

A Placebo-Controlled Study Evaluating the Efficacy and Safety of Flexible-Dose Desvenlafaxine Treatment in Outpatients with Major Depressive Disorder

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ABSTRACT

Introduction: This research compares the efficacy and safety of desvenlafaxine (administered as desvenlafaxine succinate) versus placebo in treating major depressive disorder.

Methods: In this randomized, double-blind study, outpatients with major depressive disorder ≥ 18 years of age received desvenlafaxine 200–400 mg/day or placebo for 8 weeks. Efficacy endpoints included (primary) change in 17-item Hamilton Rating Scale for Depression score at the final evaluation (last observation carried forward, analysis of covariance) and (secondary) Clinical Global Impressions—Improvement and —Severity of Illness scales.

FOCUS POINTS

- Desvenlafaxine has recently been approved by the Food and Drug Administration for the treatment of major depressive disorder (MDD).
- Desvenlafaxine blocks the reuptake of serotonin and norepinephrine.
- The purpose of this double-blind, placebo-controlled clinical trial was to assess the efficacy of flexible doses of desvenlafaxine (200–400 mg/day) for the treatment of MDD.

Results: The difference between desvenlafaxine (n=117) and placebo (n=118) on the primary endpoint was not significant (–9.1 vs –7.5, $P=.078$). Week 8 observed cases (desvenlafaxine, n=80; placebo, n=94) results were sig-

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nificant (-10.7 vs -7.9 , $P=.008$). Differences at the final evaluation (last observation carried forward) were significant for Clinical Global Impressions—Improvement (2.9 vs 2.5 , $P=.037$) and Clinical Global Impressions—Severity of Illness (-1.9 vs -1.2 , $P=.041$). Discontinuation rates due to adverse events (AEs) were 12% and 3% for desvenlafaxine and placebo, respectively ($P=.008$). The most frequently reported AE associated with desvenlafaxine was nausea (36% vs 9% [placebo]).

Conclusion: In this study, the primary analysis did not show significant differences between desvenlafaxine and placebo; discontinuations due to AEs associated with the desvenlafaxine dose range may have contributed to the lack of statistical separation.

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INTRODUCTION

Major depressive disorder (MDD) is a prevalent, chronic illness and one of the leading causes of disability worldwide.¹ The selective serotonin reuptake inhibitors and the serotonin-norepinephrine reuptake inhibitors (SNRIs) have substantially improved therapy for patients with MDD, as they provide safer, more tolerable treatment of depressive symptoms compared with previously used classes of antidepressants.² Multiple antidepressants with these mechanisms of action are available. However, because individual patient responses to a given antidepressant can vary considerably, there remains a need for additional safe and effective antidepressant treatment options for patients with MDD.

Despite the need for new therapeutic options for MDD, and the abundance of clinical evidence that drugs that modulate serotonin and norepinephrine neurotransmission are effective, demonstrating the efficacy of a new antidepressant can be challenging. Approximately 50% of clinical trials for approved antidepressants have failed to show a significant difference for active drug versus placebo in patients with MDD.³ Specific characteristics of the clinical study design, including

fixed versus flexible dosing, choice of primary outcome measure, and statistical methods are factors that can contribute to this high failure rate. Patient inclusion/exclusion criteria also may play a role. For example, in an assessment of antidepressants included in the Food and Drug Administration database, Khan and colleagues³ demonstrated that the severity of depressive symptoms in the specific patient samples studied greatly influenced the clinical trial outcome.

Desvenlafaxine (administered as desvenlafaxine succinate), the major active metabolite of venlafaxine, is a novel SNRI approved by the FDA for treatment of MDD and is in clinical development for other indications.^{4,5} Desvenlafaxine treatment in patients with a primary diagnosis of MDD has been well studied, and results from multicenter, randomized, double-blind, controlled clinical trials have demonstrated the safety and efficacy at the recommended daily dose of 50 mg.^{6,7} Efficacy also was observed with daily doses of 100, 200, and 400 mg⁸⁻¹⁰; however no additional clinical benefit was observed at doses >50 mg/day.⁵

The primary objective of this phase III study was to evaluate the efficacy, safety, and tolerability of a flexible-dose treatment regimen of desvenlafaxine 200–400 mg/day compared with placebo in adult outpatients with MDD.

METHODS

Study Design

This phase III, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study enrolled adult outpatients with MDD, and was conducted at 12 outpatient clinical research centers in the United States from July 13, 2004 to May 12, 2005. The study protocol received institutional review board approval before the study began, and the protocol amendments received approval while the study was in progress and before the data were unblinded. The study was conducted according to the FDA Code of Federal Regulations (21 CFR, Part 50) and in accordance with the ethical principles in the Declaration of Helsinki. All potential study participants provided written, informed consent prior to having screening procedures performed. Individuals who provided informed consent but failed to meet criteria at the screening or baseline visits were considered screening failures. Following a 10 ± 4 -day screening period, eligible patients

were randomly assigned at the baseline evaluation (study day -1) to treatment for 8 weeks, plus up to 2 weeks for tapering study medication. Subsequent visits were scheduled for study days 7, 14, 21, 28, 42, and 56, and a follow-up visit 7 days after discontinuation of study medication.

Participants

Inclusion criteria

Subjects were outpatients ≥ 18 years of age with a primary diagnosis of MDD, based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*¹¹ criteria, single or recurrent episode, without psychotic features. Patients had to have experienced depressive symptoms for ≥ 30 days before the screening visit, a score of ≥ 20 on the 17-item Hamilton Rating Scale for Depression (HAM-D₁₇),¹² ≥ 2 on item 1 (depressed mood item) of the HAM-D₁₇, and ≥ 4 on the Clinical Global Impressions—Severity of Illness scale (CGI-S)¹³ at screening and at baseline.

Exclusion Criteria

Exclusion criteria included previous treatment with desvenlafaxine at any time in the past; known sensitivity to venlafaxine; significant risk of suicide; current (ie, within the past 12 months) substance or alcohol abuse, personality disorder, posttraumatic stress disorder, or obsessive compulsive disorder; lifetime diagnosis of bipolar disorder; depression associated with presence of organic mental disorder; current primary generalized anxiety disorder, panic disorder, or social phobia; a Covi Anxiety Scale¹⁴ total score >9 than the Raskin Depression Scale¹⁵ or score >3 any single item at screening or baseline; history of a seizure disorder; clinically important medical disease; or use of prohibited medications, including use of venlafaxine (immediate or extended releases) within 90 days of baseline, investigational drugs, antipsychotics, fluoxetine within 30 days of baseline, or anxiolytics and other antidepressants within 14 days of baseline.

Study Medication

On study days 1–14, patients received 200 mg/day of study medication (administered as one tablet of desvenlafaxine 200 mg or matching placebo). If a patient was unable to tolerate an initial dose of 200 mg/day of study drug during the first week, the dose could be decreased to 100 mg/day at the discretion of the investiga-

tor. However, patients were required to tolerate a daily dose of 200 mg of study medication by day 8 to continue in the study. On day 14, the dose of study drug was increased to 400 mg/day (administered as two tablets of desvenlafaxine 200 mg or matching placebo), if tolerated, and was maintained until day 28. For patients whose dose of study medication was not increased to two tablets per day at day 14, the dose was increased to two tablets per day at the day 28 visit. The dose of study medication could be adjusted between days 28 and day 56; however, the minimum dose of study medication allowed was one tablet daily (ie, desvenlafaxine 200 mg or matching placebo), and the maximum dose was not to exceed two tablets daily (ie, desvenlafaxine 400 mg or matching placebo). Patients continued taking the study medication until day 56 or early withdrawal. Patients who took study medication for a duration of ≥ 53 days (ie, 56 ± 3 days) were considered to have completed treatment. On study day 56, patients had the option to enroll in a long-term extension study. For patients who did not enroll in the long-term study, at the end of the treatment period, a taper period of 7 days (for patients receiving 200 mg/day, the dose would be decreased to 100 mg/day for 1 week) or 14 days (for patients receiving 400 mg/day, the dose would be decreased to 200 mg/day for 1 week followed by 100 mg/day for 1 week) was recommended, but could be altered at the discretion of the clinical investigator.

Efficacy Measurements

The primary efficacy measure was the total score on the HAM-D₁₇, which was assessed at screening, baseline, and on study days 7, 14, 21, 28, 42, and 56 by trained raters. The Clinical Global Impressions—Improvement (CGI-I)¹³ score was assessed at all study visits after baseline. Additional secondary efficacy measures included the CGI-S score (assessed at screening, baseline, and days 7, 14, 21, 28, 42, and 56), the Montgomery-Åsberg Depression Rating Scale (MADRS) total score¹⁶ (assessed at baseline and days 14, 28, and 56), clinical response rate (defined as decrease of $\geq 50\%$ from baseline in HAM-D₁₇), and clinical remission rate (defined as HAM-D₁₇ ≤ 7). The 6-item HAM-D (HAM-D₆; Bech version: HAM-D items 1, 2, 7, 8, 10, and 13) score¹⁷ and MADRS response rates (defined as decrease $\geq 50\%$ from

baseline MADRS score) were included as ancillary efficacy variables.

Safety Measurements

Safety and tolerability were assessed by recording adverse events (AEs), patient discontinuations due to AEs, physical examination (screening and day 56 visits), standard 12-lead electrocardiogram recordings (screening, baseline, and day 56 visits), vital signs and measurements (all study visits), and clinical laboratory parameters. AEs reported by patients (spontaneous reports) or observed by the investigator were recorded on study days 7, 14, 21, 28, 42, 56, 60, 67, and 74, and at the follow-up visit and were categorized using *Standard Medical Dictionary for Regulatory Activities* dictionary terminology.¹⁸ Treatment-emergent adverse events (TEAEs) were defined as AEs not seen before the first dose of study medication was taken, or events that worsened in frequency and/or intensity during the treatment period. Taper and post-study-emergent AEs also were reported; these were defined as spontaneously reported AEs that were not present during the last 7 days of the treatment period (ie, before the taper began), or events that were present but became more severe after this 7-day period. A serious adverse event (SAE) was defined as an AE that met any of the following criteria: one which resulted in death, was life threatening, or was medically important or required intervention.

Statistical Methods

The sample size estimates were based on the HAM-D₁₇ total score, which was the primary efficacy variable. Based on experience with venlafaxine extended release, a standard deviation of 8 units was selected for use in calculations and a sample size of 111 subjects per group was determined to be sufficient to detect a statistically significant mean difference between the desvenlafaxine and placebo groups of 3.5 units at the 5% level with a power of ~90%. To compensate for patients who failed to qualify for the intent-to-treat (ITT) analysis (estimated at 5%), ~120 patients were planned for each group.

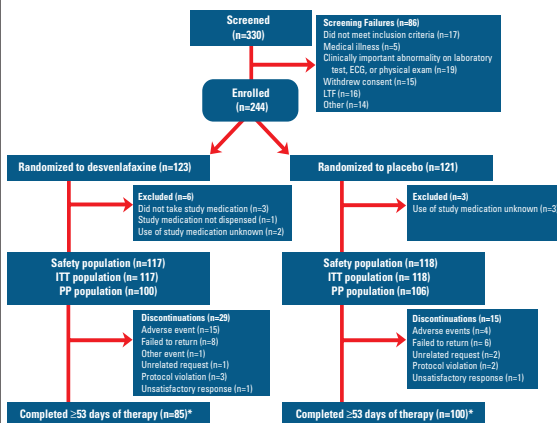
Statistical analyses were based on the data from all individual clinical trial centers. Due to the number of clinical trial sites with few subjects, the individual centers were pooled based on geographic region to form “sites” with greater numbers of patients before the

study data were unblinded, as planned in the study protocol. These “sites” were included in the statistical models.

The primary efficacy analyses were based on the ITT population, which included all randomly assigned patients who took at least one dose of study medication, had a baseline primary efficacy evaluation, and had at least one primary efficacy evaluation after the first dose of study medication. The safety analysis was based on the safety population, which included all randomly assigned patients who took at least one dose of study medication.

For all primary and secondary efficacy variables, the final evaluation using last observation carried forward (LOCF) data was defined a priori as the primary endpoint; observed-case (OC) data also were analyzed and are presented for the primary efficacy variable. The primary efficacy analysis was the change from baseline on the HAM-D₁₇ total score and was tested by analysis of covariance (ANCOVA) with treatment and site as factors and baseline HAM-D₁₇ score as covariate. Mean CGI-I scores were analyzed by analysis of variance (ANOVA) with treatment and site as factors. Changes from baseline in other secondary variables, including the CGI-S, MADRS total, and HAM-D₆ scores, were evaluated using ANCOVA, with treatment and site as main factors and baseline value as the covariate.

FIGURE 1.
Study flowchart of patient disposition



* Completers were defined as subjects who had a duration of therapy of ≥53 or more days (56±3 days) and do not necessarily equal the number of total patients minus those who discontinued.

ECG=electrocardiogram; LTYF=TK; ITT=intent to treat; PP=per-protocol.

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Rates of response (defined as decrease of $\geq 50\%$ in HAM-D₁₇ or MADRS total score from baseline) and remission (defined as HAM-D₁₇ ≤ 7) were analyzed using logistic regression model, with treatment and site as factors and baseline score as a covariate. All tests were 2-tailed and statistical significance was declared at the 0.05 level.

RESULTS

Patients

Of 330 patients screened, a total of 244 patients were enrolled and 235 were included in the ITT and safety populations (Figure 1). A total of 44 patients (19%) withdrew from the study

TABLE 1.
Patient Demographic and Baseline Clinical Characteristics*

Characteristic	Placebo (n=118)	Desvenlafaxine (n=117)
Mean age, years (range)	38.7±12.2 (18–74)	37.5±11.5 (19–70)
Sex, n (%)		
Female	81 (69)	72 (62)
Male	37 (31)	45 (38)
Ethnic origin, n (%) [†]		
White	87 (74)	79 (68)
Black	16 (14)	22 (19)
Hispanic	4 (3)	11 (9)
Asian	3 (3)	2 (2)
Native American	2 (2)	1 (1)
Other [‡]	6 (5)	2 (2)
Mean duration of current MDD episode, months (range)	27.2±62.4 (1–588)	19.3±24.7 (1–157)
Mean HAM-D ₁₇ total score	23.1±2.7	23.3±2.9
Mean CGI-S score	4.3±0.5	4.3±0.5
Mean MADRS total score	30.9	30.6
Mean HAM-D ₆ score	13.0	13.1

* Safety population

[†] Percent totals may not equal 100% due to rounding

[‡] Includes Arabic; Eastern European; African American/American Indian/Asian-Pacific Islander/White; Brazilian; White/Asian Pacific-Islander; Malaysian; Pacific Islander.

MDD=major depressive disorder; CGI-S=Clinical Global Impressions Scale–Severity of Illness; HAM-D₁₇=17-item Hamilton Rating Scale for Depression; MADRS=Montgomery-Åsberg Depression Rating Scale; HAM-D₆=6-item Hamilton Rating Scale for Depression.

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(desvenlafaxine, 25%; placebo, 13%). No significant differences were observed in demographics and baseline characteristics for patients in the desvenlafaxine (n=117) compared with the placebo (n=118) treatment groups (Table 1).

Efficacy Results

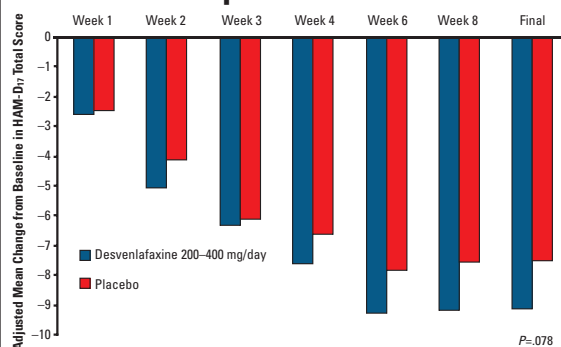
Primary Efficacy Analysis

No significant difference was observed in the adjusted mean change from baseline in the HAM-D₁₇ total score in the desvenlafaxine and placebo treatment groups at the final evaluation (difference in adjusted means: 1.6 [95% CI –0.2, 3.4]; Table 2). For the LOCF analysis, no significant differences were observed for desvenlafaxine versus placebo at any other time point (Figure 2). Analysis of OC data demonstrated significance at week 6 (difference in adjusted means: 2.5 [95% CI 0.6, 4.3]) and week 8 (desvenlafaxine, n=80; placebo, n=94; difference in adjusted means: 2.8 [95% CI 0.7, 4.9]). No significant differences between the treatment groups were observed at any other time point using the OC analysis.

Secondary Efficacy Outcomes (CGI-I, CGI-S, MADRS, and HAM-D₆ Scores)

Mean scores for the continuous secondary efficacy measures at the final evaluation (LOCF) are reported in Table 2. At the final evaluation, significant differences between the desvenlafaxine and placebo groups were observed for the CGI-I (difference in adjusted means: 0.3

FIGURE 2.
Comparison of changes from baseline in HAM-D₁₇ total score for desvenlafaxine versus placebo*



* Last observation carried forward analysis in the intent-to-treat population.

HAM-D₁₇=17-item Hamilton Rating Scale for Depression.

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[95% CI 0.0, 0.6]), CGI-S (difference in adjusted means: 0.3 [95% CI 0.0, 0.6]), MADRS (difference in adjusted means: 2.9 [95% CI 0.3, 5.4]), and HAM-D₆ (difference in adjusted means: 1.5 [95% CI 0.5, 2.6])

Response and Remission

No significant differences were observed between the desvenlafaxine and placebo treatment groups for HAM-D₁₇ clinical response rates (ie, $\geq 50\%$ reduction from baseline) at the final evaluation (Table 2); the logistic regression analysis demonstrated adjusted odds ratios of 1.456 (95% confidence limits [CL] 0.85, 2.5; $P=.175$) for HAM-D₁₇ response. A significant difference was observed between the desvenlafaxine and placebo treatment groups for MADRS clinical response rates; the logistic regression analysis demonstrated an adjusted odds ratio of 1.754 (95% CL 1.03, 3.0; $P=.04$).

No significant difference in HAM-D₁₇ remission rates (ie, HAM-D₁₇ ≤ 7) was observed between the desvenlafaxine and placebo treatment groups at the final evaluation; the logistic regression analysis showed an adjusted odds ratio of 1.158 (95% CL 0.6, 2.22; $P=0.66$).

Efficacy Results: Per-Protocol Population

Because the results of the primary efficacy analysis were not significant, data from the per-protocol (PP) population were analyzed to evaluate the extent to which the failure of 29 patients (12%; desvenlafaxine: 17, placebo: 12) in the ITT population to follow study procedures contributed to the non-significant primary findings. The PP population included all randomly assigned patients who took at least one dose of study medication, had a baseline primary efficacy evaluation, had at least one primary efficacy evaluation after the first dose of study medication,

TABLE 2.
Primary and Secondary Efficacy Outcomes in ITT Population: Final Evaluation, LOCF*

<i>Efficacy Variable</i>	<i>Placebo (n=118)</i>	<i>Desvenlafaxine (n=117)</i>	<i>P Value</i> [†]
<i>Primary outcome</i>			
HAM-D ₁₇ , final evaluation/LOCF (primary)	-7.5 (0.66)	-9.1 (0.67)	0.078
HAM-D ₁₇ , week 8 OC [‡]	-7.9 (0.74)	-10.7 (0.81)	0.008
<i>Secondary outcomes</i>			
CGI-I score, predicted mean (95% CL)	2.9 (2.6, 3.1)	2.5 (2.3, 2.8)	0.037
CGI-S score	-0.9 (0.11)	-1.2 (0.11)	0.041
MADRS total score	-9.7 (0.94)	-12.6 (0.95)	0.028
HAM-D ₆ score [§]	-4.3 (0.40)	-5.8 (0.41)	0.006
<i>Response,[¶] n (%)</i>			
HAM-D ₁₇	36 (31)	46 (39)	0.175
MADRS	37 (31)	52 (44)	0.04
<i>Remission,^{//} n (%)</i>			
	22 (19)	24 (21)	0.66

* Data presented as adjusted mean change from baseline (standard error) unless otherwise indicated.

† HAM-D₁₇, CGI-S, MADRS, and HAM-D₆ were analyzed statistically using analysis of covariance on changes from baseline, with treatment and site as the main factors, and baseline value as the covariate; CGI-I was analyzed statistically using analysis of variance with treatment and site as factors; response and remission rates were analyzed statistically using the logistic regression model, with treatment and site as factors and baseline score as the covariate.

‡ Desvenlafaxine n=80, placebo n=94.

§ Bech version including HAM-D items 1, 2, 7, 8, 10, and 13.

¶ Defined as $\geq 50\%$ reduction in total score from baseline.

// Defined as HAM-D₁₇ ≤ 7 .

ITT=intent to treat; LOCF=last observation carried forward; HAM-D₁₇=17-item Hamilton Rating Scale for Depression; OC=observed case; CGI-I=Clinical Global Impressions Scale-Global Improvement; CL=confidence limit; CGI-S=Clinical Global Impressions Scale-Severity of Illness; MADRS=Montgomery-Åsberg Depression Rating Scale; HAM-D₆=6-item Hamilton Rating Scale for Depression.

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and had no major protocol violations within 3 days after stopping the full-dose of study medication. In the PP population (n=206), patients in the desvenlafaxine treatment group (n=100) had significant reductions from baseline in the HAM-D₁₇ total score at the final evaluation compared with patients in the placebo group (n=106; adjusted mean change from baseline of -9.19 vs -7.09, respectively; $P=.031$). In addition, at the final evaluation, significant differences between desvenlafaxine and placebo were observed for the mean CGI-I score (2.5 vs 2.9, respectively; $P=.031$), and adjusted mean changes in MADRS total score (-12.6 vs -9.22; $P=.017$), CGI-S score

(-1.3 vs -0.92; $P=.016$), and HAM-D₆ total score (-3.95 vs -5.86; $P=.001$). There were no significant differences between the desvenlafaxine and placebo groups in rates of response or remission at the final evaluation; HAM-D₁₇ response rates were 42% and 30%, respectively ($P=.083$), MADRS response rates were 47% and 31%, respectively ($P=.022$), and HAM-D₁₇ remission rates were 23% and 18%, respectively ($P=.391$).

Safety Results

Exposure to Study Medication

After the initial titration period, the mean daily dose of desvenlafaxine administered during day 14 through day 56 ranged from 324–373 mg.

Adverse Events

TEAEs were reported by 112 patients (96%) in the desvenlafaxine treatment group, and 101 patients (86%) in the placebo group. TEAEs reported by at least 5% of patients in the desvenlafaxine group and at a frequency at least twice that of the placebo group included nausea, dry mouth, hyperhidrosis, insomnia, somnolence, decreased appetite, tremor, blurred vision, yawning, sedation, vomiting, mydriasis, middle insomnia, initial insomnia, erectile dysfunction, constipation, feeling jittery, and dyspepsia (Table 3). Nausea, the most frequently reported AE in the desvenlafaxine treatment group (36%), was mild or moderate in the majority of cases (37/42; 88%). TEAEs resulted in reduction in dose of study medication for six patients (5%) in the desvenlafaxine treatment group and two patients (2%) in the placebo group. Taper/poststudy-emergent AEs were consistent with what has been seen in previous studies of desvenlafaxine and with the SNRIs.

Significantly more patients in the desvenlafaxine treatment group (14/117; 12%) discontinued the study because of TEAEs compared with those in the placebo group (4/118; 3%; $P=.008$). The TEAEs reported most frequently as the reason for discontinuation were nausea (7/117; 6%) in the desvenlafaxine group and irritability (2/118; 2%) in the placebo group.

No deaths or SAEs occurred during the study. Although not meeting the definition of an SAE, events reported in the same manner as an SAE included two pregnancies (desvenlafaxine: 1, placebo: 1) and five accidental overdoses (defined as unintentionally taking >600 mg/day of study medication; desvenlafaxine: 4, placebo: 1).

TABLE 3.
TEAEs Reported in the Desvenlafaxine Treatment Group with Incidence $\geq 5\%$ and at Least Twice That of Placebo*

	Patients, n (%)	
	Placebo (n=118)	Desvenlafaxine (n=117)
Nausea	11 (9)	42 (36)
Dry mouth	12 (10)	36 (31)
Hyperhidrosis	4 (3)	23 (20)
Insomnia	7 (6)	19 (16)
Somnolence	6 (5)	18 (15)
Decreased appetite	0 (0)	18 (15)
Tremor	3 (3)	13 (11)
Blurred vision	2 (2)	12 (10)
Yawning	0 (0)	11 (9)
Sedation	0 (0)	10 (9)
Vomiting	4 (3)	10 (9)
Mydriasis	0 (0)	10 (9)
Middle insomnia	1 (1)	9 (8)
Initial insomnia	4 (3)	7 (6)
Erectile dysfunction	0 (0)	7 (6) [†]
Constipation	3 (3)	7 (6)
Feeling jittery	0 (0)	6 (5)
Dyspepsia	0 (0)	6 (5)

* Classifications of AEs are based on the *Medical Dictionary for Regulatory Activities*.

[†] Males only; n=45.

TEAEs=treatment-emergent adverse events.

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Laboratory Parameters

At the final evaluation, statistically significant mean changes from baseline were observed for the desvenlafaxine treatment compared with placebo treatment groups for the following: alkaline phosphatase (+9.9 mU/mL vs -0.5 mU/mL, respectively; $P < .001$), gamma-glutamyl transpeptidase (+10.9 mU/mL vs -0.3 mU/mL; $P < .001$), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (+1.9 mU/mL vs +0.7 mU/mL; $P = .05$) alanine aminotransferase/serum glutamic pyruvic transaminase (+3.2 mU/mL vs +0.7 mU/mL; $P = .02$), total bilirubin (-1.854 μ mol/L vs -0.428 μ mol/L; $P < .001$), fasting high density lipoprotein (+0.045 mmol/L vs -0.028 mmol/L; $P = .02$), fasting low density lipoprotein (+0.181 mmol/L vs -0.038 mmol/L; $P = .004$), fasting total cholesterol/lipids (+0.223 mmol/L vs -0.088 mmol/L; $P < .001$), and fasting triglycerides/lipids (+1.044 mmol/L vs -0.113 mmol/L; $P = .008$).

Four patients in the desvenlafaxine treatment group and none in the placebo group had values that were determined by the medical monitor to be clinically important changes compared with baseline values. One patient each experienced an increase in triglycerides from 1.78 mmol/L at baseline to 4.90 mmol/L at week 8; a decrease in red blood cells from $4.7 \times 10^{12}/L$ at baseline to $3.5 \times 10^{12}/L$ at week 8; an increase from baseline in both total cholesterol from 6.59 mmol/L to 8.66 mmol/L and low density lipoprotein from 4.68 mmol/L to 6.08 mmol/L at week 8; and hematuria.

Vital Signs

Statistically significant mean changes from baseline at the final evaluation assessment in the desvenlafaxine treatment group compared with placebo were observed for supine heart rate (+2.31 beats per minute [bpm] vs +0.1 bpm, respectively; $P = .01$), systolic blood pressure (+1.62 mmHg vs -2.21; $P < .001$) diastolic blood pressure (+1.42 mmHg vs -1.00 mmHg; $P = .003$), and weight (-1.42 kg vs +0.26 kg, respectively; $P < .001$). Changes in vital signs were determined by the medical monitor to be clinically significant for one patient in the desvenlafaxine treatment group, who had orthostatic hypotension, and none in the placebo group.

Electrocardiograms

At the final evaluation, significant differences between the desvenlafaxine and placebo groups were observed for the mean changes in heart rate (+4.04 bpm vs -2.84 bpm, respec-

tively; $P < .001$), PR interval (-6.98 vs +0.16 msec; $P < .001$), uncorrected QT interval (-4.76 msec vs +6.82 msec; $P < .001$), QT interval based on Bazett's correction (QTcB; +6.97 msec vs +0.15 msec; $P = .017$). No desvenlafaxine-treated patients had QTcB, QT interval based on the Fridericia correction (QTcF) or based on the population correction (QTcN) of >500 msec.

One patient in the desvenlafaxine group was determined by the medical monitor to have a clinically important change in ECG findings, which was a prolongation in QTcB from 440 msec (average of three measurements at baseline) to 476 msec (average of three measurements at last visit). Although not considered clinically significant, the patient also experienced an increase in heart rate from 73 bpm (average of three measurements at baseline) to 84 bpm (average of three measurements at last visit).

DISCUSSION

Results of this phase III, randomized, double-blind, placebo-controlled clinical study suggest that treatment with desvenlafaxine 200–400 mg/day improved symptoms of depression numerically but not statistically in adult outpatients with MDD. Patients who received treatment with desvenlafaxine 200–400 mg/day did not experience a significant reduction in mean HAM-D₁₇ total scores compared with those who received placebo (primary efficacy endpoint; $P = .078$). However, a significant decrease in the HAM-D₁₇ total score was observed at week 8 using the OC analysis and final evaluation (LOCF) in the PP population. The findings from the PP population may provide a more accurate measure of the effect of desvenlafaxine treatment on depressive symptoms, whereas LOCF data may more closely reflect the experience physicians have in prescribing to all patients (ie, a subset of patients may not tolerate the medication and not take it long enough to achieve efficacy). In this trial, dosing started at 200 mg/day, and subsequent studies have demonstrated that tolerability is improved at lower doses.^{6,7} Improving tolerability allows more patients to continue to receive treatment, and thus increases the opportunity for patients to experience improvement in symptoms of depression.

The nonsignificant results for desvenlafaxine 200–400 mg/day on the primary efficacy analysis in this study is somewhat unexpected, given that several clinical studies have reported the

efficacy of desvenlafaxine 50–400 mg/day.^{6–10} Several factors may have contributed to the negative findings of this study. As mentioned, an analysis of approved antidepressants listed in the FDA database found that clinical trials of antidepressant treatments fail to demonstrate a significant difference between active drug and placebo ~50% of the time.³ The same analysis also showed that only 10% of clinical trials with patient samples with mean baseline HAM-D₁₇ total scores <24 reported significance versus placebo. In agreement with these findings, a recent meta-analysis of antidepressant clinical trials listed in the FDA database demonstrated that the efficacy of established antidepressant therapies only achieved clinical significance versus placebo in studies with severely depressed patient populations (ie, high baseline HAM-D₁₇ total scores).¹⁹ Thus, the relatively low mean baseline HAM-D₁₇ score of patients in the current study (~23) may have contributed to the nonsignificant results.

The AEs reported in the current study are in line with those expected with an SNRI and were consistent with what has been observed in other controlled trials of similar doses of desvenlafaxine in patients with MDD,^{8–10} with nausea being the most commonly reported AE and the most frequently cited reason for study discontinuation. Short-term clinical trials conducted subsequent to this study have demonstrated that a dose of 50 mg/day^{6,7} is comparably efficacious but has more favorable tolerability compared with the doses used in this study. Therefore, the relatively high doses of desvenlafaxine 200–400 mg/day may have contributed to the significant withdrawal rate associated with desvenlafaxine versus placebo in the study, as there is a potentially greater risk for development of AEs associated with these higher doses of desvenlafaxine. In addition, early withdrawals due to AEs may have contributed to the lack of statistical significance on the primary outcome, which is one drawback of using LOCF data for the primary efficacy analysis. Also, AEs, particularly nausea, may have contributed to the lack of separation between active treatment versus placebo on the HAM-D₁₇ total score, because improvement in items related to mood, for example, may have been offset by worsening of items that evaluate physical symptoms (eg, gastrointestinal symptoms). In this regard, results of

the HAM-D₆ score are important to consider, as these items measure the core symptoms of depression and are less likely to be influenced by AEs related to somatic symptoms.

As with other randomized, controlled trials of antidepressant therapy, certain facets of the current study limit the overall application of the results. The patient selection criteria excluded patients with substance abuse and significant comorbid psychiatric and medical illnesses. Therefore, the patient sample in this study may not accurately represent the general population of patients with MDD seen in clinical practice. The 8-week treatment period, although common among antidepressant trials, may be considered a limitation. Findings from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study²⁰ indicated that >50% of patients who experienced response or remission to antidepressant therapy did so only after the 8-week evaluation, suggesting that a longer duration of treatment is necessary to achieve optimal response and remission rates in patients with MDD. Thus, in this study, a greater number of patients may have achieved clinical response or remission with a longer duration of desvenlafaxine treatment.

CONCLUSION

Multiple clinical studies have reported the efficacy and safety of desvenlafaxine for the treatment of adult patients with MDD. Despite the lack of statistical significance on the primary outcome measure, results from this study add to the overall body of evidence available for desvenlafaxine, suggesting that it is safe, tolerated, and improves symptoms of depression in patients with MDD. **CNS**

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