.85 (7.23) |
| Pulse, bpm | 6.64 (9.95) | 1.96 (9.50) | 6.63 (9.42) |
| Weight, kg | -5.43 (4.26) | -4.25 (5.29) | -8.29 (7.62) |
| ECG changes, mean (SD) | Week 12/ET[f,g] | Week 38/ET[f] | |
| Heart rate, bpm | 6.20 (10.48) | 2.15 (10.20) | 6.35 (10.38) |
| Fridericia-corrected QT interval, ms | -1.45 (13.91) | -2.81 (13.03) | -3.62 (13.78) |

Abbreviations: DBP, diastolic blood pressure; ECG, electrocardiogram; ET, early termination; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event.

[a] Safety analysis set, with participants receiving 1 or more open-label study drug dose.

[b] Randomized safety analysis set, with participants receiving 1 or more blinded, randomized withdrawal study drug dose. All study participants did not report a TEAE.

[c] Severe TEAEs in the open-label phase included congenital anomaly in offspring, fatigue, gastroenteritis, pneumonia, upper respiratory tract infection, aspartate aminotransferase level increased, blood creatine kinase increased, blood pressure increased, decreased appetite, arthralgia, back pain, intervertebral disc protrusion, disturbance in attention, headache, alopecia (n = 1 for each), and pain in extremity (n = 2). Severe TEAEs in the randomized withdrawal phase included neutropenia, gastrointestinal tract infection, muscle strain, and headache (n = 1 for each with lisdexamfetamine).

[d] TEAEs leading to discontinuation in the open-label phase included sinus tachycardia, tachycardia, nausea, chest discomfort, fatigue, influenza, convulsions, disturbance in attention, agitation, depression, insomnia, dyspnea, and rash (n = 1 for each); increased blood pressure, anxiety, and hypertension (n = 2 for each); and palpitations (n = 3). TEAEs leading to discontinuation in the randomized withdrawal phase included abdominal pain, abdominal tenderness, maternal exposure during pregnancy, breast cancer, dizziness, headache, depressed mood, and insomnia (n = 1 for each with lisdexamfetamine).

[e] Total of 408 participants.

[f] Vital sign assessments were collected in triplicate (separated by approximately 2 minutes) to obtain an mean; the open-label baseline ECG value consisted of 3 assessments separated by approximately 2 minutes.

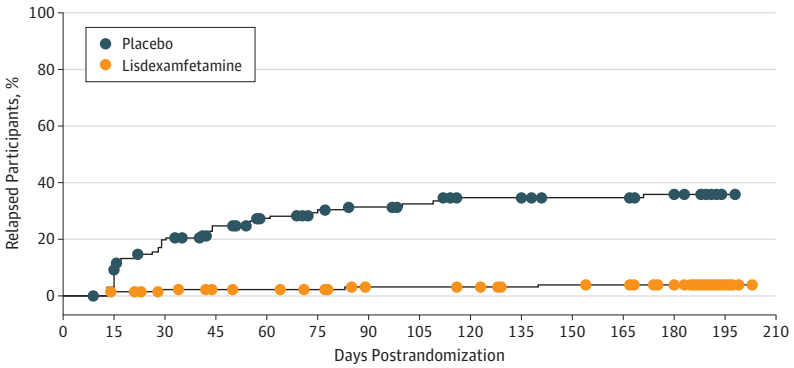
[g] Total of 396 participants.

respectively, on day 7 after the last lisdexamfetamine (n = 71) or placebo (n = 37) dose.

## Discussion

To our knowledge, this is the first study to assess the maintenance of efficacy of lisdexamfetamine in adults with BED. Following the initial response to lisdexamfetamine, continued treatment was associated with greater time to relapse to binge eating over 6 months than placebo. The relapse risk with lisdexamfetamine was markedly lower than placebo, with the estimated hazard for relapse during lisdexamfetamine therapy being 11 times lower than that with placebo. Sensitivity analyses, which used alternative relapse definitions and response criteria, supported these findings. Overall, these findings indicate that lisdexamfetamine was associated with a clinically significant reduction in the probability of relapse to binge eating and extend short-term lisdexamfetamine efficacy trial findings in adults with protocol-defined moderate to severe BED.[2,3]

Figure 2. Time to Relapse Following Randomization for Lisdexamfetamine Responders During the Randomized Withdrawal Phase, Full Analysis Set




No. at risk

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 131 | 116 | 99 | 87 | 76 | 69 | 66 | 63 | 58 | 57 | 55 | 55 | 49 | 1 | 0 |
| Lisdexamfetamine | 136 | 133 | 127 | 124 | 123 | 121 | 116 | 116 | 115 | 111 | 110 | 109 | 104 | 4 | 0 |

Randomized participants taking 1 or more study drug dose during the randomized withdrawal phase and having 1 or more postrandomization Clinical Global Impressions-Severity assessment. Symbols on the plotted lines represent censored participants.

Table 3. Time to Relapse Sensitivity Analyses, Full Analysis Set[a]

| | Placebo | | | Lisdexamfetamine Dimesylate | | | | |
|---|---|---|---|---|---|---|---|---|
| | | No. (%) | | | No. (%) | | | |
| Characteristic | No. | Relapsed | Censored[b] | No. | Relapsed | Censored[b] | $\chi^2_1$ | *P* Value[c] |
| Binge d/wk analysis (excluding CGI-S)[d] | 131 | 45 (34.4) | 86 (65.6) | 136 | 7 (5.1) | 129 (94.9) | 40.257 | <.001 |
| 18-d Exclusion analysis[e] | 110 | 25 (22.7) | 85 (77.3) | 133 | 3 (2.3) | 130 (97.7) | 27.677 | <.001 |
| 8-wk Responder analysis[f] | 100 | 33 (33.0) | 67 (67.0) | 95 | 2 (2.1) | 93 (97.9) | 34.236 | <.001 |

Abbreviation: CGI-S, Clinical Global Impressions–Severity.

[a] Randomized participants receiving 1 or more study drug dose during the randomized withdrawal phase and having 1 or more postrandomization CGI-S assessment.

[b] Participants who did not relapse were censored on the date of discontinuation or the final visit, whichever occurred later.

[c] Based on stratified log-rank test stratified by 4-week cessation status (yes/no).

[d] Relapse defined solely by the occurrence of 2 or more binge-eating days per week for 2 consecutive weeks (14 days).

[e] Participants who relapsed within 18 days after randomization were excluded.

[f] Only participants meeting 8-week cessation criteria (≤1 binge eating day per week for 8 consecutive weeks [56 days] before randomization and having a CGI-S score of ≤2 at weeks 8-12) were included.

Across other efficacy-related outcomes, continued treatment with lisdexamfetamine was associated with a maintained treatment effect, whereas placebo was associated with symptom worsening in those completing the study. However, these findings should be interpreted cautiously because participants were discontinued at the time of relapse, resulting in differences in the number of participants in each treatment group over time, potentially biasing the estimated between-group treatment differences. In addition, the *P* values for these comparisons were not adjusted for multiplicity. However, since the nominal *P* values were <.001, it is unlikely that the observed differences were due to chance.

Although the clinical significance of the finding is unclear, a large proportion of participants in the placebo group failed to relapse. This could reflect either a sustained therapeutic effect of lisdexamfetamine treatment or a nonspecific placebo-response effect among open-label lisdexamfetamine responders that continued throughout the randomized withdrawal phase despite the switch to placebo. It is not possible to disentangle the potential contributions of these 2 possibilities. However, this is an important issue because it could have implications for how recommendations about the need for long-term lisdexamfetamine use in individuals with BED who respond to lisdexamfetamine acutely are made.

The results of this study cannot be compared with those of other pharmacotherapy studies for BED because, to our knowledge, similar studies have not been conducted. Although maintenance of efficacy was suggested in a 42-week, open-label extension study for topiramate,[14] the lack of a placebo arm in that study limits inferences regarding long-term treatment effects.

The safety and tolerability of lisdexamfetamine were consistent with previous lisdexamfetamine studies for BED[2,3] and with the effects of lisdexamfetamine in attention-deficit/hyperactivity disorder.[1] The most frequently reported TEAEs with lisdexamfetamine included dry mouth, headache, and insomnia during the open-label phase and nasopharyngitis, headache, upper respiratory tract infection, and dry mouth during the randomized withdrawal phase. Increased blood pressure and pulse and decreased weight were also observed with lisdexamfetamine. Overall, there was no evidence of new trends in the safety profile of lisdexamfetamine following long-term treatment or abrupt discontinuation. No study

participant died during the study, but a death was reported in an offspring of 1 participant.

### Limitations

Several issues limit the generalizability of these findings. Treatment response magnitude in a more heterogeneous population may not be as robust as in this study because the population was enriched with lisdexamfetamine responders. Participants were also predominantly female, white, obese, and without current psychiatric comorbidities. How the observed treatment effects would generalize to a more diverse population is not known. Lastly, a 6-month study duration was used, so the stability of the findings over longer periods is unknown.

## Conclusions

This randomized withdrawal study in adults with protocol-defined moderate to severe BED demonstrated that, following initial response to open-label lisdexamfetamine, time to relapse to binge eating over 6 months was greater in those continuing lisdexamfetamine treatment than in those randomized to placebo. The estimated hazard for relapse with lisdexamfetamine was also lower than with placebo. The safety and tolerability profile was consistent with lisdexamfetamine studies in adults with moderate to severe BED[2,3] and with its profile in attention-deficit/hyperactivity disorder.[1]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*Study concept and design:* All authors.
*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* All authors.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* Radewonuk.
*Supervision:* Gasior.

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Dr Ferreira-Cornwell is a former employee of Shire Development LLC and current employee of GlaxoSmithKline; she holds stock and/or stock options in Shire Development LLC and GlaxoSmithKline. Ms Radewonuk is a former employee of Shire Development LLC and current employee of The Griesser Group; she holds stock and/or stock options in Shire Development LLC and GlaxoSmithKline. Dr Gasior is a former employee of Shire Development LLC and current employee of BTG International; she holds stock and/or stock options in Shire Development LLC and BTG.

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