Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Lisdexamfetamine Dimesylate in Adults With Attention-Deficit/Hyperactivity Disorder

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Objective: To evaluate the efficacy and safety of 30, 50, and 70 mg/day lisdexamfetamine dimesylate compared with placebo in adults with attention-deficit/hyperactivity disorder (ADHD).

Method: Following a 7- to 28-day washout, 420 adults aged 18 to 55 years with moderate to severe ADHD (DSM-IV-TR criteria) were treated with 30, 50, or 70 mg/day lisdexamfetamine or placebo, respectively, for 4 weeks (N = 119, 117, 122, and 62, respectively). The 50- and 70-mg/day groups underwent forced-dose titration. The primary efficacy measure was the clinician-determined ADHD Rating Scale (ADHD-RS) total score. The study was conducted from May 2006 to November 2006.

Results: Treatment groups were well matched at baseline, including in ADHD-RS scores. At endpoint, changes in ADHD-RS scores were significantly greater for each lisdexamfetamine dose than for placebo (placebo = –8.2, 30 mg/day lisdexamfetamine = –16.2, 50 mg/day lisdexamfetamine = –17.4, 70 mg/day lisdexamfetamine = –18.6; all p < .0001 vs. placebo), with no differences between doses. Significant differences relative to placebo were observed in each lisdexamfetamine group, beginning at week 1 and for each week throughout. The percentage of subjects who improved (Clinical Global Impressions-Improvement scale rating ≤ 2) was significantly greater for each lisdexamfetamine dose than for placebo at each week and at endpoint (placebo = 29%, 30 mg/day lisdexamfetamine = 57%, 50 mg/day lisdexamfetamine = 62%, 70 mg/day lisdexamfetamine = 61%; all p < .01). Adverse events were generally mild and included dry mouth, decreased appetite, and insomnia.

Conclusion: All 3 lisdexamfetamine doses were significantly more effective than placebo in the treatment of adults with ADHD, with improvements noted within 1 week. Lisdexamfetamine was generally well tolerated by these patients.

Trial Registration: clinicaltrials.gov Identifier: NCT00334880

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders, characterized by developmentally inappropriate levels of inattention, hyperactivity, and/or impulsivity.[1] ADHD is estimated to affect as many as 8% to 12% of children worldwide,[2–4] with approximately 65% of these showing persistence of ADHD symptoms into adolescence[5,6] and adulthood.[6,7] Overall, ADHD is estimated to affect 4.4% of adults in the United States.[8]

Adults with ADHD experience significant impairments in several domains.[9–12] ADHD in adults has been shown to be associated with immaturity, social maladjustment, higher rates of separation and divorce, fewer years of education, lower socioeconomic status, lower occupational achievement, lower rates of professional employment, increased work difficulties, poor work performance, more frequent changes in employment, and higher rates of quitting or being fired from jobs.[10,13] A survey of 500 adults in the community with self-reported diagnoses of ADHD found that, compared with controls, subjects with ADHD were significantly less likely to have graduated from high school or college or to be currently employed, and significantly more likely to have been

arrested or divorced.[10] In addition, another survey found that subjects with ADHD had poorer driving habits, as evidenced by a greater likelihood of being involved in, and at fault for, automobile accidents, including those with bodily injury, and to have received more traffic citations, especially for speeding, than non-ADHD control subjects.[14]

Adults with ADHD also have been shown to be significantly more likely than controls to have a comorbid psychiatric diagnosis of anxiety, bipolar disorder, depression, drug or alcohol abuse, or antisocial disorder.[15] The economic impact of ADHD is high, even after excluding the costs of these comorbid conditions, and includes inpatient, outpatient, prescription drug, and other medical costs, as well as more days of unexplained work absences.[15]

Stimulants are the most frequently used medications to treat adults with ADHD.[16,17] Despite mounting evidence of efficacy,[18,19] their use in adults may be coupled with concerns regarding misuse and diversion and poor adherence, particularly of short-acting compounds.[20,21] A retrospective analysis of 3-times-daily versus once-daily methylphenidate found that once-daily medication for ADHD was associated with fewer medication switches, more days on therapy, and fewer hospitalizations.[22] Together, these findings support the need to develop stimulants that are less likely to be divertible and that have consistent efficacy throughout the day with 1 daily dose.[23,24]

Lisdexamfetamine dimesylate is the first prodrug stimulant and is indicated for the treatment of ADHD. Lisdexamfetamine is a therapeutically inactive molecule. After oral ingestion, lisdexamfetamine is converted to l-lysine, a naturally occurring essential amino acid, and active d-amphetamine, which is responsible for the drug's activity.[25] The conversion of lisdexamfetamine to d-amphetamine is not affected by gastrointestinal pH and is unlikely to be affected by alterations in normal gastrointestinal transit times.[26] Lisdexamfetamine was developed with the goal of providing long duration of effect that is consistent throughout the day, with reduced potential for risk of abuse.[27]

Lisdexamfetamine treatment in children with ADHD resulted in significant improvements in ADHD Rating Scale (ADHD-RS) scores, compared with placebo, as early as the first week of treatment.[25] Efficacy was seen in both an analog classroom and a naturalistic study, with significant symptom improvements extending into the early evening after early-morning dosing.[25,28,29] In addition, lisdexamfetamine was generally well tolerated, with an adverse event (AE) profile similar to that of other stimulant medications.[29]

The primary aim of this study was to determine whether lisdexamfetamine was effective and safe in adults with ADHD. We conducted a randomized, double-blind, placebo-controlled, forced-dose titration study to evaluate the efficacy and safety of 3 lisdexamfetamine doses (30 mg/day, 50 mg/day, and 70 mg/day) compared with placebo in adults diagnosed with ADHD.

METHOD

Subjects

This randomized, double-blind, placebo-controlled, parallel-group, 4-week study with forced-dose escalation enrolled adults aged 18 to 55 years with a primary diagnosis of ADHD by *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria. ADHD diagnosis was based on a comprehensive psychiatric interview that included the Adult ADHD Clinical Diagnostic Scale. All subjects were required to meet at least 6 of the 9 DSM-IV-TR subtype criteria and to have moderate to severe ADHD as rated by a clinician at baseline (ADHD-RS scores ≥ 28). Other inclusion criteria included 12-lead electrocardiogram (ECG) with QT/QTc-F interval < 450 ms for men and < 470 ms for women, resting heart rate 40 to 100 bpm, PR interval < 200 ms, and QRS interval < 110 ms. Exclusion criteria included comorbid psychiatric diagnosis with significant symptoms that, in the judgment of the investigator, might preclude treatment with lisdexamfetamine; history of seizures; taking medications that affect the central nervous system or blood pressure (excluding current ADHD medications, which were washed out); known cardiac structural abnormality or any other condition that might affect cardiac performance; clinically significant ECG or laboratory abnormality at screening or baseline; history of hypertension, or a resting sitting systolic blood pressure (SBP) > 139 mm Hg or diastolic blood pressure (DBP) > 89 mm Hg; pregnancy or lactation; and positive urine drug results at screening or baseline (except for subject's current stimulant therapy). Women of childbearing potential had to comply with contraceptive restrictions (negative pregnancy test, double-barrier or hormonal contraceptives, or abstinence from sexual activity).

This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice according to the International Conference on Harmonisation guidelines. The study protocol was approved by the institutional review board of each institution, and all subjects provided written informed consent. The study was conducted from May 2006 to November 2006.

Trial Description

Following a 7- to 28-day washout, adults aged 18 to 55 years were randomly assigned 2:2:2:1 to 4 weeks of treatment with 30 mg/day lisdexamfetamine, 50 mg/day lisdexamfetamine (30 mg/day for week 1 with forced-dose escalation to 50 mg/day for weeks 2 to 4), 70 mg/day lisdexamfetamine (30 mg/day for week 1 with forced-dose escalation to 50 mg/day for week 2 and 70 mg/day for weeks 3 and 4), or placebo, administered orally. Both the

investigator and the patient were blinded to treatment. To maintain blinding, all investigational products were supplied as capsules identical in size, weight, and shape.

Primary Efficacy Measure

The primary efficacy measure was the clinician-determined ADHD-RS total score with adult prompts.[13,30] The ADHD-RS for adults consists of 18 items designed to reflect DSM-IV-TR–defined ADHD symptomatology, with each item scored from 0 (no symptoms) to 3 (severe symptoms). The items include questions pertaining to hyperactivity/impulsivity (even-numbered) and inattentiveness (odd-numbered), serving as 2 subscales. The ADHD-RS was administered at each study visit, beginning with the screening visit. At the baseline visit, following washout, a score of ≥ 28 was required to qualify for randomization. Change in ADHD-RS total score at treatment endpoint from baseline was assessed for the intent-to-treat (ITT) population, defined as all subjects who had a baseline and at least 1 postrandomization assessment of ADHD-RS total score.

Secondary Efficacy Measures

Secondary efficacy analyses included assessment of lisdexamfetamine dose response, as measured by change in ADHD-RS total score at endpoint and at each study week. An additional secondary measure was the Clinical Global Impressions scale (CGI),[31] an investigator-rated evaluation of a subject's improvement over time. Each subject was assessed at baseline on the CGI-Severity of Illness (CGI-S) 7-point scale, with severity rated from 1 (no symptoms) to 7 (very severe symptoms). At each subsequent study visit, subject improvement relative to baseline was determined by the investigator on the CGI-Improvement (CGI-I), a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Prior to analysis, this variable was dichotomized a priori into 2 categories: "improved," which included all subjects regarded as "much improved" and "very much improved" (CGI-I rating ≤ 2),[31] or "not improved," which included subjects at all remaining levels. A post hoc analysis further examined the percentage of subjects with $\geq 30\%$ reduction in ADHD-RS total score at endpoint as another measure of response.

Safety Measures

Safety assessments included AEs obtained by observation and close monitoring of subjects; vital signs, measured after the subject had been sitting for 5 minutes; ECGs performed at each study visit; and physical examinations and laboratory evaluations (hematology, chemistry, urinalysis) performed at screening, baseline, and endpoint. The Pittsburgh Sleep Quality Index (PSQI),[32] a self-rated questionnaire, was used at baseline and endpoint to assess sleep quality and disturbances during the study period. Each of the 7 component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction) can range from 0 to 3, yielding a maximum total score of 21 for the PSQI. A PSQI score > 5 denotes poor sleepers.

Pulse outliers were defined as any change from < (mean + 2 SD) at baseline to $\geq$ (mean + 2 SD) at any other measurement; SBP outliers were defined as any change from < 150 mm Hg at baseline to ≥ 150 mm Hg at any other measurement; and DBP outliers were defined as any change from < 95 mm Hg at baseline to ≥ 95 mm Hg at any other measurement. QTc-F and QTc-B interval outliers were defined as changes from baseline of 30 to 59 ms and ≥ 60 ms.

Statistical Analyses

Efficacy was assessed in the ITT population (defined as above), whereas safety was assessed in the safety population, defined as all subjects who were enrolled and randomized and who received the blinded investigational product.

Treatment endpoint for ADHD-RS total scores was defined as the last postrandomization treatment week for which a valid score was obtained. Using an analysis of covariance (ANCOVA) model, the change from baseline of ADHD-RS total score was assessed in the ITT population at treatment endpoint, yielding results numerically identical to the last-observation-carried-forward (LOCF) approach at the end of planned treatment. Dunnett's test for multiple mean comparisons with least squares (LS) adjustment was used to compare the ADHD-RS change from baseline of the 3 lisdexamfetamine groups with the placebo group. Weekly changes in ADHD-RS total score from baseline were analyzed in the same manner. The dose-response effectiveness of the 3 lisdexamfetamine doses was assessed by endpoint change in ADHD-RS total score from baseline (LOCF), and at treatment weeks 3 and 4 (observed case analysis), when subjects were at their assigned daily dose, using the same ANCOVA model.

The same ANCOVA model and analytic approach were used to assess CGI-I at treatment endpoint in the ITT population, using CGI-S as baseline score, followed by Dunnett's test for multiple mean comparisons with LS adjustment to compare the CGI-I scores of the 3 lisdexamfetamine groups with placebo. Similar methods were used to analyze change in CGI for each treatment week. A nonparametric Cochran-Mantel-Haenszel test was used to assess the differences in the dichotomized differences in CGI-I scores between subjects who were "improved" and "not improved."

For safety analyses, length of exposure to study drug was based on the dates of first dispensing and last dose of study medication, and categorized by week. AEs were categorized as prerandomization or treatment-emergent (TEAEs), based on when the AE was first documented.

Table 1. Subject Disposition for Adult Patients With ADHD Enrolled in a Study of Lisdexamfetamine[a]

Characteristic	Total Patients	Placebo	Lisdexamfetamine 30 mg/d	Lisdexamfetamine 50 mg/d	Lisdexamfetamine 70 mg/d
Enrolled/randomized (safety population), N	420	62	119	117	122
ITT population, N	414	62	115	117	120
Completed, N (%)	349 (83)	52 (84)	103 (87)	96 (82)	98 (80)
Postrandomization withdrawals, N (%)	71 (17)	10 (16)	16 (13)	21 (18)	24 (20)
Adverse event(s)	22 (5)	1 (2)	4 (3)	8 (7)	9 (7)
Lack of efficacy	8 (2)	4 (6)	1 (1)	2 (2)	1 (1)
Protocol violation	16 (4)	2 (3)	3 (3)	7 (6)	4 (3)
Lost to follow-up	7 (2)	1 (2)	2 (2)	1 (1)	3 (2)
Withdrew consent	12 (3)	2 (3)	5 (4)	1 (1)	4 (3)
Physician decision	2 (< 1)	0	0	0	2 (2)
Other	4 (1)	0	1 (1)	2 (2)	1 (1)

[a]Denominator for percentages is the total number of randomized patients (safety population) in the treatment group.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ITT = intent to treat.

Table 2. Baseline Demographic and Clinical Characteristics of Enrolled Subjects (safety population, N = 420)

Characteristic	Placebo (N = 62)	Lisdexamfetamine 30 mg/d (N = 119)	Lisdexamfetamine 50 mg/d (N = 117)	Lisdexamfetamine 70 mg/d (N = 122)
Age, mean ± SD, y	35.2 ± 10.9	35.3 ± 10.1	34.2 ± 10.0	35.8 ± 10.5
Male, N (%)	32 (52)	67 (56)	66 (56)	63 (52)
White, N (%)	48 (77)	94 (79)	99 (85)	108 (89)
Weight, mean ± SD, lb	181.3 ± 39.1	178.1 ± 38.9	173.1 ± 37.8	174.3 ± 37.3
Height, mean ± SD, in	67.9 ± 3.7	67.9 ± 3.9	67.6 ± 3.6	67.4 ± 3.7
ADHD-RS total score at baseline, mean ± SD	39.4 ± 6.4	40.7 ± 6.3	40.8 ± 7.3	41.1 ± 6.0
CGI-S score at baseline, N (%)				
Moderate	27 (44)	39 (33)	39 (33)	37 (30)
Marked	25 (40)	67 (56)	67 (57)	61 (50)
Severe	10 (16)	13 (11)	10 (9)	24 (20)
Extreme	0	0	1 (1)	0

Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale.

Changes from baseline in vital signs and ECG parameters in the safety population were analyzed for differences among treatment groups using ANCOVA at each postrandomization visit and at endpoint, with the baseline measurement as the covariate. Changes from baseline in PSQI total score in the safety population were analyzed for differences at study exit among treatment groups using the same analysis model as used for the ADHD-RS.

RESULTS

Subject Disposition

The disposition of the 420 enrolled subjects is shown in Table 1. Participants were randomly assigned 2:2:2:1 to 30 mg/day lisdexamfetamine (N = 119), 50 mg/day lisdexamfetamine (N = 117), 70 mg/day lisdexamfetamine (N = 122), or placebo (N = 62). Of these, 414 subjects were included in the ITT population (N = 115, 117, 120, and 62, respectively). Of the 420 enrolled subjects, 71 (17%) terminated before study completion. Primary reasons for discontinuation are shown in Table 1. Discontinuation rates in each lisdexamfetamine group (13% to 20%) were similar to that in the placebo group (16%).

Demographic and Baseline Characteristics

The demographic and baseline characteristics of all recruited study participants are summarized in Table 2. The 4 groups were well matched at baseline. Mean ± SD age in the 3 lisdexamfetamine groups ranged from 34.2 ± 10.0 years to 35.8 ± 10.5 years, with 35.2 ± 10.9 years in the placebo group. Men were 52% to 56% of the 3 lisdexamfetamine groups and 52% of the placebo group. Whites comprised 79% to 89% of the lisdexamfetamine groups and 77% of the placebo group. CGI-S at baseline was scored as moderate in 30% to 33%, marked in 50% to 57%, and severe in 9% to 20% of the patients in the lisdexamfetamine groups, and as moderate in 44%, marked in 40%, and severe in 16% of patients in the placebo group. Mean ADHD-RS score at baseline was 40.7 to 41.1 in the lisdexamfetamine groups and 39.4 in the placebo group. None of these differences was statistically significant.

Primary Efficacy Results

All 4 groups showed improvements in mean change from baseline to endpoint in ADHD-RS total score (Figure 1). The LS mean ± SE changes in the placebo, 30-mg/day, 50-mg/day, and 70-mg/day lisdexamfetamine groups at

Figure 1. ADHD-RS Total Scores at Endpoint: ITT Population
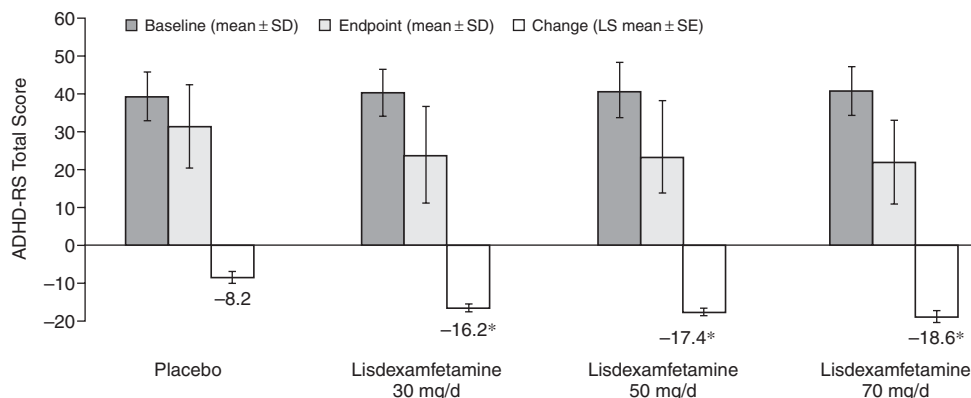
*p < .0001 (adjusted Dunnett's test compared with placebo following analysis of covariance with baseline score as covariate).
Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale, ITT = intent-to-treat, LS = least squares.

Figure 2. Change From Baseline in ADHD-RS Total Scores at Each Week: ITT Population
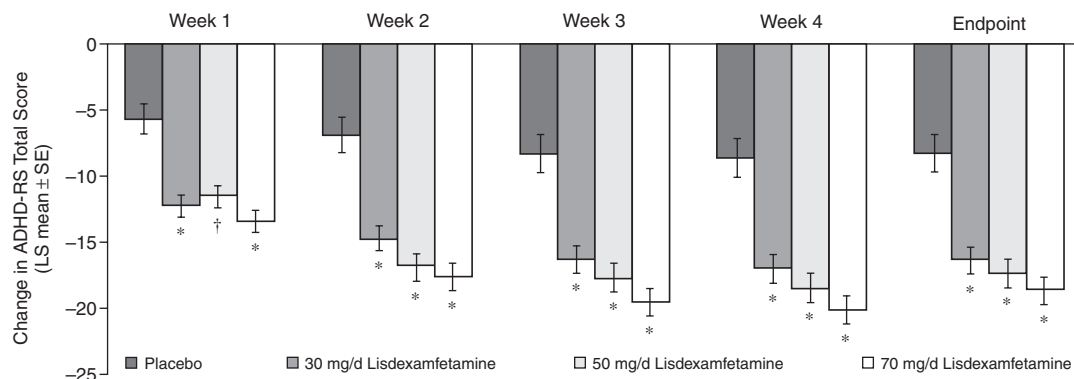
*p < .0001 vs. placebo.
†p < .001 vs. placebo.
Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale, ITT = intent-to-treat, LS = least squares.

endpoint were –8.2 ± 1.43, –16.2 ± 1.06, –17.4 ± 1.05, and –18.6 ± 1.03, respectively. The differences over the treatment period were significant for the 3 lisdexamfetamine groups (p < .0001 by 2-way ANCOVA, Figure 1), but not for the placebo group. The placebo-adjusted LS mean (95% confidence interval [CI]) differences for the 30-mg/day, 50-mg/day, and 70-mg/day lisdexamfetamine groups were –8.0 (–12.1 to –3.9), –9.2 (–13.2 to –5.1), and –10.4 (–14.5 to –6.3), respectively (p < .0001 each).

Secondary Efficacy Results

Changes from baseline in ADHD-RS total scores were significant at each postbaseline visit, starting at week 1 (p < .001), and the reductions in ADHD-RS scores for the 3 lisdexamfetamine groups were similar throughout the entire treatment period (Figure 2). Relative to placebo, the LS mean reduction in each of the lisdexamfetamine groups was significantly greater at the end of each week.

The post hoc analysis showed that, relative to the placebo group, a significantly greater percentage of subjects in each lisdexamfetamine group showed a ≥ 30% reduction in ADHD-RS total scores at each week and at study endpoint (p < .01, Figure 3). In assessing the dose-response effectiveness of lisdexamfetamine, we found that differences between lisdexamfetamine doses were not significant at endpoint, although the comparisons between 30 mg/day lisdexamfetamine and 70 mg/day lisdexamfetamine were significant at weeks 3 and 4 (data not shown).

An effect size versus placebo can be calculated using raw mean changes in ADHD-RS score. These effect sizes at endpoint were 0.73, 0.89, and 0.99 for the 30-mg/day, 50-mg/day, and 70-mg/day lisdexamfetamine groups, respectively (Figure 4).

CGI-I scores based on clinician impressions were significantly lower at endpoint for all lisdexamfetamine groups compared with placebo. Of subjects taking
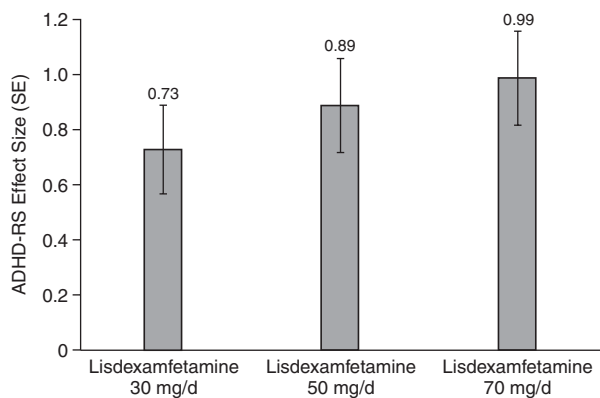
Figure 3. Frequency of Subjects With ≥ 30% Reductions in ADHD-RS Total Scores at Each Week and at Endpoint: ITT Population
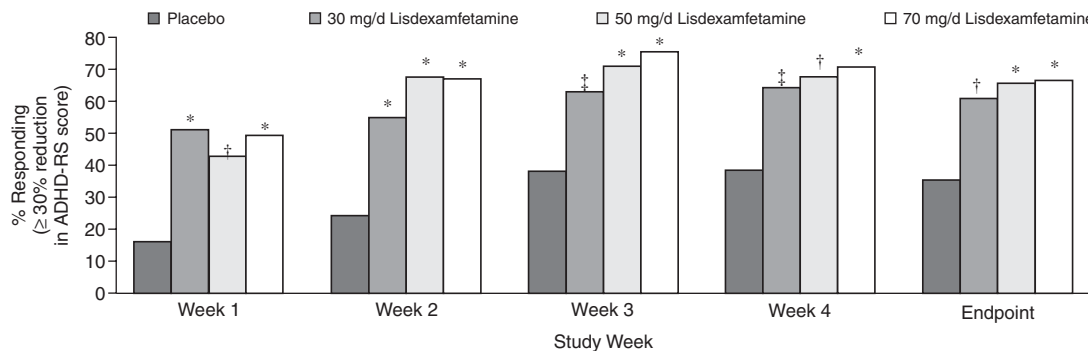
*p < .0001 vs. placebo.
†p < .001 vs. placebo.
‡p < .01 vs. placebo.
Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale, ITT = intent-to-treat.

Figure 4. Effect Size by Dose at Study Endpoint[a]

[a]Analyses using last-observation-carried-forward, intent-to-treat analysis. Numbers above bars are mean values.
Abbreviation: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale.

30 mg/day, 50 mg/day, and 70 mg/day lisdexamfetamine, 57%, 62%, and 61%, respectively, were rated "improved" or "very much improved" at study endpoint, significantly greater than the 29% of subjects taking placebo similarly rated (Figure 5). In addition, at the end of each week, the percentages of subjects rated "improved" or "very much improved" were significantly higher for each of the lisdexamfetamine groups than for the placebo group (p < .01, Figure 5).

Safety Analyses

Adverse events were reported by 282/358 (79%) of subjects taking all doses of lisdexamfetamine, by 90/119 (76%), 90/117 (77%), and 102/122 (84%) of subjects in the 30-mg/day, 50-mg/day, and 70-mg/day lisdexamfetamine groups, respectively, and by 36/62 (58%) of subjects in the placebo group. The most common TEAEs, with subject incidence > 5% and incidence twice that of placebo in any lisdexamfetamine group, were decreased appetite, anorexia, dry mouth, insomnia, nausea, diarrhea, feeling jittery, and anxiety (Table 3). A total of 68% of lisdexamfetamine-treated subjects experienced mild AEs, and 39% experienced moderate AEs.

No deaths were reported in this study. Two serious AEs (SAEs) were reported in 2 subjects: a 28-year-old white man, assigned to lisdexamfetamine 30 mg/day, experienced leg injuries (fracture of the right metatarsal bone and left knee meniscal injury) due to an automobile accident, and a 26-year-old white man, assigned to lisdexamfetamine 70 mg/day, experienced postoperative knee pain. Both subjects were discontinued from the study. Both SAEs were considered severe but not related to study treatment.

Twenty-three severe TEAEs were reported in 15 lisdexamfetamine-treated subjects (4% of subjects), compared with 3 severe AEs in 2 placebo-treated subjects (3% of subjects). Of the 358 subjects treated with lisdexamfetamine, 21 (6%) discontinued due to AEs compared with 1 (2%) of the 62 subjects in the placebo group. Common lisdexamfetamine-emergent AEs leading to discontinuation (alone or sometimes in combination) in more than 1 subject were insomnia (8 subjects), tachycardia (3 subjects), irritability (2 subjects), headache (2 subjects), increased blood pressure/hypertension (4 subjects), anxiety (2 subjects), and dyspnea (3 subjects).

The highest number of AEs took place within the first week of lisdexamfetamine, when all subjects in the active treatment groups were taking 30 mg/day lisdexamfetamine (Table 4).

Vital signs

Blood pressure. Small LS mean changes from baseline to endpoint were observed in SBP and DBP. The placebo and 30-mg/day, 50-mg/day, and 70-mg/day lisdexamfet-

Figure 5. Improvement According to CGI-I Score of 1 or 2 by Treatment Week and at Endpoint: ITT Population
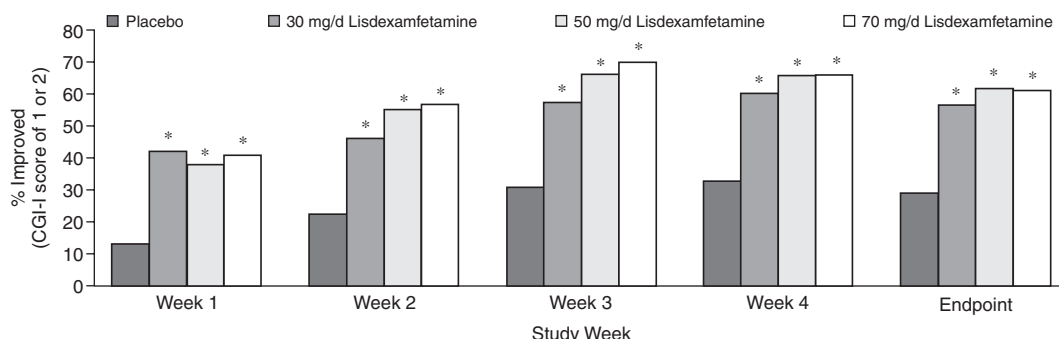
*p < .01 vs. placebo (Cochran-Mantel-Haenszel test).
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, ITT = intent-to-treat.

Table 3. Treatment-Emergent Adverse Events With Subject Incidence > 5% in Any Treatment Group and Twice That of Placebo for Any Dose Group[a]

Adverse Event	Placebo (N = 62)	Lisdexamfetamine 30 mg/d (N = 119)	Lisdexamfetamine 50 mg/d (N = 117)	Lisdexamfetamine 70 mg/d (N = 122)
Any event	36 (58)	90 (76)	90 (77)	102 (84)
Anorexia	0	4 (3)	8 (7)	6 (5)
Anxiety	0	5 (4)	7 (6)	9 (7)
Decreased appetite	1 (2)	34 (29)	33 (28)	28 (23)
Diarrhea	0	8 (7)	12 (10)	4 (3)
Dry mouth	2 (3)	25 (21)	29 (25)	38 (31)
Feeling jittery	0	2 (2)	4 (3)	9 (7)
Insomnia	3 (5)	23 (19)	20 (17)	26 (21)
Nausea	0	10 (8)	7 (6)	8 (7)

[a]Values shown as N (%).

Table 4. Treatment-Emergent Adverse Events With Active Treatment Incidence ≥ 5% and Twice That of Placebo by Treatment Week[a]

Adverse Event	Placebo	Lisdexamfetamine
Week 1, N	62	358
Any event	20 (32)	222 (62)
Decreased appetite	1 (2)	80 (22)
Diarrhea	0	16 (5)
Dry mouth	0	65 (18)
Headache	3 (5)	43 (12)
Insomnia	2 (3)	50 (14)
Week 2, N	59	344
Any event	15 (25)	125 (36)
Headache	1 (2)	18 (5)
Week 3, N	57	322
Any event	15 (26)	101 (31)
Dry mouth	0	15 (5)
Week 4+, N	52	300
Any event	7 (13)	77 (26)

[a]Values shown as N (%) unless otherwise noted.

amine groups experienced LS mean (95% CI) changes in SBP of –0.5 (–2.6, 1.5), 0.8 (–0.7, 2.3), 0.3 (–1.2, 1.8), and 1.3 (–0.2, 2.7) mm Hg, respectively and LS mean (95% CI) changes in DBP of 1.1 (–0.5, 2.7), 0.8 (–0.4, 2.0), 1.1 (–0.1, 2.3), and 1.6 (0.4, 2.7) mm Hg, respectively. No trends were observed, and there were no statistically significant changes in SBP or DBP from baseline to endpoint or to the end of each treatment week. Blood pressure outliers were defined as subjects with SBP ≥ 150 mm Hg after a baseline SBP < 150 mm Hg, or DBP ≥ 95 mm Hg after a baseline DBP < 95 mm Hg. There were 3 occurrences for SBP outliers and 15 for DBP outliers (subjects could have an outlier reading at more than 1 visit). The number of DBP outliers increased with increasing dose, but this was expected and the overall number of outliers was small (Table 5).

Pulse. ANCOVA analysis showed statistically significant (p = .0018) treatment effects for pulse at endpoint. All active doses showed an increase in pulse relative to placebo. LS mean (95% CI) changes in pulse from baseline to endpoint for the placebo and 30-mg/day, 50-mg/day, and 70-mg/day lisdexamfetamine groups were 0.0 (–2.2, 2.2), 2.8 (1.2, 4.4), 4.2 (2.6, 5.9), and 5.2 (3.6, 6.8) bpm, respectively. Significant increases in pulse were also observed for treatment weeks 2, 3, and 4. The distributions of pulse outliers indicated that treatment with lisdexamfetamine was associated with an increase in pulse rate (Table 5).

Electrocardiogram

LS mean (95% CI) changes from baseline to endpoint in heart rate for the placebo and 30-mg/day, 50-mg/day, and 70-mg/day lisdexamfetamine groups were 1.1 (–1.2,

Table 5. Outlier Analysis of SBP and DBP Levels, Pulse Rates, and Changes in QTc-F and QTc-B Intervals at Any Postbaseline Visit[a]

Parameter	Placebo	Lisdexamfetamine 30 mg/d	Lisdexamfetamine 50 mg/d	Lisdexamfetamine 70 mg/d
SBP change to ≥ 150 mm Hg from < 150 mm Hg	0	1	0	2
DBP change to ≥ 95 mm Hg from < 95 mm Hg	0	1	5	9
Pulse change to ≥ (mean + 2 SD) from < (mean + 2 SD)	4	31	43	26
QTc-F interval change				
≥ 60 ms	0	0	0	0
30–59 ms	3	9	7	15
QTc-B interval change				
≥ 60 ms	0	0	1	1
30–59 ms	11	39	34	46

[a]An outlier could be counted multiple times from week 1 to week 4.
Abbreviations: DBP = diastolic blood pressure, SBP = systolic blood pressure.

3.3), 4.3 (2.6, 5.9), 5.3 (3.6, 6.9), and 5.3 (3.7, 6.9) bpm, respectively, similar to the results observed for pulse. In contrast, LS mean (95% CI) changes from baseline to endpoint in QRS interval and QTc-F interval were similar for the placebo and 30-mg/day, 50-mg/day, and 70-mg/day lisdexamfetamine groups. For QRS interval, the LS mean (95% CI) changes for these 4 groups were 0.0 (–1.2, 1.3), –0.1 (–1.1, 0.8), –0.1 (–1.0, 0.9), and 0.1 (–0.8, 1.0) ms, respectively, whereas for QTc-F interval, the LS mean (95% CI) changes for these 4 groups were –0.3 (–4.1, 3.4), 4.0 (1.3, 6.8), –1.8 (–4.6, 0.9), and 2.7 (0.0, 5.4) ms, respectively. LS mean PR interval in the lisdexamfetamine groups decreased from –1.5 to –3.7 ms, compared with a 1.2-ms increase in the placebo group. LS mean QT interval in the active treatment groups decreased from –4.3 to –10.3 ms, compared with –2.4 ms in the placebo group. LS mean QTc-B interval increased from 2.8 to 8.6 ms in the active treatment groups, compared with an increase of 0.9 ms in the placebo group. No QT, QTc-F, or QTc-B interval exceeded 480 ms after baseline. During the study, no change in QTc-F interval was ≥ 60 ms, while 2 changes in QTc-B interval were ≥ 60 ms (Table 5). No clinically significant ECG abnormalities were identified by the physician investigators during the course of this study or at baseline.

Physical Examinations and Laboratory Measures

LS mean ± SE decreases in body weight from baseline at study endpoint for the 30-mg/day, 50-mg/day, and 70-mg/day lisdexamfetamine groups were –2.8 ± 0.46, –3.1 ± 0.45, and –4.3 ± 0.45 lb, respectively, compared with a 0.5 ± 0.62 lb gain for the placebo group (p < .0001 by ANCOVA). No other clinically meaningful changes in physical examination results or laboratory measures were observed during the study.

Sleep Measures

As measured by the PSQI, there were no statistically significant changes in sleep quality across treatment groups (p = .1563 by ANCOVA).

DISCUSSION

This large, double-blind, placebo-controlled, randomized clinical trial indicated that treatment with lisdexamfetamine was effective in reducing ADHD-RS total scores in adults with ADHD and was well tolerated. At endpoint, mean changes in ADHD-RS and CGI-I were statistically and clinically superior to placebo for each lisdexamfetamine dose. Significant differences relative to placebo were observed in each lisdexamfetamine group, beginning at week 1 and for each week throughout the duration of the study. Additionally, the effect sizes at endpoint, based on ADHD-RS raw mean change scores were 0.73, 0.89, and 0.99 for the 30-mg/day, 50-mg/day, and 70-mg/day lisdexamfetamine groups, respectively.

Subjects treated with the highest dose of 70 mg/day of lisdexamfetamine showed significantly greater improvements in ADHD symptoms than did subjects treated with 30 mg/day lisdexamfetamine at weeks 3 and 4, when all subjects were receiving their assigned drug, but not at endpoint, when there were numerical but not statistically significant differences between the doses. Given the larger effect size observed in the 70-mg dose group, development of tolerance to medication effect is an unlikely explanation for loss of statistical differences between doses at endpoint. More likely, early dropouts and differences in statistical methods for the analysis of week 3 and 4 data (observed case comparisons) versus the LOCF may explain these apparent discrepancies. For the endpoint analysis of the 70-mg group, inclusion of early dropouts (from weeks 1 and 2), who were initially randomly assigned to the 70-mg treatment group but who did not have the opportunity to benefit from this maximum dose, would decrease the observed differences between dose groups in the LOCF analysis.

Of note, the doses used in this adult study were the same as those used in the pediatric studies, and lisdexamfetamine was efficacious at all of these doses.[25]

Treatment with lisdexamfetamine was relatively well tolerated. Very few subjects had to be discontinued from

the study due to adverse effects. As expected with stimulants, the most common lisdexamfetamine-emergent AEs were decreased appetite, dry mouth, insomnia, nausea, diarrhea, and anxiety, and TEAEs in most subjects were mild or moderate in severity. Moreover, the greatest number of AEs were reported within the first week of treatment with lisdexamfetamine; subsequently, the incidence of AEs declined.

There were no clinically meaningful changes in SBP or DBP values or ECG parameters in lisdexamfetamine-treated subjects. Although all active doses showed an increase in pulse at endpoint, these were small (mean 2.8 to 5.2 bpm), and were not associated with clinical concerns. A non–clinically meaningful increase in heart rate was observed that was similar in magnitude to that for pulse, while changes in QRS interval and QTc-F were similar to those seen with placebo.

The findings in this study should be viewed in light of some methodological limitations. Subjects with comorbid psychiatric disorders were excluded; thus, the study population may not reflect the population of adult ADHD patients seen in clinical practice. The study enrolled subjects with normal blood pressure and pulse and excluded subjects with cardiovascular disorders. Therefore, the effects of lisdexamfetamine in patients with significant blood pressure abnormalities or cardiovascular dysfunction are not known. In addition, the forced dose titration design and limited duration of this trial do not reflect actual clinical practice.

Despite these considerations, we have shown that short-term treatment with lisdexamfetamine was effective and generally well tolerated in adults with ADHD, with improvements in ADHD symptoms beginning at week 1 and continuing throughout the 4-week study period. Future studies in adult ADHD patients should strive to better characterize the duration of action of lisdexamfetamine, as well as to further investigate its full safety profile.

Drug names: lisdexamfetamine dimesylate (Vyvanse), methylphenidate (Daytrana, Ritalin, and others).

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