Desvenlafaxine 50 and 100 mg/d Versus Placebo for the Treatment of Major Depressive Disorder: A Phase 4, Randomized Controlled Trial

Anita H. Clayton, MD; Karen A. Tourian, MD; Kristen Focht, MBA; Eunhee Hwang, PhD; Ru-fong J. Cheng, MD; and Michael E. Thase, MD

ABSTRACT

Objective: To assess short-term efficacy and safety of desvenlafaxine 50 and 100 mg/d versus placebo for treating major depressive disorder (MDD). Assessment of sexual function was a secondary objective.

Method: Outpatients (≥ 18 years) who met criteria for MDD from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision and had screening and baseline 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) total scores ≥ 20 were randomly assigned to placebo or desvenlafaxine 50 or 100 mg/d in an 8-week study conducted from October 2011 to August 2012. The primary efficacy end point was change from baseline in $HDRS_{17}$ total score at week 8, analyzed using a mixed-effects model for repeated measures. Sexual function was assessed using the Arizona Sexual Experiences Scale (ASEX).

Results: The safety population included 909 patients (intent-to-treat population, n = 886). Significantly greater improvement in adjusted mean $HDRS_{17}$ total score from baseline to week 8 was observed for desvenlafaxine 50 mg (–11.28; $P = .006$) and desvenlafaxine 100 mg (–11.67; $P < .001$) compared with placebo (–9.71), with adjustment for multiplicity. In the ASEX total score analysis (n = 422), the treatment by gender interaction was not significant; thus, genders were combined for subsequent analyses. Comparisons for desvenlafaxine versus placebo for change from baseline in ASEX total and all item scores found $P > .05$, with no adjustment for multiplicity. Rates of sexual dysfunction based on ASEX were comparable among treatment groups.

Conclusions: These results support previous findings demonstrating antidepressant efficacy, safety, and tolerability of desvenlafaxine 50 and 100 mg/d versus placebo. Sexual function was comparable between desvenlafaxine and placebo.

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Corresponding author: *Anita H. Clayton, MD, University of Virginia Health System, PO Box 800623, Charlottesville, VA 22908-0623 (ahc8v@virginia.edu).*

The serotonin-norepinephrine reuptake inhibitor desvenlafaxine (administered as desvenlafaxine succinate) is a first-line treatment for moderate to severe major depressive disorder (MDD).[1,2] Clinical studies have demonstrated antidepressant efficacy for desvenlafaxine doses of 50 to 400 mg/d, although no additional efficacy benefit was observed at doses greater than 50 mg/d.[3–9] No evidence of efficacy has been observed at desvenlafaxine doses lower than 50 mg/d.[7,10] The current recommended dose for desvenlafaxine is 50 mg once daily; both the 50- and 100-mg/d dose formulations have been approved by the US Food and Drug Administration (FDA) for adults with MDD.

The phase 4, randomized, double-blind, placebo-controlled study reported here was conducted to assess efficacy and tolerability of the 2 FDA-approved desvenlafaxine doses. The primary objective was to evaluate the efficacy of the 50- and 100-mg/d doses compared with placebo over 8 weeks of treatment in adult outpatients with MDD. One of the secondary objectives of the study was to compare sexual function in MDD patients treated with desvenlafaxine 50 or 100 mg/d versus placebo using a structured assessment tool. Sexual dysfunction is a common concern for patients treated with antidepressants, including serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors.[11–14] Low rates of adverse events (AEs) related to sexual function based on spontaneously reported AEs were observed in a pooled analysis of clinical trial data for desvenlafaxine 50- to 400-mg/d doses.[15] However, the use of spontaneous reports of sexual dysfunction is known to underestimate its rates.[16,17] This study employed a validated outcome measure, the Arizona Sexual Experiences Scale[18] (ASEX), to assess sexual dysfunction.

METHOD

Study Design

This multicenter, randomized, double-blind, placebo-controlled, 8-week study was conducted from October 2011 to August 2012. Patients were randomized at a total of 56 US sites, including private and institutional practice and research centers. This study was conducted exclusively in the United States, as the ASEX has only been validated in American English.[18] Patients were randomly assigned in a site-balanced, 1:1:1 ratio to placebo or desvenlafaxine 50- or 100-mg/d doses. Patients assigned to desvenlafaxine 100 mg/d received 50 mg/d on study days 1 through 7 and started the 100-mg/d dose on day 8; dose was tapered to 50 mg/d for 1 week at the completion of the 8 weeks (or at early discontinuation). Patients randomized to desvenlafaxine 50 mg/d or placebo received 1 week of placebo at the completion of the 8 weeks (or at early discontinuation).

The protocol and 1 study amendment received institutional review board or independent ethics committee approval before initiation. The study was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice[19] and the ethical principles that have their origin in the Declaration of Helsinki, and was

listed on the ClinicalTrials.gov website prior to patient recruitment (study identifier NCT01432457). Written informed consent was obtained from all participants before any protocol-required procedures were performed.

Patients

Adult outpatients, 18 years or older, who met criteria for MDD from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision[20] as the primary diagnosis were enrolled. All enrolled patients had depressive symptoms for at least 30 days prior to screening and a 17-item Hamilton Depression Rating Scale[21] ($HDRS_{17}$) total score of at least 20, $HDRS_{17}$ item 1 (depressed mood) score of at least 2, and Clinical Global Impressions Scale–Severity[22] (CGI-S) score of at least 4 at screening and baseline visits. All patients reviewed the ASEX instrument at screening and were enrolled only if they agreed to complete the ASEX throughout the study.

Patients were excluded if they had current (within 12 months from baseline) psychoactive substance abuse or dependence (including alcohol), manic episodes, posttraumatic stress disorder, obsessive-compulsive disorder, lifetime diagnosis of bipolar or psychotic disorder, or clinically important personality disorder, as assessed by the modified Mini-International Neuropsychiatric Interview[23] at the screening visit, or if they had depression due to a general medical condition or neurologic disorder, history of a seizure disorder, or severe acute or chronic medical disease (including unstable hepatic, renal, pulmonary, or cardiovascular disease). Patients were excluded if they had clinically important laboratory or physical findings or a significant risk of suicide based on clinical judgment, Columbia–Suicide Severity Rating Scale[24] (C-SSRS) responses, a Suicidal Behaviors Questionnaire–Revised[25] (SBQ-R) score of 8 or greater, or a score greater than 3 on $HDRS_{17}$ item 3 (suicide) at the screening visit. Patients who had received treatment with desvenlafaxine at any time in the past, or with venlafaxine within the past year, or had a known or suspected sensitivity to venlafaxine were also excluded.

Assessments

The primary efficacy end point for the study was the change from baseline in $HDRS_{17}$ total score at final on-therapy evaluation (week 8). Secondary efficacy end points included Clinical Global Impression Scale–Improvement[22] (CGI-I) score, change from baseline in CGI-S score, and rates of $HDRS_{17}$ response (≥ 50% decrease from baseline in total score) and $HDRS_{17}$ remission (total score ≤ 7) at the final on-therapy evaluation. Efficacy evaluations were administered at baseline (except CGI-I) and weeks 1, 2, 4, 6, and 8 (or at early termination).

Sexual function was assessed using the ASEX, a validated, patient-rated sexual function scale. The ASEX was selected because it is a brief but sensitive tool, less burdensome to patients than a more in-depth scale, and has been utilized in previous trials for desvenlafaxine[8] and other antidepressant drugs.[26] It measures 5 core elements of sexual function (sexual drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm), each on a 6-point Likert scale (1 [hyperfunction] to 6 [hypofunction]).[18] A total score is calculated as the sum of all 5 individual item scores; negative numbers for change from baseline indicate improvement in sexual function. The ASEX is designed to evaluate sexual function during the past week only, and the total score was derived only for those visits during which sexual activity was indicated within the past week via a separate questionnaire. The ASEX was collected at baseline and at each postbaseline study visit. The study protocol specified change in total score as a secondary end point for the study. However, a recent FDA regulatory science forum on measuring sexual dysfunction in depression trials concluded that the ASEX is more appropriately used as a dichotomous measure of sexual dysfunction using the scale designers' criteria (total score ≥ 19, any 1 item with a score ≥ 5, or any 3 items with a score ≥ 4) to define sexual dysfunction.[18] Both total score as prespecified and sexual dysfunction rates as a post hoc analysis were therefore determined.

Safety assessments included physical examination, vital signs and weight, laboratory evaluations, electrocardiogram (ECG), and the C-SSRS. Laboratory evaluations, vital signs, and ECGs were evaluated for mean changes from baseline and between treatments. Findings of potential clinical importance for laboratory evaluations, vital signs, and ECGs were identified based on criteria prespecified by the sponsor, the FDA, or the European Medicines Agency. Clinically important results were identified by the medical monitor based on a review of patient data, relevant clinical information pertaining to a patient, and clinical judgment. Treatment-emergent AEs (TEAEs), discontinuations due to AEs, and serious AEs (SAEs) were monitored at each visit.

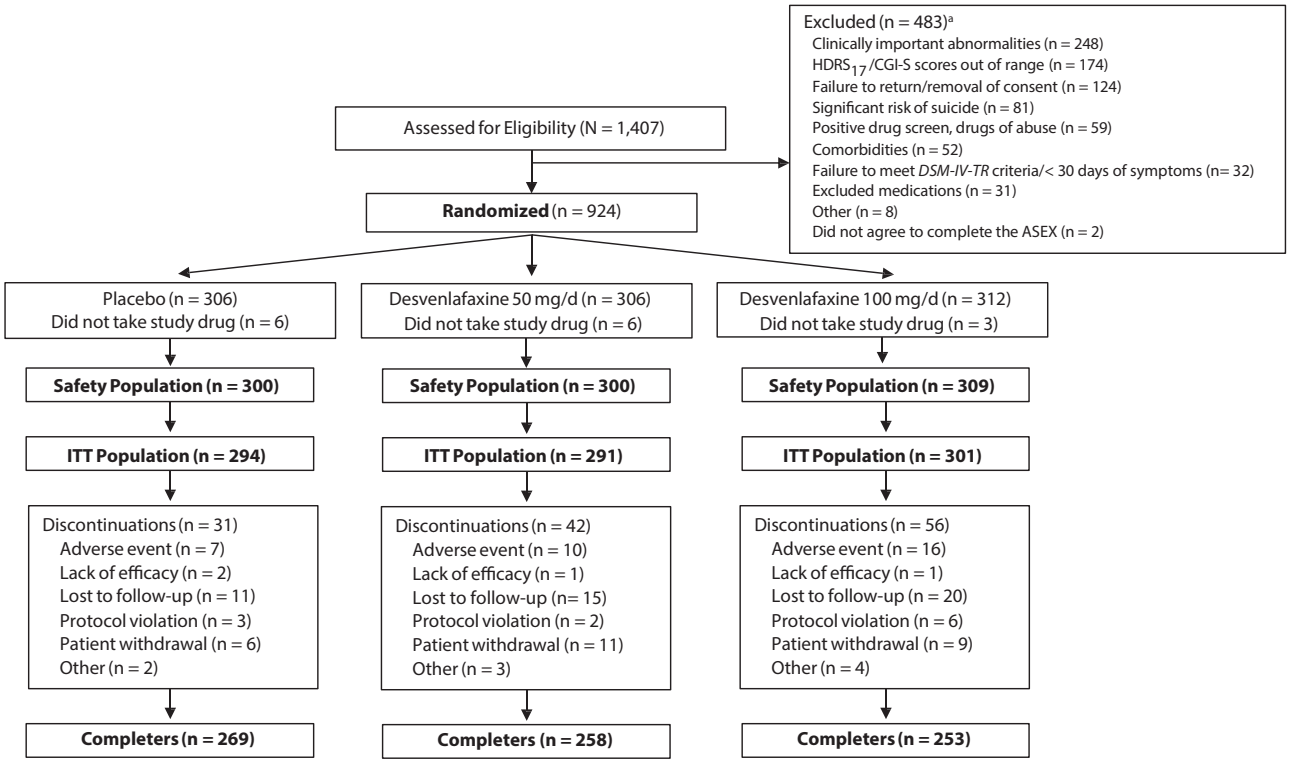
Statistical Analysis

The primary analysis population for efficacy evaluations was the intent-to-treat (ITT) population (all randomly assigned patients who received ≥ 1 dose of study drug and had a baseline and ≥ 1 postbaseline $HDRS_{17}$ total score); the time point of interest for each analysis was the final evaluation (week 8). The primary analysis of $HDRS_{17}$ total score was a mixed-effects model for repeated measures (MMRM) with treatment, visit, treatment by visit interaction, and site as fixed

Clinical Points

- Sexual dysfunction is a common concern for patients with major depressive disorder. Some antidepressants may cause sexual dysfunction.
- In the current study, sexual function, assessed using the Arizona Sexual Experiences Scale, was comparable between placebo and desvenlafaxine groups.
- Phase 4 study results support previous findings demonstrating antidepressant efficacy, safety, and tolerability of desvenlafaxine 50 and 100 mg/d versus placebo.

Figure 1. Patient Disposition



[a]Patients may have had multiple reasons for not being enrolled.
Abbreviations: ASEX = Arizona Sexual Experiences Scale, CGI-S = Clinical Global Impressions Scale–Severity, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale.

effects and baseline $HDRS_{17}$ score as a covariate. A Hochberg step-up procedure was used to control for multiplicity associated with the inclusion of 2 active dose arms. Two sensitivity analyses based on last observation carried forward (LOCF) and observed cases (OC) data were conducted using analysis of covariance (ANCOVA) models.

Change from baseline on the CGI-S score was analyzed using an MMRM with treatment, visit, treatment by visit interaction and site as fixed effects and baseline score as a covariate. CGI-I scores (LOCF) were analyzed using the Cochran-Mantel-Haenszel row-mean-score-difference test using ridit scores. Response and remission rates were analyzed using a logistic regression model with treatment and site as fixed factors and baseline $HDRS_{17}$ score as a covariate, based on LOCF data. There was no multiplicity control in analyses of secondary end points or in any safety parameters including ASEX.

Analysis of ASEX total score included only those patients in the safety population who were sexually active at baseline and at least 1 postbaseline assessment. The primary ASEX analysis (both genders combined vs genders tested separately) was determined based on the results of an analysis of change from baseline in the ASEX total score at week 8 (LOCF) using an ANCOVA model including the treatment by gender interaction term. If the *P* value for the treatment by gender interaction was found to be .05 or less, results were to be presented separately by gender using a model including the interaction. If the *P* value for the interaction was greater than .05, the primary ANCOVA model would include treatment, site, and gender with no interaction term. Change from baseline in ASEX item scores was analyzed using the same model as the ASEX total score.

Incidence of sexual dysfunction was assessed in a post hoc analysis of ASEX data. Sexual dysfunction status was determined as "yes, dysfunctional" for each evaluation if any of 3 criteria were met (total score ≥ 19, any 1 item score ≥ 5, or any 3 item scores ≥ 4), or "no" if none were met. Sexual dysfunction status was analyzed using a logistic regression model, based on LOCF data, with sex, age, baseline sexual dysfunction status, and treatment in the model.

Incidence of TEAEs, discontinuations due to AEs, and SAEs were summarized by treatment group. The proportions of patients with laboratory, vital sign, or ECG parameter values of clinical importance were summarized. C-SSRS data were summarized without statistical inference, as 1 study does not provide sufficient power to analyze between-group differences in these low-frequency events.

RESULTS

Patients

Of the 924 patients randomly assigned to treatment, 909 took at least 1 dose of study drug and were included in the safety population (placebo, n = 300; desvenlafaxine 50 mg, n = 300; desvenlafaxine 100 mg, n = 309; Figure 1). The ITT population included 886 patients (placebo, n = 294; desvenlafaxine 50 mg, n = 291; desvenlafaxine 100 mg, n = 301).

Table 1. Demographic and Baseline Characteristics, Safety Population

Characteristic	Placebo (n = 300)	Desvenlafaxine 50 mg/d (n = 300)	Desvenlafaxine 100 mg/d (n = 309)
Age, y			
Mean (SD)	41.7 (12.4)	41.8 (13.6)	41.3 (12.8)
Female, n (%)	173 (57.7)	172 (57.3)	165 (53.4)
Race, n (%)			
Asian	8 (2.7)	12 (4.0)	9 (2.9)
Black	87 (29.0)	77 (25.7)	77 (24.9)
White	198 (66.0)	199 (66.3)	216 (69.9)
Other	7 (2.3)	12 (4.0)	7 (2.3)
Weight, kg			
Mean (SD)	87.1 (23.1)	88.4 (23.8)	85.9 (23.2)
Body mass index, kg/m^2			
Mean (SD)	30.4 (7.9)	30.6 (8.4)	29.7 (8.1)
Baseline $HDRS_{17}$ score			
Mean (SD)	23.6 (2.6)	23.4 (2.7)	23.5 (2.8)
Duration of current depressive episode, mo			
Median	7.9	7.0	6.9
Range	1.1–156.9	1.1–228.4	1.1–226.5
Sexually active (within past wk), n/n (%)	144/300 (48.0)	146/300 (48.7)	155/308 (50.3)

Abbreviations: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, SD = standard deviation.

Table 2. $HDRS_{17}$ Total Score at Week 8; MMRM, ITT Population

	N	Adjusted Mean	Adjusted Change From Baseline Mean (SE)	Adjusted Mean Difference (95% CI)	*P* Value vs Placebo
Baseline					
Placebo	294	23.4			
Desvenlafaxine 50 mg	291	23.4			
Desvenlafaxine 100 mg	301	23.4			
Week 8					
Placebo	267	13.7	−9.7 (0.42)		
Desvenlafaxine 50 mg	257	12.2	−11.3 (0.42)	1.57 (0.44, 2.69)	.006
Desvenlafaxine 100 mg	252	11.8	−11.7 (0.42)	1.96 (0.84, 3.08)	< .001

Abbreviations: CI = confidence interval, $HDRS_{17}$ = 17-Item Hamilton Depression Rating Scale, ITT = intent-to-treat, MMRM = mixed-effects model for repeated measures analysis, SE = standard error.

A total of 129 of 909 patients (14.2%) discontinued early. The placebo group had the lowest rate of early discontinuations (10.3%), followed by the desvenlafaxine 50-mg group (14.0%), and the desvenlafaxine 100-mg group (18.1%). The most common reason for discontinuation was "lost to follow-up" (overall, 5.1%; Figure 1). Seven patients (2.3%) taking placebo, 10 patients (3.3%) taking desvenlafaxine 50 mg, and 16 patients (5.2%) taking desvenlafaxine 100 mg discontinued due to AEs.

The safety population was 56.1% female and 67.4% white, and the mean age at baseline was 41.6 years. No statistically significant differences among treatment groups in demographics or baseline characteristics were observed (Table 1).

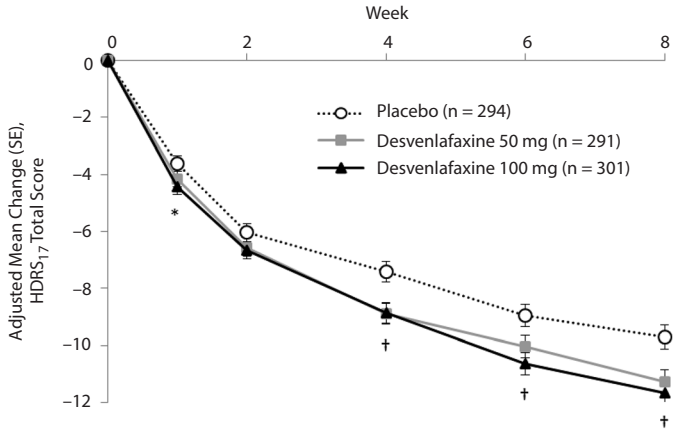
Efficacy

Primary efficacy end point. In the primary efficacy analysis, a statistically significantly greater change from baseline in $HDRS_{17}$ total score was observed for both desvenlafaxine groups compared with placebo after adjusting for multiplicity (desvenlafaxine 50 mg, $P = .006$; desvenlafaxine 100 mg, $P < .001$). The adjusted mean difference (95% CI) from placebo at week 8 was 1.57 (0.44, 2.69) for desvenlafaxine 50 mg/d and 1.96 (0.84, 3.08) for desvenlafaxine 100 mg/d (Table 2). Significant differences from placebo were observed for both desvenlafaxine dose groups from week 4 on (Figure 2). Results of the ANCOVA sensitivity analyses were consistent with results of the primary analysis.

Secondary efficacy end points. Statistically significant improvement from baseline in CGI-S scores was observed at week 8 for both desvenlafaxine dose groups compared with placebo. The adjusted mean difference (95% CI) versus placebo was 0.20 (0.05, 0.34; $P = .009$) for the desvenlafaxine 50-mg group and 0.28 (0.13, 0.43; $P < .001$) for the desvenlafaxine 100-mg group. Pairwise comparisons of CGI-I scores for each desvenlafaxine group versus placebo were statistically significant (desvenlafaxine 50 mg, $P = .029$; desvenlafaxine 100 mg, $P < .001$, without adjustment for multiplicity). The proportions of patients evaluated as "much improved" or "very much improved" on the CGI-I were 44.6%, 55.3%, and 59.5% at week 8 (LOCF) for the placebo, desvenlafaxine 50-mg, and desvenlafaxine 100-mg groups, respectively.

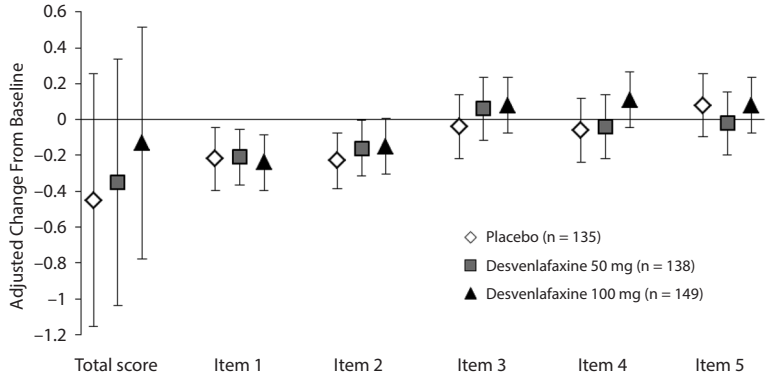
Response rate was 39.5% for the placebo group at week 8 (LOCF) compared with 45.0% and 47.5% for the desvenlafaxine 50- and 100-mg groups, respectively. Neither desvenlafaxine group differed significantly from placebo in rate of response, although the rate for desvenlafaxine 100 mg/d approached significance ($P = .054$). Remission rates

Figure 2. Adjusted Mean Change of $HDRS_{17}$ Total Score at Week 8 (LOCF, ITT Population)



*$P < .05$, desvenlafaxine 100 mg vs placebo.
†$P < .05$, desvenlafaxine 50 mg and 100 mg vs placebo.
Abbreviations: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ITT = intent to treat, LOCF = last observation carried forward, SE = standard error.

Figure 3. Arizona Sexual Experiences Scale Adjusted Mean (95% CI) Change From Baseline at Week 8 (LOCF), Sexually Active Males and Females[a]



Item 1: How strong is your sex drive?
Item 2: How easily are you sexually aroused (turned on)?
Item 3: Male: Can you easily get and keep an erection? Female: How easily does your vagina become moist or wet during sex?
Item 4: How easily can you reach an orgasm?
Item 5: Are your orgasms satisfying?
Total: Sum of items 1 to 5.
[a]Only patients who reported sexual activity within the past week at baseline and week 8 (LOCF) were included in the analysis.
Abbreviations: ASEX = Arizona Sexual Experiences Scale, LOCF = last observation carried forward.

at week 8 (LOCF) did not differ significantly between groups (placebo, 21.8%; desvenlafaxine 50 mg, 24.1%; desvenlafaxine 100 mg, 28.6%).

Safety and Tolerability

At baseline, 49% of the safety population was sexually active, and the proportion of patients was comparable across treatment groups (placebo, 48.0%; desvenlafaxine 50 mg, 48.7%; desvenlafaxine 100 mg, 50.3%). The proportions of patients who had had sexual activity at baseline and at least 1 time during the double-blind period and were included in the ASEX total score analysis were 45%, 46%, and 48%, respectively. The treatment by gender interaction was greater than .05 ($P = .208$); therefore, the primary ASEX analysis combined genders. At week 8 (LOCF), ASEX total and individual item scores were comparable for both 50- and 100-mg doses of desvenlafaxine and placebo, with widely overlapping confidence intervals (Figure 3). All *P* values versus placebo were greater than .05, with no adjustment for multiplicity (Table 3). In a post hoc analysis of ASEX total score by gender, *P* values for desvenlafaxine groups versus placebo were greater than .05 for both males and females (Table 3).

The results of the post hoc analysis of sexual dysfunction rates based on the ASEX were consistent with results of the pre-planned ASEX total score analysis. Baseline and week 8 rates of sexual dysfunction are shown in Table 3. At week 8, rates of sexual dysfunction were comparable among treatment groups, with *P* value versus placebo equal to .486 and .610 for desvenlafaxine 50 mg and desvenlafaxine 100 mg, respectively. The treatment by gender interaction was not significant for the post hoc analysis of sexual dysfunction ($P = .4167$).

Treatment-emergent AEs were reported by 191/300 patients (63.7%) in the placebo group compared with 217/300 patients (72.3%) and 229/309 patients (74.1%) in the desvenlafaxine 50- and 100-mg/d groups, respectively. The most common TEAEs (reported by ≥ 5% of patients in either desvenlafaxine group) were headache, nausea, dry mouth, dizziness, diarrhea, constipation, somnolence, insomnia, and decreased appetite. Serious AEs reported on-therapy by patients receiving placebo were constipation, abnormal ECG, and lymphadenopathy (n = 1 each). Serious AEs reported by patients receiving placebo in the follow-up period were increased depressive symptoms, fractured leg, and abnormal behavior (n = 1 each). In the desvenlafaxine 50-mg group, 1 suicide attempt (intentional alprazolam and study drug overdose) was reported with hyperthermia, increased serotonin level, and impaired motor coordination. The patient was withdrawn from the study, admitted to the hospital, and released after 5 days. The patient received referrals for mental health follow-up from the hospital and from the investigator but refused to provide further information for the purposes of study follow-up. The SAEs for this patient were listed for the on-therapy and follow-up periods. A second desvenlafaxine 50-mg–treated patient reported suicidal ideation in the follow-up period. Serious AEs reported by patients on therapy in the desvenlafaxine

Table 3. ASEX Prespecified and Post Hoc Analyses

ASEX Adjusted Mean Scores,[a] Week 8 (LOCF)	N	Adjusted Mean	Adjusted Change From Baseline Mean (SE)	Adjusted Mean Difference (95% CI)	*P* Value vs Placebo
Total score					
Overall					
Placebo	135	15.09	−0.45 (0.36)		
Desvenlafaxine 50 mg	138	15.18	−0.35 (0.35)	−0.09 (−0.98, 0.80)	.837
Desvenlafaxine 100 mg	149	15.41	−0.13 (0.33)	−0.32 (−1.19, 0.55)	.471
Females					
Placebo	70	16.85	0.07 (0.48)		
Desvenlafaxine 50 mg	74	16.32	−0.47 (0.47)	0.53 (−0.70, 1.77)	.397
Desvenlafaxine 100 mg	75	16.46	−0.32 (0.46)	0.39 (−0.83, 1.61)	.529
Males					
Placebo	65	13.12	−1.00 (0.49)		
Desvenlafaxine 50 mg	64	13.91	−0.21 (0.50)	−0.79 (−2.10, 0.53)	.240
Desvenlafaxine 100 mg	74	14.21	0.09 (0.46)	−1.09 (−2.35, 0.18)	.091
Item scores					
Item 1					
Placebo	135	3.10	−0.22 (0.09)		
Desvenlafaxine 50 mg	138	3.11	−0.21 (0.08)	−0.01 (−0.22, 0.21)	.950
Desvenlafaxine 100 mg	149	3.08	−0.24 (0.08)	0.02 (−0.19, 0.23)	.864
Item 2					
Placebo	135	2.97	−0.23 (0.08)		
Desvenlafaxine 50 mg	138	3.04	−0.16 (0.08)	−0.07 (−0.28, 0.14)	.518
Desvenlafaxine 100 mg	149	3.05	−0.15 (0.08)	−0.08 (−0.28, 0.13)	.455
Item 3					
Placebo	135	2.85	−0.04 (0.09)		
Desvenlafaxine 50 mg	138	2.94	0.06 (0.09)	−0.09 (−0.31, 0.13)	.416
Desvenlafaxine 100 mg	149	2.96	0.08 (0.08)	−0.11 (−0.33, 0.10)	.311
Item 4					
Placebo	135	3.25	−0.06 (0.09)		
Desvenlafaxine 50 mg	138	3.27	−0.04 (0.09)	−0.02 (−0.24, 0.20)	.846
Desvenlafaxine 100 mg	149	3.42	0.11 (0.08)	−0.17 (−0.38, 0.05)	.122
Item 5					
Placebo	135	2.91	0.08 (0.09)		
Desvenlafaxine 50 mg	138	2.80	−0.02 (0.09)	0.10 (−0.12, 0.33)	.373
Desvenlafaxine 100 mg	149	2.90	0.08 (0.08)	0.00 (−0.21, 0.22)	.965

ASEX Sexual Dysfunction Rates, Safety Population	Baseline SD Rate, n/N (%)	Week 8 (LOCF) SD Rate, n/N (%)	Adjusted OR (95% CI)	*P* Value vs Placebo
Placebo	155/299 (51.8)	135/300 (45.0)		
Desvenlafaxine 50 mg	167/300 (55.7)	146/297 (49.2)	1.14 (0.78, 1.67)	.486
Desvenlafaxine 100 mg	165/307 (53.7)	145/307 (47.2)	1.10 (0.76, 1.61)	.610

Item 1: How strong is your sex drive?
Item 2: How easily are you sexually aroused (turned on)?
Item 3: Male: Can you easily get and keep an erection? Female: How easily does your vagina become moist or wet during sex?
Item 4: How easily can you reach an orgasm?
Item 5: Are your orgasms satisfying?
Total = Sum of items 1 to 5.
[a]Includes only patients who reported sexual activity within the past week at baseline and week 8 (LOCF).
Abbreviations: ASEX = Arizona Sexual Experiences Scale, CI = confidence interval, LOCF = last observation carried forward, OR = odds ratio, SD = standard deviation, SE = standard error.

100-mg group were suicidal ideation (1 patient) and atrial fibrillation (1 patient). The patient who reported suicidal ideation was withdrawn from the study, and the event was reported for both the on-therapy and follow-up periods. No deaths occurred in this study. New suicidal ideation (without prior history reported at baseline), as measured by the C-SSRS, was reported by 72 patients; there was no evidence that patients taking active drug were more likely to report suicidal ideation than those taking placebo (31 placebo, 15 desvenlafaxine 50 mg, 26 desvenlafaxine 100 mg).

No new safety findings were observed for vital signs and laboratory findings. Clinically important vital signs results included elevated blood pressure (BP) (1 patient), orthostatic pulse changes (1 patient), hypertension (2 patients), hypotension (1 patient), and increased weight (1 patient) for the placebo group; heart rate increase (1 patient), BP increase (2 patients), orthostatic pulse changes (2 patients), and orthostatic hypotension (1 patient) for desvenlafaxine 50 mg/d; and elevated diastolic BP (1 patient), orthostatic pulse changes (1 patient), orthostatic BP changes (1 patient), weight gain (1 patient), and BP increase (2 patients) for desvenlafaxine 100 mg/d. One patient (desvenlafaxine 100 mg) had clinically important increased QTcB and QTcF intervals (ie, corrected QT interval according to Bazett and Fridericia formulas). Clinically important laboratory findings included creatine kinase levels (which were not routinely collected in previous studies; placebo, 8 patients; desvenlafaxine 50 mg, 7 patients; desvenlafaxine 100 mg,

10 patients); positive hepatitis C test (placebo, 1 patient); positive liver function test (placebo, 1 patient); positive serum β-HCG (desvenlafaxine 50 mg, 1 patient); hepatic enzymes (desvenlafaxine 100 mg, 3 patients); positive hepatitis B core antibody (desvenlafaxine 100 mg, 1 patient); and alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase (desvenlafaxine 100 mg, 1 patient).

DISCUSSION

The primary objective of this phase 4 clinical trial was to assess the antidepressant efficacy of desvenlafaxine at the approved 50- and 100-mg/d doses. As in previous studies, statistically significant improvement was observed for both desvenlafaxine doses compared with placebo based on the primary end point $HDRS_{17}$ total score. The study was not designed to evaluate differences between desvenlafaxine doses; desvenlafaxine doses greater than 50 mg/d have not previously demonstrated greater efficacy, with tolerability declining with increasing dose.[9,15] Rates of discontinuations due to AEs in this study were low (≤ 5%), but also increased numerically from the 50- to the 100-mg dose. Results of this study are thus supportive of results from previously published studies[9,15]; no new efficacy findings were observed.

In adult outpatients with MDD with baseline sexual activity and at least 1 postbaseline assessment, effects on ASEX total and item scores were comparable for the 50- and 100-mg desvenlafaxine dose groups and placebo. However, because the ASEX total score was analyzed only for patients reporting baseline and week 8 sexual activity (46% of the safety population), treatment group sizes for the analysis were low. A post hoc analysis of sexual dysfunction rates, the analysis with which the ASEX scale was validated,[18] included all patients who completed the ASEX at baseline and at least 1 postbaseline time point (99% of the safety population). The results of the post hoc analysis supported the preplanned total score analysis: rates of sexual dysfunction were comparable between each desvenlafaxine dose and placebo at baseline (placebo, 52%; desvenlafaxine 50 mg/d, 56%; desvenlafaxine 100 mg/d, 54%) and at week 8 (placebo, 45%; desvenlafaxine 50 mg/d, 49%; desvenlafaxine 100 mg/d, 47%). It is important to note that this study was not powered to formally test the noninferiority of desvenlafaxine compared with placebo with regard to sexual dysfunction as measured with the ASEX. Further, although no statistically significant differences between placebo and desvenlafaxine groups were observed in either the preplanned or the post hoc analysis, a potentially clinically relevant effect of desvenlafaxine treatment on sexual function might be observed in individual patients.

The generalizability of the results reported here is limited by exclusions used in recruiting patients for the study: the study population was generally healthy, with few significant medical or psychological comorbidities. The higher proportion of female patients in this study (56%) compared with the general population is in line with the higher prevalence of MDD in women compared with men.[27] The proportion of black patients (26%) was higher than in previous short-term desvenlafaxine studies (< 1%–19%),[3,5–8,10,28,29] but the proportion across desvenlafaxine studies approximates that in the US population (13%).[30]

The ASEX total score analysis was limited by exclusion of patients who were not sexually active both at baseline and at 1 or more postbaseline time points. More than 50% of the safety population was excluded from the analysis based on those criteria, and the results therefore cannot be generalized to the large percentage of MDD patients who are not sexually active.[31] However, the post hoc analysis of sexual dysfunction rates was valid for all patients who completed the ASEX regardless of sexual activity. Finally, only short-term (8-week) effects on sexual function were assessed in the current study; this study does not address possible long-term effects of desvenlafaxine on sexual function.

CONCLUSIONS

Current recommended dose of desvenlafaxine 50 mg/d and the 100-mg/d dose demonstrated antidepressant efficacy compared with placebo in this phase 4 study. Sexual functioning was comparable for patients in the desvenlafaxine 50- or 100-mg/d groups and those in the placebo group based on the ASEX total score or rates of sexual dysfunction. The safety results of this study indicate that desvenlafaxine at both 50 and 100 mg/d was generally safe and well tolerated; there were no new safety signals identified.

Drug names: alprazolam (Xanax, Niravam, and others), desvenlafaxine (Pristiq), venlafaxine (Effexor and others).

Author affiliations: Psychiatric Medicine, Division of Outpatient Psychiatry, University of Virginia Health System, Charlottesville, Virginia (Dr Clayton); Pfizer, Collegeville, Pennsylvania (Drs Tourian, Hwang, and Cheng and Ms Focht); Mood and Anxiety Disorders Treatment and Research Program, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia (Dr Thase); Drs Tourian is now with inVentiv Health Clinical, Princeton, New Jersey, and Dr Cheng is now with Bayer, Whippany, New Jersey.

Study investigators who randomized patients: M. Y. Alam, R. H. Anderson, F. J. Arguello, A.-L. W. Arias, R. A. Baber, C. E. Bailey, M. A. Bari, B. Bastani, P. K. Bhatia, B. S. Bortnick, R. Brenner, E. M. Coskinas, B. C. Diner, M. J. Downing, B. B. D'Souza, N. P. Emmanuel, B. G. Essink, C. M. Figueroa, D. J. Garcia, L. D. Ginsberg, I. D. Glick, A. K. Goenjian, S. K. Goldstein, M. S. Greenbaum, P. K. Gross, D. M. Gruener, S. S. Hatti, W. Holloway, K. M. Jacobs, S. L. Johnson-Quijada, A. M. Jonas, J. M. Joyce, M. S. Kane, A. M. Klymiuk, J. A. Knutson, D. G. Krefetz, S. Malhotra, C. H. Merideth, J. L. Miller, P. R. Miller, J. J. Murphy, P. W. Murphy, W. R. Murphy, M. C. Nunez, S. Rajadhyaksha, R. K. Ricardi, R. A. Riesenberg, N. A. Shapira, T. M. Shiovitz, R. K. Shrivastava, W. T. Smith, J. C. Steiert, R. Sullivan, N. G. Vatakis, L. J. Wallhausser, and J. J. Whalen.

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