Research Article

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, FIXED-DOSE PHASE III STUDY OF VILAZODONE IN PATIENTS WITH GENERALIZED ANXIETY DISORDER

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Background: *Vilazodone, a selective serotonin reuptake inhibitor and 5-HT$_{1A}$ receptor partial agonist, is approved for treating major depressive disorder in adults. This study (NCT01629966 ClinicalTrials.gov) evaluated the efficacy and safety of vilazodone in adults with generalized anxiety disorder (GAD).* **Methods:** *A multicenter, double-blind, parallel-group, placebo-controlled, fixed-dose study in patients with GAD randomized (1:1:1) to placebo (n = 223), or vilazodone 20 mg/day (n = 230) or 40 mg/day (n = 227). Primary and secondary efficacy parameters were total score change from baseline to week 8 on the Hamilton Rating Scale for Anxiety (HAMA) and Sheehan Disability Scale (SDS), respectively, analyzed using a predefined mixed-effect model for repeated measures (MMRM). Safety outcomes were presented by descriptive statistics.* **Results:** *The least squares mean difference (95% confidence interval) in HAMA total score change from baseline (MMRM) was statistically significant for vilazodone 40 mg/day versus placebo (–1.80 [–3.26, –0.34]; P = .0312 [adjusted for multiple comparisons]), but not for vilazodone 20 mg/day versus placebo. Mean change from baseline in SDS total score was not significantly different for either dose of vilazodone versus placebo when adjusted for multiplicity; significant improvement versus placebo was noted for vilazodone 40 mg/day without adjustment for multiplicity (P = .0349). The incidence of adverse events was similar for vilazodone 20 and 40 mg/day (~71%) and slightly lower for placebo (62%). Nausea, diarrhea, dizziness, vomiting, and fatigue were reported in ≥5% of patients in either vilazodone group and at least twice the rate of placebo.* **Conclusions:** *Vilazodone was effective in treating anxiety symptoms of GAD. No new safety concerns were identified. Depression and Anxiety 32:451–459, 2015.* *© 2015 The Authors. Depression and Anxiety published by Wiley Periodicals, Inc.*

Key words: *generalized anxiety disorder; antidepressant; anxiety/anxiety disorders; pharmacotherapy; clinical trials*

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INTRODUCTION

Generalized anxiety disorder (GAD), a disorder characterized by pervasive and highly distressing worries, is associated with impairment that is comparable to major depressive disorder (MDD).[1] Although numerous agents from various drug classes are available to treat GAD, as many as 50% of patients have inadequate response,[2] constituting a considerable unmet medical need.

Vilazodone is a selective serotonin reuptake inhibitor (SSRI) and 5-HT_{1A} receptor partial agonist approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDD in adults. The efficacy of vilazodone 40 mg in MDD was established in two short-term, double-blind, placebo-controlled Phase III trials (NCT00285376 and NCT00683592).[3,4] Two recent positive Phase IV randomized, placebo-controlled clinical trials (NCT01473394[5] and NCT01473381[6]) confirmed and supported the evidence base for vilazodone 40 mg; in one of the trials,[6] evidence for efficacy of a 20-mg dose in MDD was also supported. Safety and tolerability findings were supported in a 1-year, open-label trial of vilazodone 40 mg/day (NCT00644358).[7] Vilazodone was generally well tolerated in all trials; common adverse events (AEs), including diarrhea, nausea, and insomnia, were generally transient in nature and considered mild in severity.[8]

The potential for vilazodone to have efficacy in treating GAD is suggested by its pharmacodynamic profile. Agents approved for treating anxiety disorders support the hypothesis that SSRI and 5 HT_{1A} receptor partial agonist activities may produce positive outcomes in GAD. SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) are considered first-line GAD treatments[9] and buspirone, a 5-HT_{1A} receptor partial agonist, has demonstrated clinical trial efficacy in conditions that roughly correspond to GAD and is approved for the treatment of anxiety disorders.[10] In addition, a pooled post hoc analysis of patients with anxious depression from two vilazodone MDD studies demonstrated statistically significant improvements in favor of vilazodone versus placebo on most anxiety measures, suggesting efficacy potential in treating anxiety symptoms associated with MDD.[11] The objective of the current study (NCT01629966) was to characterize the efficacy, safety, and tolerability of vilazodone for the treatment of anxiety in patients with GAD.

METHODS

The study was conducted at 37 study centers in the United States between June 2012 and March 2014 in full compliance with FDA guidelines for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. The protocol was approved by each site's institutional review board and all patients provided written informed consent.

STUDY DESIGN

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study of vilazodone in adult patients with GAD. The 10-week study duration consisted of a 1-week screening period, 8-week double-blind treatment, and 1-week double-blind down-taper if it was considered medically appropriate by the investigator. Following screening, eligible patients were randomized (1:1:1) to placebo, vilazodone 20 mg/day, or vilazodone 40 mg/day, to be taken once daily with food. Vilazodone was initiated at 10 mg/day for week 1; dosage was increased to 20 mg/day at week 2 and maintained for the remainder of double-blind treatment for patients in the 20-mg/day group; patients in the 40-mg/day group received 20 mg/day at week 2 for 7 days and then increased to 40 mg/day for the remainder of treatment.

Patients were randomized by computer-generated numbers and assigned to identically appearing treatment. Investigators and patients were blinded to the allocation of study drug throughout treatment and down-taper. The blind was maintained via a secured randomization code list and was broken only in case of emergency; removing the blind for any reason disqualified a patient from further participation.

PATIENTS

Male or female outpatients (18–70 years of age, inclusive) who met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[12] criteria for GAD were included. Participants were required to have a Hamilton Rating Scale for Anxiety (HAMA)[13] total score ≥20, HAMA items 1 (Anxious Mood) and 2 (Tension) scores ≥2, Clinical Global Impressions-Severity (CGI-S)[14] score ≥4, and 17-item Hamilton Depression Rating Scale ($HAMD_{17}$)[15] total score ≤17. Patients had normal physical examination, clinical laboratory, and electrocardiogram (ECG) findings, or abnormal results that were judged to be not clinically significant; females of childbearing potential had a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test.

Patients were excluded for a DSM-IV-TR–based Axis I diagnosis other than GAD within 6 months of screening; secondary diagnoses of comorbid social anxiety disorder, and/or specific phobias were allowed. Additional exclusion criteria included a lifetime diagnostic history of various psychiatric disorders (e.g., bipolar disorder, depressive episode with psychotic/catatonic features, psychotic disorder, substance abuse, cognitive disorders); suicide risk (including suicide attempt within 1 year); nonresponse to ≥2 adequate treatment trials of antidepressants (≥8 weeks of treatment at an adequate dose based on approved package insert recommendations) for the treatment of GAD; and intolerance/hypersensitivity to vilazodone, SNRIs, or SSRIs. Psychoactive drugs and required concomitant treatment with prohibited medications were barred; eszopiclone, zopiclone, zaleplon, or zolpidem could be continued for insomnia. Patients with medical conditions that could interfere with study conduct, confound the interpretation of results, or endanger patient well-being were excluded.

EFFICACY AND SAFETY ASSESSMENTS

Efficacy was assessed by the HAMA (weeks –1 [screening], 0 [baseline], 1, 2, 4, 6, 8), Sheehan Disability Scale (SDS)[16] (weeks 0, 2, 4, 6, 8), $HAMD_{17}$ (weeks –1, 0, 8), CGI-S (all weeks), and CGI-Improvement (CGI-I)[14] (weeks 1, 2, 4, 6, 8). Safety was assessed by AE reports (patients were asked a nonleading question to elicit reporting of any AEs that had occurred since the previous visit), physical examination, clinical laboratory and vital sign measures, ECGs, the Columbia-Suicide Severity Rating Scale (C-SSRS)[17] (all weeks and down-taper), and Changes in Sexual Functioning Questionnaire (CSFQ)[18] (weeks 0, 4, 8).

STATISTICAL ANALYSES

Safety analyses were based on the safety population, which consisted of all randomized patients who received ≥1 dose of double-blind study drug; efficacy analyses were based on the intent-to-treat (ITT) population, which consisted of patients in the safety population with a baseline and ≥1 postbaseline HAMA assessment. All statistical tests were two-sided hypothesis tests performed at the 5% significance level; all confidence intervals (CIs) were two-sided 95% CIs.

The primary efficacy parameter, change from baseline to week 8 in HAMA total score, was analyzed using the predefined mixed-effect model for repeated measures (MMRM) with treatment group, study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline-value-by-visit interaction as covariates. An unstructured covariance matrix was used for modeling the covariance of within-patient scores; the Kenward-Roger approximation was used to estimate denominator degrees of freedom using the observed cases (OC) approach without imputation of missing values. Two prespecified sensitivity analyses were performed on the primary efficacy parameter: a pattern-mixture model (PMM) approach based on nonfuture-dependent missing value restrictions[19] and a last observation carried forward (LOCF) approach. Both approaches were based on an analysis of covariance (ANCOVA) model using treatment group and study center as factors and baseline HAMA total score as a covariate.

The secondary efficacy parameter, change from baseline to week 8 in SDS total score, was analyzed using an MMRM approach; a prespecified LOCF sensitivity analysis was also conducted. SDS total score was based on a modified ITT population and was calculated as the sum of the individual domain items (Work/School, Social Life, Family Life) for patients with evaluable assessments on all three items.

To control the overall Type I error rate for multiple comparisons between the two vilazodone dose groups versus the placebo group, *P*-values for the primary and secondary efficacy analyses were adjusted using a matched parallel gatekeeping procedure[20]; significance of the secondary endpoint for each dose was not claimed unless the corresponding primary outcome was significant.

Additional efficacy parameters included response rates on the HAMA (≥50% improvement from baseline) and CGI-I (score ≤2), CGI-I score at week 8, and change from baseline on the CGI-S, SDS individual items, $HAMD_{17}$, HAMA items 1 and 2, and HAMA-derived subscales.[13] The Psychic Anxiety Subscale consisted of items 1, 2, 3 (Fears), 4 (Insomnia), 5 (Intellectual), 6 (Depressed Mood), and 14 (Anxious Behavior at Interview). The Somatic Anxiety Subscale consisted of items 7 (Somatic [Muscular]), 8 (Somatic [Sensory]), 9 (Cardiovascular Symptoms), 10 (Respiratory Symptoms), 11 (Gastrointestinal Symptoms), 12 (Genitourinary Symptoms), and 13 (Autonomic Symptoms). Rates of response were analyzed using a generalized linear mixed model (GLMM) with random intercept and fixed terms of treatment group, visit, treatment-by-visit interaction, and baseline score; other additional efficacy parameters were analyzed using an MMRM approach without adjustment for multiplicity. Baseline CGI-S score was used as an explanatory variable for analysis of the CGI-I score.

Safety analyses included the number and percentage of patients with AEs; descriptive statistics were presented for change from baseline in laboratory values and vital signs. The severity of suicidal ideation and behavior was monitored by the C-SSRS. Patient-rated change in sexual function was evaluated by the CSFQ.

RESULTS

PATIENT DISPOSITION AND DEMOGRAPHIC CHARACTERISTICS

Six hundred eighty patients were randomized to double-blind treatment; 667 and 673 patients were included in the ITT and safety populations, respectively (Table 1). There were higher rates of discontinuation in the vilazodone 40-mg/day group (29%) than in the placebo (19%) and 20-mg/day (23%) groups. AEs were the most frequent reason for discontinuation in all groups; the rate of discontinuation due to AEs was higher for vilazodone 40 mg/day than placebo ($P < .05$ [Fisher exact test]). Demographics and other patient characteristics were similar among groups (Table 2); mean age was 40.2 years, 65% of patients were women, and 76% were White. Most patients reported a long duration of illness with GAD; approximately 17% of patients had received previous GAD treatment and almost half reported nonresponse (Table 2).

TABLE 1. Patient disposition and reasons for discontinuation

Patient populations	Placebo	Vilazodone 20 mg/day	Vilazodone 40 mg/day
Randomized population, *n*	223	230	227
Intent-to-treat population, *n*	221	223	223
Safety population, *n*	221	227	225
Patient disposition, *n* (%) (safety population)			
Completed study	180 (81.4)	175 (77.1)	159 (70.7)
Reason for premature discontinuation			
Adverse event	11 (5.0)	18 (7.9)	30 (13.3)*
Insufficient therapeutic response	5 (2.3)	2 (0.9)	4 (1.8)
Protocol violation	7 (3.2)	9 (4.0)	7 (3.1)
Withdrawal of consent	8 (3.6)	9 (4.0)	16 (7.1)
Lost to follow-up	10 (4.5)	13 (5.7)	9 (4.0)
Other	0	1 (0.4)	0
Entered double-blind down-taper	182 (82.4)	177 (78.0)	163 (72.4)

*$P = .0028$ for 40 mg/d versus placebo.

Mean baseline scores were similar among groups on most efficacy measures. HAMA Anxious Mood baseline score distribution was significantly different for vilazodone 20 mg/day versus placebo ($P = .0339$); mean baseline SDS Work/School score was significantly higher for vilazodone 20 mg/day versus placebo ($P = .0482$), suggesting greater baseline functional impairment in this domain for this vilazodone group. CGI-S baseline scores showed that the majority of patients in the placebo and vilazodone 20- and 40-mg/day groups, respectively, were moderately ill (75%, 69%, 74%) and had severe symptoms on the HAMA Anxious Mood (70%, 72%, 67%) and Tension (63%, 69%, 63%) items. Mean $HAMD_{17}$ baseline scores were approximately 13 in each group, indicating a non- or mildly depressed patient population.[21]

ANALYSIS OF EFFICACY

The least squares mean difference (LSMD) in change from baseline to week 8 in HAMA total score was statistically significant for vilazodone 40 mg/day versus placebo

TABLE 2. Demographic characteristics and GAD history (safety population)

Characteristics		Placebo, $n = 221$	Vilazodone 20 mg/day, $n = 227$	Vilazodone 40 mg/day, $n = 225$
Age, mean (SD), years		40.0 (13.7)	40.6 (13.7)	39.9 (13.3)
Women, *n* (%)		143 (64.7)	149 (65.6)	142 (63.1)
Race, *n* (%)				
White		174 (78.7)	167 (73.6)	167 (74.2)
Black or African American		35 (15.8)	50 (22.0)	46 (20.4)
Asian		4 (1.8)	3 (1.3)	5 (2.2)
Other		8 (3.6)	7 (3.0)	7 (3.1)
Body weight, mean (SD), kg		80.2 (16.8)	81.0 (17.3)	80.8 (19.0)
BMI, mean (SD), kg/m^2		28.3 (5.3)	28.3 (5.4)	28.0 (5.5)
GAD history				
Duration of GAD, mean (SD), years		13.90 (13.25)	13.94 (13.29)	12.84 (12.03)
Age at GAD onset, mean (SD), years		26.1 (14.4)	26.7 (14.2)	27.1 (14.5)
Previous treatment for	Yes	38 (17.2)	39 (17.2)	40 (17.8)
GAD	No	183 (82.8)	188 (82.8)	185 (82.2)
Nonresponders to previous treatment[a]		20 (53)	17 (44)	18 (45)

[a]Percentage based on number of patients with previous treatment.
BMI, body mass index; GAD, generalized anxiety disorder.

using the predefined MMRM primary analysis (adjusted for multiple comparisons: $P = .0312$) (Table 3); the difference in HAMA total score for vilazodone 20 mg/day versus placebo was not statistically significant. The statistically significant difference in HAMA total score for vilazodone 40 mg/day versus placebo was seen as early as week 2 and it persisted for the remainder of the study (Fig. 1). PMM sensitivity analysis supported the primary results for vilazodone 40 mg/day versus placebo (results not shown); the LOCF analysis did not show a statistically significant difference for either vilazodone dose versus placebo.

Using the predefined MMRM analysis, the LSMD in change from baseline to week 8 in SDS total score was not statistically significant for either vilazodone group versus placebo when adjusted for multiple comparisons (Table 3); a significant difference versus placebo was noted for vilazodone 40 mg/day without adjustment for multiplicity ($P = .0349$). In the sensitivity analysis, the differences between vilazodone 20 or 40 mg/day

TABLE 3. Primary and secondary efficacy outcomes (ITT population)

Efficacy measure		Placebo, $n = 221$	Vilazodone 20 mg/day, $n = 223$	Vilazodone 40 mg/day, $n = 223$
HAMA total score (primary efficacy)				
	Baseline, mean (SD)	24.4 (3.5)	24.7 (3.8)	24.4 (3.5)
MMRM	Change from baseline to week 8, LS mean (SE)	–11.68 (0.52)	–12.95 (0.53)	–13.48 (0.55)
	LSMD (95% CI)	—	–1.27 (–2.71, 0.17)	–1.80 (–3.26, –0.34)
	P-value	—	.0830	.0156
	Adjusted *P*-value[a]	—	.0830	.0312
LOCF	Change from baseline to week 8, LS mean (SE)	–10.83 (0.52)	–11.70 (0.51)	–11.91 (0.52)
	LSMD (95% CI)		–0.87 (–2.24, 0.50)	–1.08 (–2.45, 0.29)
	P-value[b]		.2136	.1213
SDS total score (secondary efficacy)[c]				
	Baseline, mean (SD)	15.8 (6.1)	16.7 (5.9)	15.7 (5.9)
MMRM	Change from baseline to week 8, LS mean (SE)	–7.41 (0.51)	–8.77 (0.51)	–8.93 (0.53)
	LSMD (95% CI)	—	–1.37 (–2.75, 0.02)	–1.52 (–2.94, –0.11)
	P-value	—	.0536	.0349
	Adjusted *P*-value[a]	—	.0830	.0697
LOCF	Change from baseline to week 8, LS mean (SE)	–7.10 (0.51)	–8.21 (0.50)	–7.93 (0.50)
	LSMD (95% CI)	—	–1.11 (–2.44, 0.21)	–0.83 (–2.16, 0.50)
	P-value[b]	—	.0999	.2200

[a]Adjusted *P*-values were obtained from the matched parallel gatekeeping procedure.
[b]Based on an ANCOVA model.
[c]SDS total score based on a modified ITT population and calculated as the sum of the three subscales.
CI, confidence interval; HAMA, Hamilton Rating Scale for Anxiety; LOCF, last observation carried forward; LS, least squares; LSMD; least squares mean difference; MMRM, mixed-effects model for repeated measures; SE, standard error; SDS, Sheehan Disability Scale.

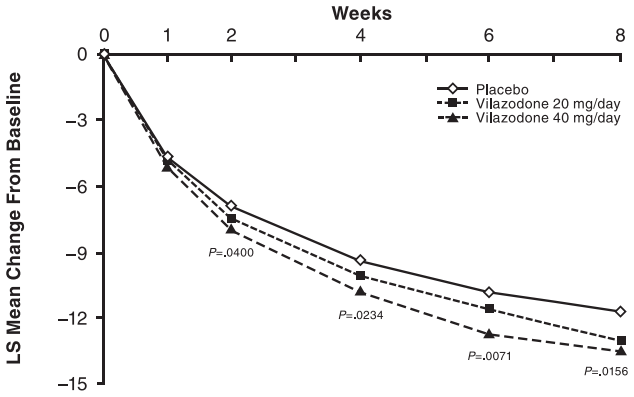

Figure 1. HAMA total score mean change from baseline (MMRM, ITT population). The least squares mean change from baseline in HAMA total score was significantly greater for vilazodone 40 mg/day versus placebo beginning at week 2; the significant difference persisted throughout double-blind treatment. *P*-values shown are for vilazodone 40 mg/day versus placebo and were not adjusted for multiplicity. Vilazodone 20 mg/day was not statistically different versus placebo at any visit.

and placebo were not statistically significant using the ANCOVA with LOCF approach.

Additional efficacy parameters are presented in Table 4. Improvement from baseline was statistically significant in favor of vilazodone 40 mg/day versus placebo on the HAMA Psychic and Somatic Anxiety Subscales, SDS Social Life and Family Life items, and CGI-S. HAMA response rates were also significantly greater in the vilazodone 40-mg/day group versus placebo; the difference in HAMA response rate for the 20-mg/day group and placebo was not statistically significant. The difference in CGI-I score at week 8, change in the HAMA Tension item, and CGI-I response rates were statistically significant for both vilazodone 20 and 40 mg/day versus placebo.

SAFETY AND TOLERABILITY

Extent of Exposure. For the placebo and vilazodone 20- and 40-mg/day groups, mean duration of treatment was 51, 48, and 45 days, respectively; patient years of exposure (total treatment duration in days divided by 365.25) were 30.6, 30.0, and 28.0, respectively.

Adverse Events. An overall summary of AEs is presented in Table 5. The incidence of treatment-emergent AEs (TEAEs) was similar in the vilazodone 20- and 40-mg/day groups (~71%) and slightly lower in the placebo group (62%). TEAEs reported at ≥5% in either vilazodone group and at least twice the rate of placebo were nausea, diarrhea, dizziness, vomiting, and fatigue. Discontinuation due to AEs was more frequent with vilazodone 40 mg/d than placebo ($P < .05$); nausea and headache were the most frequent AEs leading to discontinuation. Approximately, 97% of TEAEs in each group were considered by the investigator to be mild or moderate in severity; TEAEs were considered related to treatment in 54%, 69%, and 71% of placebo and vilazodone 20- and 40-mg/day patients, respectively.

Serious AEs (SAEs) were reported by two patients (hematoma [one placebo patient]; suicidal ideation [one vilazodone 20-mg/day patient]); neither event was considered related to treatment and both patients discontinued. The incidence of newly emergent AEs during down-taper was similar in all treatment groups.

Clinical Laboratory, Vital Sign, ECG Evaluation. Mean changes from baseline to the end of double-blind treatment were generally small and similar among groups for most laboratory parameters and vital signs. Changes in liver enzyme/function parameters were small and similar across groups and no patient met Hy's law criteria (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] elevation ≥3 × upper limit of normal [ULN], total bilirubin elevation >2 × ULN, and alkaline phosphatase <2 × ULN).

Potentially clinically significant (PCS) laboratory and vital sign values were generally low and similar for placebo and vilazodone. The most frequently reported PCS changes in metabolic parameters were for total cholesterol (>1.1 × ULN) and triglycerides (>1.2 × ULN), which occurred with similar frequency in the placebo and vilazodone 20- and 40-mg groups (total cholesterol: 11%, 13%, 16%; triglycerides: 16%, 11%, 12%, respectively). PCS change in high serum glucose (>1.2 × ULN) was more frequent with vilazodone 40 mg/day (6%) than placebo (2%) and vilazodone 20 mg/day (2%); PCS changes in creatine kinase (>1.5 × ULN) were similar across treatment groups (6–8%).

Orthostatic hypotension (≥20 mmHg reduction in systolic BP or ≥10 mmHg reduction in diastolic BP while changing from a supine to standing position) was reported in 14 (6%) placebo, 24 (11%) vilazodone 20-mg/day, and 11 (5%) vilazodone 40-mg/day patients; no related AE pattern was noted. Mean changes in body weight were low for placebo (0.12 kg), and vilazodone 20-mg/day (0.36 kg) and 40-mg/day (0.39 kg) patients; PCS weight increase (>7%) was low in each group (1%, 2%, 1%, respectively). No patient had a QTc Bazett (QTcB) or QTc Fridericia (QTcF) interval increase >500 ms.

Suicidality and Suicide-Related AEs. During the study, C-SSRS–based suicidal ideation was more common in placebo patients (22 [10%]) than in vilazodone 20-mg/day (15 [7%]) or 40-mg/day (15 [7%]) patients, and no suicidal behavior was reported. TEAEs of suicidal ideation were reported in one vilazodone 20-mg/day patient (severe; resulted in discontinuation from the study) and one vilazodone 40-mg/day patient (nonserious; resolved on treatment). Neither event was considered related to treatment.

Sexual Functioning. At the end of double-blind treatment, systematic assessment of sexual functioning using the CSFQ showed small and similar mean score changes in the placebo (1.6), and vilazodone 20-mg/day (1.3) and 40-mg/day (1.5) groups; in these treatment

TABLE 4. Additional efficacy outcomes (ITT population)

Additional efficacy outcomes (MMRM)		Placebo, $n = 221$	Vilazodone 20 mg/day, $n = 223$	Vilazodone 40 mg/day, $n = 223$
HAMA Psychic Anxiety Subscale	Baseline, mean (SD)	14.2 (2.1)	14.3 (2.3)	14.2 (2.2)
	Change from baseline to week 8, LS mean (SE)	–6.62 (0.31)	–7.37 (0.31)	–7.65 (0.32)
	LSMD (95% CI)	—	–0.75 (–1.59, 0.10)	–1.03 (–1.89, –0.17)
	P-value	—	.0825	.0184
HAMA Somatic Anxiety Subscale	Baseline, mean (SD)	10.2 (2.8)	10.4 (2.9)	10.2 (3.0)
	Change from baseline to week 8, LS mean (SE)	–5.07 (0.26)	–5.61 (0.26)	–5.86 (0.27)
	LSMD (95% CI)	—	–0.54 (–1.24, 0.17)	–0.79 (–1.51, –0.08)
	P-value	—	.1349	.0301
HAMA Anxious Mood item	Baseline, mean (SD)	2.8 (0.49)	2.9 (0.51)*	2.8 (0.53)
	Change from baseline to week 8, LS mean (SE)	–1.26 (0.07)	–1.41 (0.07)	–1.44 (0.07)
	LSMD (95% CI)	—	–0.15 (–0.33, 0.04)	–0.18 (–0.37, 0.01)
	P-value	—	.1320	.0706
HAMA Tension item	Baseline, mean (SD)	2.7 (0.53)	2.8 (0.52)	2.7 (0.55)
	Change from baseline to week 8, LS mean (SE)	–1.25 (0.07)	–1.49 (0.07)	–1.50 (0.07)
	LSMD (95% CI)	—	–0.24 (–0.43, –0.05)	–0.25 (–0.45, –0.06)
	P-value	—	.0146	.0111
SDS Work/School item[a]	Baseline, mean (SD)	4.9 (2.5)	5.4 (2.4)*	5.0 (2.3)
	Change from baseline to week 8, LS mean (SE)	–2.41 (0.19)	–2.83 (0.19)	–2.76 (0.20)
	LSMD (95% CI)	—	–0.42 (–0.94, 0.10)	–0.34 (–0.87, 0.19)
	P-value	—	.1116	.2035
SDS Social Life item[a]	Baseline, mean (SD)	5.5 (2.5)	5.8 (2.3)	5.7 (2.3)
	Change from baseline to week 8, LS mean (SE)	–2.69 (0.18)	–2.96 (0.18)	–3.34 (0.18)
	LSMD (95% CI)	—	–0.28 (–0.75, 0.20)	–0.65 (–1.13, –0.17)
	P-value	—	.2533	.0086
SDS Family Life item[a]	Baseline, mean (SD)	5.2 (2.4)	5.4 (2.4)	5.2 (2.4)
	Change from baseline to week 8, LS mean (SE)	–2.36 (0.17)	–2.78 (0.17)	–2.98 (0.18)
	LSMD (95% CI)	—	–0.41 (–0.88, 0.05)	–0.62 (–1.10, –0.15)
	P-value	—	.0810	.0103
CGI-S	Baseline, mean (SD)	4.3 (0.5)	4.4 (0.6)	4.3 (0.5)
	Change from baseline to week 8, LS mean (SE)	–1.40 (0.08)	–1.61 (0.08)	–1.69 (0.09)
	LSMD (95% CI)	—	–0.21 (–0.43, 0.02)	–0.29 (–0.52, –0.06)
	P-value	—	.0749	.0148
CGI-I	Score at week 8, mean (SE)	2.4 (0.08)	2.2 (0.08)	2.1 (0.08)
	P-value	—	.0157	.0050
$HAMD_{17}$ total score	Baseline, mean (SD)	13.0 (2.5)	12.8 (2.5)	12.9 (2.5)
	Change from baseline to week 8, LS mean (SE)	–4.67 (0.37)	–4.84 (0.38)	–5.56 (0.39)
	LSMD (95% CI)	—	–0.17 (–1.15, 0.81)	–0.88 (–1.89, 0.13)
	P-value	—	.7359	.0863
Response (GLMM)				
HAMA responders at week 8 (%; ≥50% improvement from baseline)		48.1	53.9	62.1
	OR (95% CI)	—	1.458 (0.780, 2.728)	2.141 (1.115, 4.109)
	P-value	—	.2375	.0222
CGI-I responders at week 8 (%; CGI-I ≤2)		54.1	64.0	65.2
	OR (95% CI)	—	1.944 (1.019, 3.709)	1.964 (1.011, 3.815)
	P-value	—	.0436	.0463

Statistical significance for additional efficacy parameters was nominal without adjustment for multiplicity. *$P < .05$ versus placebo.
[a]Based on the number of patients with an SDS analysis value at baseline and week 8 (Work/School: placebo = 145, vilazodone 20 mg = 141, vilazodone 40 mg = 129; Social Life and Family Life: placebo = 185, vilazodone 20 mg = 178, vilazodone 40 mg = 161).
CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; CI, confidence interval; HAMA, Hamilton Rating Scale for Anxiety; $HAMD_{17}$, Hamilton Depression Rating Scale; GLMM, generalized linear mixed model; LS, least squares; LSMD; least squares mean difference; MMRM, mixed-effects model for repeated measures; SE, standard error; SDS, Sheehan Disability Scale.

groups, respectively, small mean score increases, indicating improvement on the scale, were seen in male (3.0, 0.6, 1.5) and female (0.9, 1.6, 1.4) patients. AEs related to sexual function were more common in vilazodone- than placebo-treated patients, except for ejaculation delayed, which occurred in one male patient in each treatment group; the most frequently reported sexual function related TEAE was libido decreased (placebo = 2 [0.9%]; vilazodone 20 mg/day = 3 [1.3%]; vilazodone 40 mg/day = 5 [2.2%]). Most sexual function AEs were considered mild or moderate; three male patients discontinued due to sexual AEs (one [0.5%] placebo [libido decreased], one

TABLE 5. Adverse events (safety population)

Adverse events summary, *n* (%)	Placebo, *n* = 221	Vilazodone	
		20 mg/day, *n* = 227	40 mg/day, *n* = 225
Deaths	0	0	0
Patients with ≥1 TEAE	138 (62.4)	163 (71.8)	160 (71.1)
Patients who discontinued due to AE	11 (5.0)	18 (7.9)	30 (13.3)
Patients with SAE	1 (0.5)	1 (0.4)	0
Patients with newly emergent AE[a]	7 (3.2)	9 (4.0)	9 (4.0)
Common adverse events during double-blind treatment (≥5% in any treatment group)			
Nausea	25 (11.3)	55 (24.2)	58 (25.8)
Diarrhea	23 (10.4)	57 (25.1)	48 (21.3)
Headache	18 (8.1)	32 (14.1)	25 (11.1)
Dizziness	8 (3.6)	12 (5.3)	21 (9.3)
Vomiting	5 (2.3)	13 (5.7)	17 (7.6)
Fatigue	6 (2.7)	7 (3.1)	13 (5.8)
Insomnia	11 (5.0)	12 (5.3)	13 (5.8)
Upper respiratory tract infection	16 (7.2)	11 (4.8)	12 (5.3)
Dry mouth	12 (5.4)	10 (4.4)	10 (4.4)
Adverse events leading to discontinuation of ≥2 patients in any group			
Nausea	2 (0.9)	4 (1.8)	9 (4.0)
Headache	1 (0.5)	3 (1.3)	7 (3.1)
Anxiety	1 (0.5)	1 (0.4)	3 (1.3)
Diarrhea	1 (0.5)	3 (1.3)	3 (1.3)
Dizziness	1 (0.5)	2 (0.9)	3 (1.3)
Vomiting	0	4 (1.8)	1 (0.4)
Hyperhidrosis	0	2 (0.9)	0

Coded by preferred term using MedDRA Version 15.1.
[a]Newly emergent AEs occurred during the double-blind down-taper period or within 30 days after the last dose of double-blind study drug.
AE, adverse event; TEAE, treatment-emergent adverse event; SAE serious adverse event.

[0.4%] vilazodone 20 mg/day [sexual dysfunction], one [0.4%] vilazodone 40 mg/day [anorgasmia]).

DISCUSSION

This 8-week clinical trial met its primary efficacy endpoint and demonstrated statistically significant improvement in HAMA total score for patients treated with vilazodone 40 mg/day compared with placebo; the difference for the 20-mg/day group versus placebo was not statistically significant. Changes consistent with improvement in anxiety symptoms were observed on most efficacy measures for vilazodone 40-mg/day patients; greater overall improvement in illness versus placebo was suggested by statistically significant differences from placebo on the CGI-I score (vilazodone 20 and 40 mg/day) and CGI-S change (vilazodone 40 mg/day). The proportion of HAMA and CGI-I responders in the vilazodone 40-mg/day group was comparable to other antidepressants in the treatment of GAD.[22]

Since improvement in functional impairment generally lags behind symptomatic improvement in psychiatric disorders such as depression,[23] an 8-week study in GAD may not have been adequate to capture SDS changes. Only patients with assessments on all three individual domains are included in the calculation for SDS total score and in this trial, the differences versus placebo were not statistically significant in either vilazodone group. Statistically significant differences for the vilazodone 40-mg/day group versus placebo were observed on the Social Life ($P = .0086$) and Family Life ($P = .0103$) items, indicating improvements in these areas of functional impairment. It may have been more difficult to demonstrate improvement on the Work/School item since patients were less likely to experience these activities than social or family activities. Fewer 8-week assessments were available for placebo and vilazodone 20- and 40-mg/day patients, respectively, on the Work/School item (145, 141, 129) than the Family Life and Social Life items (185, 178, 161 both), suggesting that a smaller sample size may have contributed to difficulty in detecting an efficacy signal.

Vilazodone acts as an SSRI, similar to some antidepressants that are approved for GAD treatment,[24,25] and also possesses partial agonist activity at the 5-HT_{1A} receptor similar to buspirone, an approved anxiolytic with demonstrated efficacy in short-term clinical trials in GAD.[26] Buspirone is not recommended as first-line treatment because of its slow onset of action, variable tolerability, and limited benefit in comorbid conditions.[27–29] Acute and chronic administration of vilazodone has produced anxiolytic-like activity in several animal models, with results suggesting that both serotonin reuptake inhibition and partial

5-HT_{1A} receptor agonist activity contributed to the effects (Vilazodone HCl Investigator's Brochure, 2013). Although vilazodone 40 mg/day was significantly different than placebo on the primary efficacy parameter in this trial, additional investigation is necessary before any specific conclusions can be drawn about the mechanism of action for vilazodone and potential benefits in GAD.

Although our results demonstrated more robust efficacy for the vilazodone 40-mg/day than 20-mg/day dose, this study was not powered to detect a dose response. Other randomized, placebo-controlled, fixed-dose studies of SSRIs and SNRIs have not provided clear evidence of a dose–response relationship in the treatment of GAD. Paroxetine, escitalopram, and duloxetine have demonstrated efficacy versus placebo in GAD studies, but higher dosages were not found to be superior.[30–32] Conversely, venlafaxine XR has demonstrated evidence for dose response in 12-week[33] and 6-month GAD trials.[34]

Due to the waxing and waning course of GAD, it is recommended that treatment continue for at least a year to maximize the probability of remission.[35] Over time, some antidepressant-related AEs, including weight gain, sleep disturbance, and sexual dysfunction, may impair treatment acceptance.[22] In our short-term study, the incidence of these AEs were generally low and resulted in few study discontinuations. Body weight increases were small and similar across groups, and weight-related AEs were reported in only two vilazodone patients; PCS weight gain occurred in ≤2% of patients in any group. The incidence of insomnia TEAEs in the placebo (5%) and vilazodone 20-mg/day (5%) and 40-mg/day (6%) groups was lower than the percentage of patients from each group who reported a history of insomnia (16%, 14%, and 13%, respectively).

CSFQ scores indicated that sexual functioning did not worsen with vilazodone treatment during this trial; there were no observed differences using this systematic assessment of sexual function for patients being treated with vilazodone or placebo. However, there were more AEs related to sexual function in the vilazodone group than in the placebo group, suggesting that some treatment-related sexual side effects may have occurred. Of note, no sexual function related TEAE occurred in >2% of patients in any group and discontinuations due to sexual function AEs were only reported for one male patient in each treatment group. Knowledge of the sexual function profile of vilazodone is important since sexual dysfunction, a class effect of SSRIs, is considered a particularly unacceptable side effect[36] and it can lead to treatment nonadherence.[37]

Limitations of this study include its short duration, which may have limited assessment of maximum SDS improvement, and lack of an active comparator. No patients with significant depressive symptoms or MDD were enrolled; as such, these findings may not generalize to GAD patients with a broader symptom profile or comorbid MDD.

CONCLUSION

Statistically significant improvements for vilazodone 40 mg/day versus placebo were seen on the primary efficacy measure and on several additional efficacy measures in this clinical trial in patients with GAD; differences from placebo for vilazodone 20 mg/day were not statistically significant on most outcome measures. The safety profile of vilazodone was consistent with findings in studies of patients with MDD and what has been described in the prescribing information; no new safety concerns were identified. Future studies of vilazodone in this population are warranted.

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