Efficacy and Safety of Desvenlafaxine 50 mg/d in a Randomized, Placebo-Controlled Study of Perimenopausal and Postmenopausal Women With Major Depressive Disorder

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ABSTRACT

Objective: Evaluate the 8-week efficacy and safety of desvenlafaxine at the recommended dose of 50 mg/d in perimenopausal and postmenopausal women with major depressive disorder (MDD) based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision.

Method: This phase 4, multicenter, parallel-group, randomized, double-blind, placebo-controlled study was conducted from June 30, 2010, to June 8, 2011. Patients received placebo or desvenlafaxine 50 mg/d (1:1 ratio; n = 217 in each group). The primary outcome measure was the change at week 8 in the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) total score. Secondary outcome measures included change in the Sheehan Disability Scale (SDS), the Clinical Global Impressions-Improvement scale (CGI-I), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Visual Analog Scale–Pain Intensity (VAS-PI).

Results: At end point, compared to placebo, desvenlafaxine was associated with a significantly greater decrease in $HDRS_{17}$ total scores (last-observation-carried-forward analysis; adjusted mean change from baseline –9.9 vs –8.1, respectively; $P = .004$) and significant improvements on the CGI-I ($P < .001$), MADRS ($P = .002$), SDS ($P = .038$), and VAS-PI ($P < .001$). Improvements on the SDS and VAS-PI reached significance by week 2. Desvenlafaxine was generally safe and well tolerated.

Conclusions: Short-term treatment with desvenlafaxine 50 mg/d was effective for the treatment of MDD in perimenopausal and postmenopausal women, with significant benefits on pain and functional outcomes evident as early as week 2. The safety and tolerability of desvenlafaxine were consistent with data in other populations.

Trial Registration: ClinicalTrials.gov identifier: NCT01121484

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Epidemiologic studies indicate that major depressive disorder (MDD) is 1.5 to 3 times more prevalent in women than men, and research suggests that this increased prevalence may correspond to the oscillation of estrogen levels occurring during women's reproductive years.[1,2] A still higher vulnerability to depression is associated with the more pronounced, less predictable hormonal fluctuations occurring in the perimenopausal period.[2–5] Evidence also suggests that, compared to the premenopausal years, depression at the menopausal transition can be more severe and more resistant to conventional antidepressants.[6]

Despite these observations, there has been relatively little specific investigation of antidepressant therapies in perimenopausal and postmenopausal patients. Some studies evaluating selective serotonin reuptake inhibitors (SSRIs) in this population have suggested that they are less effective in menopausal women or older women compared with premenopausal or younger women.[7–9] The antidepressant benefit of estrogen in these patients has also been studied; however, results have been inconsistent, and for many women the potential risks of long-term estrogen use outweigh the potential benefit.[10–15] As a result, antidepressants remain the first-line treatment for MDD in perimenopausal and postmenopausal women.[16]

Preclinical observations support the idea that estrogens may have specific effects on norepinephrine signaling.[17] Because estrogens contribute to regulatory aspects of norepinephrine (NE) and serotonin (5-hydroxytryptamine, or 5-HT),[2] it is possible that an antidepressant targeting NE or 5-HT alone may not fully compensate for loss of estrogenic activity. As such, the presence of estrogen may be necessary for full SSRI efficacy,[7,9,18–20] and effective treatment of MDD in the context of low and fluctuating estrogen levels may require therapies that address potential dysregulation in both NE and 5-HT systems.[7] It has been hypothesized that serotonin-norepinephrine reuptake inhibitors (SNRIs) could compensate for the potential dysregulation in both systems and thus be able to more effectively treat MDD in perimenopausal and postmenopausal women. Duloxetine, for example, has been demonstrated to be an effective treatment for MDD in this patient population.[21]

Desvenlafaxine (administered as desvenlafaxine succinate) is an SNRI with established efficacy for treatment of adults with MDD.[22,23] In addition, desvenlafaxine has demonstrated efficacy for treating MDD in perimenopausal and postmenopausal women in an 8-week, double-blind, placebo-controlled, flexible-dose (100–200 mg/d) study.[24] The primary objective of the current study was to evaluate the short-term efficacy and safety of desvenlafaxine at the recommended lower dose of 50 mg/d compared with placebo in perimenopausal and postmenopausal women with MDD.

METHOD

This phase 4, multicenter, parallel-group, randomized, double-blind, placebo-controlled, efficacy and safety study was conducted from June

30, 2010, to June 8, 2011, at 43 sites in the United States in the Northeast, Midwest, South, and West geographical regions.[25] This study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the ethical principles that have their origins in the Declaration of Helsinki. Written informed consent was obtained from all subjects. The study is registered at ClinicalTrials.gov (identifier: NCT01121484).

Patients

The study enrolled perimenopausal and postmenopausal women aged 40 to 70 years with a primary diagnosis of MDD (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision), single or recurrent episodes, without psychotic features (as assessed with the modified Mini-International Neuropsychiatric Interview[26]), and with depressive symptoms for ≥ 30 days before the baseline visit.

Postmenopausal status was defined by any of the following: 12 consecutive months of spontaneous amenorrhea, < 12 consecutive months of spontaneous amenorrhea but ≥ 6 consecutive months of spontaneous amenorrhea and a prebaseline follicle-stimulating hormone level > 40 mIU/mL, or at least 6 months postsurgical bilateral oophorectomy. Perimenopausal status was defined by the presence of any of the following within 6 months before baseline: absolute change ≥ 7 days in menstrual cycle length, change in menstrual flow amount (2 or more flow categories), change in duration of menses (≥ 2 days), or amenorrhea lasting ≥ 3 months. Eligible participants had screening and baseline Montgomery-Asberg Depression Rating Scale (MADRS)[27] total scores ≥ 25 and ≤ 5-point improvement from screening to baseline.

Exclusion criteria included previous treatment with desvenlafaxine; treatment with venlafaxine within 1 year prior to baseline; treatment-resistant depression; potential for violence or significant risk of suicide; current (ie, past year) psychoactive substance abuse or dependence, manic episode, posttraumatic stress disorder, or obsessive-compulsive disorder; any current anxiety disorder considered to be primary; clinically important personality disorder; lifetime diagnosis of bipolar or psychotic disorder; clinically important medical disease or major illness; and clinically important abnormalities on screening physical examination, electrocardiogram, or laboratory evaluations.

Prohibited treatments included investigational drugs or procedures; medicinal marijuana; antipsychotics; antidepressants; sedative hypnotics (other than zaleplon, zolpidem, eszopiclone, ramelteon, or chloral hydrate); psychotropic drugs; triptans; herbal products intended to treat anxiety, insomnia, or depression; or formal cognitive-based therapy or interpersonal therapy for 30 days prior to baseline. Additional prohibited treatments were transcranial magnetic stimulation and vagus nerve stimulation.

Treatment

Patients were randomly assigned to receive placebo or desvenlafaxine 50 mg/d (1:1 ratio) for 10 weeks. (The 10-week treatment period was used to avoid the reduction in differences between active drug and placebo sometimes observed at the final study visit of antidepressant trials, which is thought to result from an expectancy effect.) Treatment compliance was monitored at each visit by pill count. If a patient missed taking the investigational product for 3 consecutive days at any time, or was < 80% compliant since the previous study visit, the investigator was instructed to discuss withdrawing the patient from the study with the sponsor.

Clinical Points

- Depression in perimenopausal and postmenopausal women may be more common, and more difficult to treat, than depression in premenopausal women.
- Desvenlafaxine, at the recommended dose of 50 mg/d, is an effective option for the treatment of depression in perimenopausal and postmenopausal women.
- The safety and tolerability findings demonstrated with desvenlafaxine treatment in this study are similar to those observed in other desvenlafaxine clinical trials, supporting a favorable benefit/risk profile of desvenlafaxine in perimenopausal and postmenopausal women.

Efficacy, Safety, and Tolerability Assessments

The primary efficacy end point was change from baseline in the $HDRS_{17}$ total score[28] at week 8.

Secondary measures included the 6-item Hamilton Depression Rating Scale ($HDRS_6$ [items 1, 2, 7, 8, 10, 13]),[28] MADRS,[27] Clinical Global Impressions-Improvement scale (CGI-I),[29] CGI-Severity of Illness scale (CGI-S),[29] Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR),[30] Visual Analog Scale–Pain Intensity (VAS-PI),[31] Sheehan Disability Scale (SDS),[32] EuroQol Health State-5 Dimensions (EQ-5D),[33] and Menopause Rating Scale.[34] The Menopause Rating Scale reflects the severity of women's aging symptoms and their impact on health-related quality of life by allowing the assessment of 11 items within 3 domains: psychological, somato-vegetative, and urogenital.[34]

An exploratory objective was to assess whether desvenlafaxine nonresponders at week 8 could achieve response (≥ 50% decrease from baseline in $HDRS_{17}$ total score) or remission ($HDRS_{17}$ total score ≤ 7) at week 10.

Safety assessments were collected during the study. A comprehensive physical examination was performed at baseline and at visit 7. A 12-lead electrocardiogram recording was made at screening and as needed during the trial. In addition, the Columbia Suicide Severity Rating Scale[35] was administered at each study visit.

Statistical Methods

Data from all sites were pooled and analyzed. All efficacy and health outcome analyses were based on the full analysis set (FAS) population: all patients who took 1 or more doses of double-blind study medication and had $HDRS_{17}$ evaluations

at baseline and postbaseline. Safety analyses were based on all patients who took 1 or more doses of double-blind study medication. All analyses were carried out based on the statistical analysis plan written a priori. The primary analysis used $\alpha = .05$ (2-tailed). Nominal (unadjusted) *P* values were reported for all other analyses.

The primary analysis compared the change from baseline to week 8 in the $HDRS_{17}$ total score between 2 treatment groups, using an analysis of covariance model. The model used treatment and site as factors and the baseline $HDRS_{17}$ total score as a covariate. The last-observation-carried-forward (LOCF) method was used to impute missing data. To examine the effect of missing data, an analysis based on mixed-effects model for repeated measures (MMRM) was applied, using baseline $HDRS_{17}$ score as a covariate and factors for treatment, investigator site, week of study visit, and treatment-by-week interaction. In addition, a pattern mixture model was used to evaluate the impact of patient dropout. A full mixed-effects model was fit incorporating patient dropout (yes/no). The 3-way interaction in the model, treatment by study week by dropout, was used to evaluate how the treatment effect over time varied between patients who did and did not complete the study.

The primary efficacy analysis was also carried out separately in perimenopausal and postmenopausal women and was repeated in the subgroup of subjects with $HDRS_{17}$ score ≥ 18. The changes from baseline in the $HDRS_{17}$ total score at postbaseline visits other than week 8 were also analyzed using analysis of covariance.

CGI-I was analyzed as a categorical variable by the Cochran-Mantel-Haenszel row mean-score-difference test using ridit scores and controlling for the geographical region effect. The continuous secondary efficacy measures (CGI-S, MADRS total score, $HDRS_6$ total score, QIDS-SR total score, VAS-PI total score, and 4 individual component pain scores) were analyzed using analysis of covariance models similar to those in the primary analysis.

A logistic regression model with treatment, geographical region, and baseline score was used to evaluate $HDRS_{17}$ response (≥ 50% decrease from baseline) and remission ($HDRS_{17}$ total score ≤ 7) rates, MADRS response (≥ 50% reduction from baseline score) and remission (MADRS score ≤ 10) rates, and CGI-I response rates (CGI-I score of 1 or 2).

RESULTS

Subjects

Subjects (N = 434) who received at least 1 dose of study drug were included in the safety population (Figure 1). The full analysis set included 432 patients who received at least 1 dose of study drug and had at least 1 postbaseline $HDRS_{17}$ assessment. Overall, 178 subjects (82.0%) receiving placebo and 185 (85.3%) receiving desvenlafaxine completed the study.

There were no statistically significant differences in demographic and baseline characteristics between treatment groups (Table 1). The mean age of subjects was 53 years, most were white, and about two-thirds were postmenopausal. The mean (SD) baseline $HDRS_{17}$ score was 22.6 (3.4). Concomitant medications were used by 187 patients (86.2%) in the placebo group and 196 patients (90.3%) in the desvenlafaxine group. There was minimal use of the sedative hypnotic zolpidem (n = 11) during the first 14 days of the study.

Efficacy

There was a significantly greater decrease in $HDRS_{17}$ total scores from baseline to week 8 for patients receiving desvenlafaxine versus those receiving placebo (LOCF analysis; adjusted mean change from baseline, –9.9 vs –8.1, respectively; $P = .004$) (Figure 2). The MMRM sensitivity analysis supported the results from the primary analysis. Analyses using the pattern mixture model confirmed the similar treatment benefit over time between patients who completed and did not complete the study ($P = .3548$). A significant difference between groups ($P < .001$) was also seen in $HDRS_6$ total scores. The logistic regression models found no significant differences in the $HDRS_{17}$ response and remission rates between the 2 groups (Table 2).

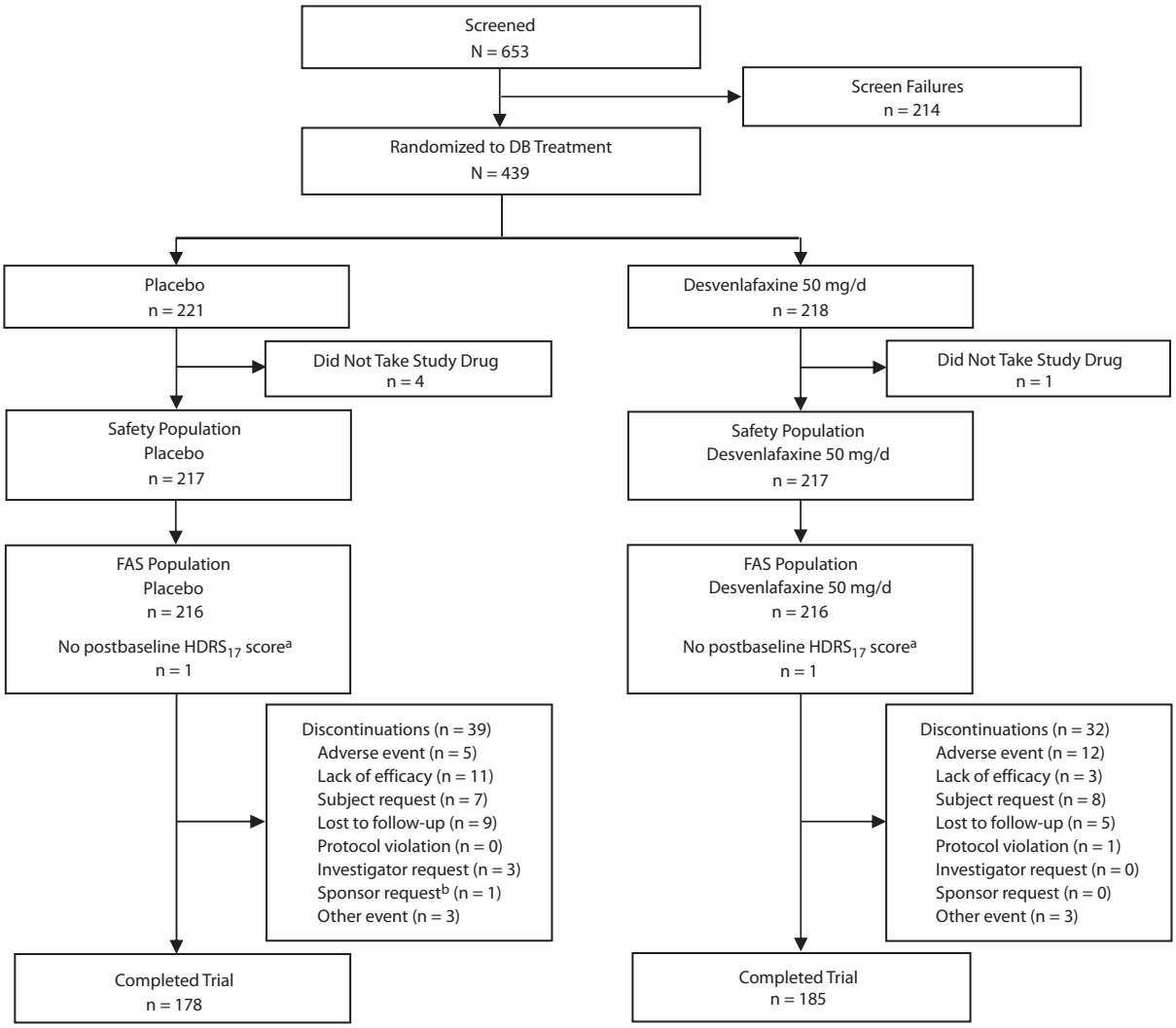
Approximately 6% of the study population was receiving either an oral contraceptive or hormone therapy. In an analysis of the subpopulation of women not receiving either therapy, there was a significant decrease in $HDRS_{17}$ total scores from baseline to week 8 for patients receiving desvenlafaxine versus those receiving placebo (LOCF analysis; adjusted mean change from baseline, –10.0 vs –8.1, respectively; $P = .004$), which was similar to that seen in the FAS population.

In subgroup analyses, significant mean reductions from baseline in $HDRS_{17}$ total scores for desvenlafaxine 50 mg/d compared with placebo were observed in both perimenopausal (–10.0 vs –7.1, $P = .008$) and postmenopausal (–9.9 vs –8.0, $P = .015$) women at week 8. For patients with a baseline $HDRS_{17}$ total score ≥ 18, the desvenlafaxine group experienced significant improvements at week 8 compared with the placebo group (–10.2 vs –8.3, respectively; $P = .004$), with a drug-placebo difference (–1.9) similar in magnitude to that of the overall population (–1.8).

At week 8, patients receiving desvenlafaxine had significantly improved CGI-S ($P = .002$) and CGI-I ($P < .001$) scores compared with those receiving placebo. A significantly greater proportion in the desvenlafaxine group were CGI-I responders compared with the placebo group (54.6% vs 35.2%, respectively [$P < .001$]).

At week 8, desvenlafaxine-treated patients had significantly improved MADRS scores versus placebo-treated patients ($P = .002$), and a significantly greater proportion of desvenlafaxine-treated patients were MADRS responders compared with placebo-treated patients (50.2% vs 37.4%, respectively; $P = .010$). There were no significant differences between treatment groups in the proportion of patients in MADRS remission. For nonresponders at week 8, there was no significant difference between treatment groups in the proportion of $HDRS_{17}$ responders or remitters at week 10.

Figure 1. Study Flowchart



[a]Discontinued after taking 1 dose, but before providing efficacy data (included in discontinuations).
[b]The sponsor requested 1 patient be withdrawn due to low compliance with dosing of study drug.
Abbreviations: DB = double-blind, FAS = full analysis set.

Desvenlafaxine was associated with a greater adjusted mean reduction in the VAS-PI overall score than placebo at week 8 (–1.5 vs –0.5, $P < .001$) and all other time points it was measured ($P \leq .002$, weeks 2–10).

Health Outcome Measures

There was a significant improvement in SDS total scores at week 8 in the desvenlafaxine group versus the placebo group (–9.13 vs –7.54, $P = .038$), as well as at weeks 2 and 4 ($P < .05$, weeks 2, 4, and 8). Desvenlafaxine-treated patients had significantly improved EQ-5D health index scores versus placebo at all evaluated time points (weeks 4–10, all $P \leq .030$). Improvement in EQ-5D health state score and QIDS-SR did not differ at week 8; significance between groups was achieved at week 10 only ($P = .032$ and $P = .038$, respectively). Improvement from baseline to week 8 in Menopause Rating Scale total scores with desvenlafaxine approached significance compared with placebo ($P = .051$).

Safety and Tolerability

Throughout the 10-week treatment period, treatment-emergent adverse events (TEAEs) were reported by 155 desvenlafaxine patients (71.4%) and 148 placebo patients (68.2%). Most TEAEs were mild to moderate in severity; the most commonly reported TEAEs for the desvenlafaxine group were headache and nausea (Table 3). No TEAE that was the primary reason for withdrawal occurred in more than 1 patient in either treatment group. TEAEs related to sexual function included decreased libido (desvenlafaxine, 1.4%; placebo, 0%) and anorgasmia (desvenlafaxine, 1.4%; placebo, 0%).

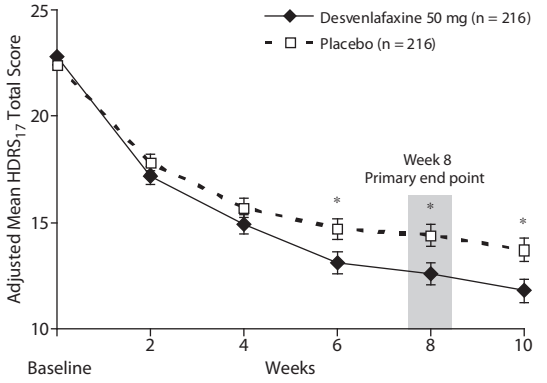
The final on-therapy assessment of blood pressure (BP) showed an adjusted mean change from baseline in supine diastolic BP and systolic BP of –0.2 mm Hg and –0.7 mm Hg, respectively, for placebo-treated patients compared with +1.0 mm Hg and +0.5 mm Hg, respectively, for desvenlafaxine-treated patients. For diastolic BP, 11 patients (5.1%) in each

Table 1. Demographics and Baseline Characteristics (FAS population)

Characteristic	Placebo (n = 216)	Desvenlafaxine (n = 216)
Age, y		
Mean (SD)	52.8 (6.6)	53.2 (6.8)
Range	41–69	40–69
Menopausal status, n (%)[a]		
Perimenopause	70 (32.0)	65 (30.0)
Postmenopause	140 (65.0)	151 (70.0)
Race, n (%)		
White	174 (80.6)	168 (77.8)
Black or African-American	33 (15.3)	43 (19.9)
Other	9 (4.2)	5 (2.3)
Using hormone therapy, n (%)	8 (3.7)	13 (6.0)
Using oral contraceptives, n (%)	3 (1.4)	2 (0.9)
Baseline score, mean (SD)		
$HAM\text{-}D_{17}$ total	22.4 (3.5)	22.8 (3.3)
MADRS total	30.6 (3.8)	31.0 (3.8)
CGI-S	4.3 (0.5)	4.4 (0.6)
QIDS-SR	14.8 (3.6)	15.1 (3.2)
VAS-PI	3.8 (2.7)	3.9 (2.6)
SDS	16.9 (6.2)	17.1 (6.1)

[a]Menopausal status was not reported for 6 patients in the placebo group.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, FAS = full analysis set, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report, SDS = Sheehan Disability Scale, VAS-PI = Visual Analog Scale–Pain Intensity.

Figure 2. Adjusted Mean $HDRS_{17}$ Total Scores (ANCOVA,[a] LOCF), FAS Population



[a]Adjusted for investigator site and baseline $HDRS_{17}$ score.
*$P \leq .009$.
Abbreviations: ANCOVA = analysis of covariance, FAS = full analysis set, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, LOCF = last observation carried forward.

of the desvenlafaxine and placebo treatment groups had an increase ≥ 10 mm Hg and an absolute value ≥ 95 mm Hg; no patients in the desvenlafaxine group had a decrease ≥ 15 mm Hg and absolute value ≤ 50 mm Hg, compared with a single patient (0.5%) in the placebo group. For systolic BP, 8 patients (3.7%) in each treatment group had an increase of ≥ 15 mm Hg and an absolute value ≥ 150 mm Hg; no patients receiving desvenlafaxine had a decrease ≥ 20 mm Hg and absolute value ≤ 90 mm Hg, compared with a single patient (0.5%) receiving placebo.

There was a small but significant decrease in adjusted mean body weight at the final evaluation for desvenlafaxine (–0.2 [0.15] kg) versus placebo (+0.4 [0.15] kg; $P = .0070$). Five patients (2.3%) receiving desvenlafaxine had a decrease in body weight of at least 7% compared with 3 patients (1.4%) receiving placebo; an increase in body weight of at least 7% occurred in no patients in the desvenlafaxine group compared to a single patient (0.5%) in the placebo group.

Four patients (2 in each group) experienced serious TEAEs; none were deemed related to investigational product or to the protocol. No occurrences of new-onset suicidal behavior or ideation were reported in either group. No deaths occurred during the study.

Overall, 32 patients (14.7%) in the desvenlafaxine group and 39 patients (18.0%) in the placebo group discontinued the study; AEs were the most common reason for discontinuation (12 desvenlafaxine [5.5%]; 5 placebo [2.3%]). The other most common reasons for early withdrawal were unsatisfactory response (3 desvenlafaxine [1.4%], 11 placebo [5.1%]), subject request (8 desvenlafaxine [3.7%], 7 placebo [3.2%]), and loss to follow-up (5 desvenlafaxine [2.3%], 9 placebo [4.1%]).

DISCUSSION

This was the first large, double-blind, placebo-controlled clinical trial designed specifically to evaluate efficacy and safety of desvenlafaxine at the recommended dose of 50 mg/d in treating MDD in perimenopausal and postmenopausal women. The primary end point of a significant reduction in $HDRS_{17}$ total score in the desvenlafaxine group compared with placebo was met for the overall study population, as well as for the perimenopausal and postmenopausal subpopulations. Most of the secondary measures of efficacy were also significantly improved for patients who received desvenlafaxine compared with those who received placebo.

In a previous trial of similar design, women aged 40 to 70 years were randomly assigned to placebo or desvenlafaxine; the post-titration dosage of desvenlafaxine was 100 or 200 mg/d.[24] The mean reduction in adjusted $HDRS_{17}$ total scores from baseline to week 8 was significantly greater for desvenlafaxine (−12.64) compared with placebo (−8.33; $P < .001$), and significant reduction was seen in the perimenopausal and postmenopausal subgroups. Reductions were apparent as early as 1 week and were sustained throughout the study.[24]

Apart from dose level, the current study and the previous one were similar in design, but some differences should be noted. Hormone therapy was permitted in this study but excluded in the previous study. The current study also used a different MADRS inclusion criterion, with a MADRS total score ≥ 25 at screening and baseline compared with ≥ 22 in the previous study; as such, the patient population in the current study may better represent moderate to severe disease. In each study, the primary end point was reduction in the $HDRS_{17}$ total score at week 8, although the current study included a 10-week, on-therapy study period. For both studies, while the screening and randomization criteria were based on the MADRS, the primary efficacy end point was

Table 2. Secondary Efficacy and Health Outcomes End Points, Week 8 (LOCF), FAS Population

End Point	n	Adjusted Mean	Adjusted Mean Change From Double-Blind Baseline (SE)	Adjusted Difference From Placebo (95% CI)	*P* Value
$HDRS_6$ total score					
Placebo	216	7.5	−4.8 (0.25)		
Desvenlafaxine	216	6.3	−6.0 (0.25)	−1.2 (−1.9 to −0.5)	<.001
CGI-S					
Placebo	216	3.3	−1.1 (0.07)		
Desvenlafaxine	216	2.9	−1.5 (0.07)	−0.3 (−0.5 to −0.1)	.002
MADRS total score					
Placebo	203	18.3	−12.4 (0.67)		
Desvenlafaxine	203	15.6	−15.1 (0.67)	−2.7 (−4.4 to −0.9)	.002
QIDS-SR					
Placebo	203	9.6	−5.4 (0.33)		
Desvenlafaxine	203	9.1	−6.0 (0.33)	−0.6 (−1.5 to 0.2)	.158
VAS-PI					
Placebo	216	3.3	−0.5 (0.14)		
Desvenlafaxine	216	2.4	−1.5 (0.14)	−1.0 (−1.3 to −0.6)	<.001
SDS					
Placebo	164	9.31	−7.54 (0.63)		
Desvenlafaxine	154	7.72	−9.13 (0.62)	−1.59 (−3.09 to −0.09)	.038
EQ-5D–Health State Index Score					
Placebo	211	0.66	0.09 (0.019)		
Desvenlafaxine	210	0.72	0.15 (0.019)	0.06 (0.02 to 0.11)	.007
EQ-5D–Health State Score					
Placebo	211	65.9	8.1 (1.63)		
Desvenlafaxine	211	68.1	10.2 (1.62)	2.2 (−1.63 to 5.95)	.264
Menopause Rating Scale					
Placebo	211	13.6	−5.6 (0.56)		
Desvenlafaxine	211	12.3	−6.9 (0.54)	−1.3 (−2.55 to 0.00)	.051
	Proportion (n/N)		%	Adjusted Odds Ratio (95% CI)	
Response[a]					
Placebo	72/216		33.3		
Desvenlafaxine	89/216		41.2	1.41 (0.95 to 2.10)	.087
Remission[b]					
Placebo	37/216		17.1		
Desvenlafaxine	51/216		23.6	1.59 (0.98 to 2.59)	.060

[a]≥ 50% reduction from baseline in $HDRS_{17}$ total score.
[b]$HDRS_{17}$ total score ≤ 7.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, EQ-5D = EuroQol Health State–Five Dimension, FAS = full analysis set, LOCF = last observation carried forward, $HDRS_6$ = 6-Item Hamilton Depression Rating Scale, $HDRS_{17}$ = 17-Item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report, SDS = Sheehan Disability Scale, SE = standard error, VAS-PI = Visual Analog Scale–Pain Intensity.

Table 3. Patients Reporting Treatment-Emergent Adverse Events With Incidence ≥ 5% in Either Treatment Group, n (%)

	Placebo (n = 217)	Desvenlafaxine 50 mg/d (n = 217)
Any treatment-emergent adverse events	148 (68.2)	155 (71.4)
Headache	25 (11.5)	33 (15.2)
Nausea	16 (7.4)	24 (11.1)
Upper respiratory tract infection	19 (8.8)	17 (7.8)
Constipation	9 (4.1)	17 (7.8)
Nasopharyngitis	12 (5.5)	15 (6.9)
Dry mouth	17 (7.8)	14 (6.5)
Dizziness	10 (4.6)	14 (6.5)
Diarrhea	12 (5.5)	13 (6.0)

change in $HDRS_{17}$ score, in an attempt to minimize rater expectation bias.

Statistical separation was apparent as early as week 2 on functional and pain measures, including the SDS and VAS-PI, indicating that desvenlafaxine provides benefits earlier than, and in addition to, its positive effects on depression. A significant improvement in health state index measures (EQ-5D) was seen at the first assessment (week 4) and at all subsequent time points.

A significant treatment effect on Menopause Rating Scale total score was observed in a previous, higher-dose (100–200 mg/d) study of desvenlafaxine for depression in menopausal women.[24] In the current study, the difference between desvenlafaxine and placebo in Menopause Rating Scale total score only approached significance ($P = .051$). A correlation between reduction in menopausal symptoms and improvement in depressive symptoms might be expected in this population, as hot flushes are associated with an increased risk of new-onset depression during the menopausal transition,[36,37] and improvements in mood have been observed in women treated for moderate to severe hot flushes.[38] However, the current study was not designed to assess the role of menopausal symptoms in antidepressant treatment response. In postmenopausal women treated for depression with the SNRI duloxetine, no correlation was observed between improvement in depression scale scores and vasomotor symptoms (although a trend was

described).[21] The results of post hoc analyses examining Menopause Rating Scale scores (including hot flush scores) from the current study are reported in a separate manuscript (S.G.K., manuscript in preparation).

Prior studies suggest that some antidepressants, including SSRIs, are not as effective during the menopausal transition or in older women[7–9] and that SSRIs may be more effective in these patients when enhanced by coadministration of estrogen.[7,9,18–20] In contrast, there is currently no evidence of age or gender effects with the SNRIs venlafaxine or duloxetine. The results of this study support the efficacy of the SNRI desvenlafaxine at the recommended 50-mg/d dose in the treatment of MDD in both perimenopausal and postmenopausal women, without need for coadministration of estrogen. These observations are consistent with the idea that SNRIs may be able to better compensate for potential dysregulation in both NE and 5-HT systems occurring with menopause[2] and suggest that SNRIs may be effective in treating MDD across a broad age range.

Safety and tolerability were consistent with other desvenlafaxine trials.[24,39] Overall, no new safety signals were observed, and the benefit/risk profile of desvenlafaxine remains favorable.

There are some limitations to this study. Enrolled patients were medically stable with a primary diagnosis of MDD; therefore, these findings may not generalize to other populations. The trial was 10 weeks in duration; a longer period of time may have allowed for more patients to respond. Concomitant hormonal therapy was permitted in this study, potentially reducing detectable differences between treatment groups; however, the percentage of patients actually receiving hormonal therapy was very low (6% in overall population), and thus any impact was modest. Finally, this was a fixed-dose study, and thus some patients may not have received an adequate therapeutic dose.

CONCLUSION

Short-term treatment with desvenlafaxine at the recommended dose of 50 mg/d was effective and generally well tolerated in this placebo-controlled study of perimenopausal and postmenopausal women with MDD, thus replicating the results of other clinical studies in which higher doses of desvenlafaxine were administered.

Drug names: desvenlafaxine (Pristiq), duloxetine (Cymbalta), eszopiclone (Lunesta), ramelteon (Rozerem), venlafaxine (Effexor and others), zaleplon (Sonata and others), zolpidem (Ambien, Edluar, and others).

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Potential conflicts of interest: **Dr Clayton** has received grants from BioSante, Palatin Technologies, Pfizer, and Takeda; has received advisory board fee/consultant fees from Euthymics, Forest, Palatin Technologies, Pfizer, S1 Biopharmaceuticals, Sprout, Sunovion, Takeda, Trimel, and Valeant; has received royalties/copyright from Ballantine Books/Random House, Changes in Sexual Functioning Questionnaire, and Guilford Publications; and shares/restricted stock units from Euthymics and S1 Biopharmaceuticals. **Dr Dunlop** is a consultant for Bristol-Myers Squibb, Pfizer, MedAvante, and Roche and has received grants/research support from National Institute of Mental Health, GlaxoSmithKline, Bristol-Myers Squibb, and Transcept. **Dr Kornstein** has served as a consultant and on advisory boards for Pfizer, Eli Lilly, Takeda, Trovis, and Forest and has received grants/research support from Pfizer, Eli Lilly, Euthymics, Rexahn, Boehringer-Ingelheim, Bristol-Myers Squibb, Forest, and Otsuka. **Ms Focht**; **Mr Musgnung**; and **Drs Ramey**, **Bao**, and **Ninan** are Pfizer employees. **Dr Ramey** is a stock shareholder in Pfizer and Eli Lilly.

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