

# Efficacy and safety of vilazodone 20 and 40 mg in major depressive disorder: a randomized, double-blind, placebo-controlled trial

Maju Mathews<sup>a</sup>, Carl Gommoll<sup>a</sup>, Dalei Chen<sup>a</sup>, Rene Nunez<sup>a</sup> and Arif Khan<sup>b,c</sup>

Vilazodone is a selective serotonin reuptake inhibitor and 5-HT<sub>1A</sub> partial agonist approved for major depressive disorder (MDD) treatment in adults. This was a 10-week, multicenter, double-blind, placebo-controlled and active-controlled, fixed-dose trial (NCT01473381). Adult patients with MDD (*Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision criteria) were randomized 1 : 1 : 1 : 1 to vilazodone 20 or 40 mg/day, citalopram 40 mg/day, or placebo. Primary efficacy: Montgomery-Åsberg Depression Rating Scale (MADRS); secondary efficacy: Clinical Global Impressions-Severity and sustained response (MADRS total score  $\leq 12$  for at least the last two consecutive double-blind visits). The intent-to-treat population comprised 1133 patients, (placebo = 281; vilazodone 20 mg/day = 288; vilazodone 40 mg/day = 284; citalopram = 280). MADRS and Clinical Global Impressions-Severity score change from baseline to week 10 was significantly greater for vilazodone 20 mg/day, vilazodone 40 mg/day, and citalopram versus placebo. Sustained response rates were numerically higher, but not significantly different, in all active treatment groups versus placebo. The

most common adverse events ( $\geq 5\%$  of vilazodone patients, twice the rate of placebo) were diarrhea, nausea, vomiting (vilazodone 40 mg/day only), and insomnia. Improved sexual function (Changes in Sexual Functioning Questionnaire scores) was seen in all groups; between-group differences were not significant. Vilazodone 20 and 40 mg/day demonstrated efficacy and tolerability in the treatment of MDD. *Int Clin Psychopharmacol* 30:67–74 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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<sup>a</sup>Forest Research Institute, Jersey City, New Jersey, <sup>b</sup>Northwest Clinical Research Center, Bellevue, Washington and <sup>c</sup>Department of Psychiatry, Duke University School of Medicine, Durham, North Carolina, USA

Correspondence to Carl Gommoll, Forest Research Institute, Harborside Financial Center, Jersey City, NJ 07311, USA  
Tel: +1 201 427 8124; fax: +1 201 427 8100; e-mail: carl.gommoll@frx.com

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## Introduction

Major depressive disorder (MDD) is a heterogeneous disorder and patients can vary considerably in disease history, severity, symptomatology, and response and tolerability to different medications. Selective serotonin reuptake inhibitors (SSRIs) are effective treatments for MDD and the most commonly prescribed first-line treatment options. Many patients, though, do not adequately respond to or do not tolerate their initial SSRI (Rush, 2007); however, these patients may show strong response to or tolerate a different SSRI (Rush *et al.*, 2006; Rush, 2007). Although all SSRIs modulate serotonin reuptake, they differ in their pharmacologic profiles, which may influence efficacy and tolerability in individual patients. Access to multiple antidepressant options with different pharmacological profiles may improve the management of MDD and patient outcomes.

Vilazodone is an SSRI and 5-HT<sub>1A</sub> receptor partial agonist approved by the Food and Drug Administration (FDA) for the treatment of MDD in adults. The efficacy

of vilazodone 40 mg/day was demonstrated in two 8-week, double-blind, placebo-controlled phase III trials (Rickels *et al.*, 2009; Khan *et al.*, 2011). A phase IV trial supported the efficacy and tolerability of vilazodone 40 mg/day (Pomara *et al.*, 2013). Long-term safety and tolerability were supported in a 1-year, open-label trial of vilazodone 40 mg/day (Robinson *et al.*, 2011).

Data from phase II and phase III trials suggested that vilazodone 20 mg may be effective in treating MDD. This study was designed to fulfill a postmarketing commitment with the FDA to identify the minimum effective dose of vilazodone. The efficacy, safety, and tolerability of vilazodone 20 and 40 mg/day were evaluated in patients with MDD; citalopram was included as an active control for assay sensitivity.

## Methods

### Study design

This 10-week multicenter, randomized, double-blind, placebo-controlled and active-controlled, parallel-group, fixed-dose study (NCT01473381) was conducted at 54 US study centers between December 2011 and June 2013 in full compliance with FDA guidelines for Good Clinical Practice and the ethical principles of the

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Declaration of Helsinki. The protocol was approved by the institutional review board at each investigational site and all patients provided written informed consent.

The study comprised a 1- to 4-week screening period, a 10-week double-blind period and a 1-week double-blind down-taper. Patients were randomly assigned by computer-generated numbers (1:1:1:1) to placebo, vilazodone 20 mg/day, vilazodone 40 mg/day, or citalopram 40 mg/day. Investigators and patients were blinded to allocation of the study drug throughout treatment and down-taper period.

Patients assigned to the vilazodone 20 and 40 mg/day groups were dosed as follows: week 1, 10 mg/day, week 2, 20 mg/day (subsequently maintained for 20 mg/day arm), week 3, 40 mg/day. Patients assigned to citalopram were titrated from 20 to 40 mg/day over a 2-week period. All study drug was taken once daily in the morning with food.

#### Inclusion criteria

This study included adult (18–70 years of age, inclusive) male and female outpatients who met *Diagnostic and Statistical Manual of Mental Health*, 4th ed., text revision (DSM-IV-TR) (APA, 2000) criteria for MDD, had an ongoing major depressive episode lasting 8 or more weeks and up to 12 months, and had a Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) total score of at least 26. Female patients of childbearing potential were required to have a negative  $\beta$ -hCG pregnancy test and be currently using a reliable method of contraception. Patients were required to have normal physical examination findings, clinical laboratory test results, and ECG result, or abnormal results that were judged to be not clinically significant.

#### Exclusion criteria

Patients with a DSM-IV-TR-defined axis I disorder other than MDD within 6 months of study or a history of other specific psychiatric diagnoses, including bipolar disorder or any psychotic disorder, were excluded; secondary comorbid generalized anxiety disorder, social anxiety disorder and/or specific phobias were allowed. Patients at risk for suicide [defined as attempt within the past year, score  $\geq 5$  on MADRS Item 10 (Suicidal Thoughts), investigator judgment based on interview or the Columbia-Suicide Severity Rating Scale (C-SSRS)] (Posner *et al.*, 2011) were excluded. Exclusion criteria also included history of nonresponse to two or more antidepressants, use of psychoactive drugs (within 2 weeks of the study), or requiring concomitant treatment with prohibited medications (exceptions were eszopiclone, zopiclone, zaleplon, zolpidem, or zolpidem extended release). Medical conditions that could interfere with study conduct, confound the interpretation of results, or endanger patient well-being led to exclusion.

#### Efficacy and safety assessments

The primary efficacy measure was the MADRS [assessed at screening, baseline (week 0), and weeks 1, 2, 4, 6, 8, 10]. The Clinical Global Impressions-Severity (CGI-S) (Guy, 1976) was assessed at weeks 0, 1, 2, 4, 6, 8, and 10. Other measures included the CGI-Improvement (CGI-I) (Guy, 1976) (weeks 1, 2, 4, 6, 8, 10) and Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1959) (weeks 0, 4, 6, 8, 10). Safety was assessed by adverse event (AE) recording (MedDRA, version 15.1), physical examination, clinical laboratory and vital sign measures, ECGs, C-SSRS (all visits), and the Changes in Sexual Functioning Questionnaire (CSFQ) (Clayton *et al.*, 1997) (weeks 0, 4, 8, 10).

#### Statistical analyses

Safety analyses were based on the safety population, which comprised all randomized patients who received one or more doses of double-blind study drug. The intent-to-treat population was used for all efficacy analyses and comprised all patients in the safety population who had one or more postbaseline MADRS assessments.

The primary efficacy outcome was MADRS total score change from baseline to week 10, which was analyzed using a mixed-effects 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.

CGI-S score change from baseline to week 10 was a secondary efficacy outcome and was analyzed using an MMRM approach similar to the primary measure. MADRS sustained response (defined as MADRS total score  $\leq 12$  for at least the last two consecutive double-blind visits) rate, also a secondary efficacy outcome, was analyzed using the Cochran–Mantel–Haenszel test controlling for study center. Additional efficacy measures included MADRS response (defined as  $\geq 50\%$  improvement in total score compared with baseline), CGI-I score at endpoint, CGI-I response rate (defined as CGI-I  $\leq 2$ ), and change from baseline to week 10 in HAMA total score. CGI-I and HAMA outcomes were analyzed using an MMRM approach similar to the primary analyses. MADRS and CGI-I response rates were analyzed using a generalized linear mixed model.

Sensitivity analyses for the primary and secondary outcomes were conducted using a pattern-mixture model (PMM) based on non-future-dependent missing value restrictions (Kenward *et al.*, 2003) and an analysis of covariance based on the last observation carried forward (LOCF) approach. All efficacy analyses were performed for each active treatment group versus placebo; the study was not powered to detect differences between active treatment groups. A matched parallel gatekeeping procedure (Chen *et al.*, 2005) was applied to control type I error at the 0.05 significance level across the primary and secondary efficacy parameters and vilazodone doses.

Demographic and baseline characteristics were tested using a two-way analysis of variance with treatment group and study center as factors for continuous variables and the Cochran–Mantel–Haenszel test (controlling for study center) for categorical variables. Descriptive statistics were used for all safety parameters except CSFQ. Change from baseline to week 10 in CSFQ total score was analyzed for vilazodone 20 and 40 mg versus citalopram and for citalopram versus placebo using an MMRM approach with treatment group, sex, study center, visit, and treatment-group-by-visit interaction as fixed effects and baseline CSFQ total score as covariate and a Hochberg procedure (Hochberg, 1988) to control for multiple comparisons.

## Results

### Patient disposition and demographic characteristics

Of the 1162 patients who were randomized, 1138 patients received one or more doses of double-blind study drug (safety population); 1133 patients had a baseline and at least 1 postbaseline MADRS assessment (intent-to-treat population). Patient disposition and demographics are described in Table 1. Approximately 70% of patients completed the study. The rate of discontinuation was higher in the vilazodone 40 mg/day group compared with placebo ( $P < 0.05$ ). Discontinuations due to AEs were significantly higher for vilazodone 20 and 40 mg/day patients relative to placebo patients. A significantly lower percentage of patients in both vilazodone groups

compared with placebo discontinued because of insufficient therapeutic response.

Overall, there were no significant differences in demographic characteristics between groups except for a significantly higher percentage of Hispanic or Latino patients in the placebo group (21.0%) relative to the vilazodone 40 mg/day group (15%;  $P = 0.0314$ ). Depression history was similar between treatment groups (Table 1); ~80% of patients had recurrent major depression.

### Analysis of efficacy

#### Primary efficacy outcome

Mean MADRS total scores at baseline were ~30 (Table 2). Vilazodone treatment (20 and 40 mg/day) compared with placebo was associated with significantly greater reduction in MADRS total scores from baseline to week 10 (Fig. 1 and Table 2). Statistical significance in favor of both vilazodone groups appeared at week 2 and was sustained throughout the double-blind period (Fig. 1). Sensitivity analyses (LOCF and PMM) confirmed the robustness of the primary efficacy outcome. MADRS mean change from baseline to week 10 was also significantly greater for citalopram versus placebo, demonstrating sensitivity of the study to detect treatment effects in the primary efficacy measure.

#### Secondary and additional efficacy outcomes

Both vilazodone groups relative to placebo showed significantly greater improvement from baseline in CGI-S

**Table 1 Patient disposition, demographics, and reasons for discontinuation**

	Placebo	Vilazodone 20 mg/day	Vilazodone 40 mg/day	Citalopram 40 mg/day
Randomized population ( <i>n</i> )	290	292	291	289
Safety population ( <i>n</i> <sup>a</sup> )	281	288	287	282
Completed study [ <i>n</i> (%)]	210 (74.7)	199 (69.1)	189 (65.9)	200 (70.9)
Prematurely discontinued [ <i>n</i> (%)]	71 (25.3)	89 (30.9)	98 (34.1)*	82 (29.1)
Reason for discontinuation				
Adverse event	7 (2.5)	20 (6.9)*	25 (8.7)*	17 (6.0)
Insufficient therapeutic response	10 (3.6)	1 (0.3)*	2 (0.7)*	3 (1.1)
Protocol violation	15 (5.3)	21 (7.3)	18 (6.3)	16 (5.7)
Withdrawal of consent	18 (6.4)	21 (7.3)	20 (7.0)	23 (8.2)
Lost to follow-up	21 (7.5)	26 (9.0)	32 (11.1)	20 (7.1)
Other	0	0	1 (0.3)	3 (1.1)
Intent-to-treat population ( <i>n</i> )	281	288	284	280
Entered down-taper period <sup>b</sup>	214 (76.2)	198 (68.8)	194 (67.6)	199 (70.6)
Patient demographic characteristics (safety population)				
Age [mean (SD)] (years)	42.0 (13.0)	41.7 (12.7)	40.8 (13.2)	42.6 (12.6)
Women (%)	56.2	57.6	57.1	58.5
Race (%)				
White	70.1	71.2	70.4	65.2
Black or African American	25.3	25.3	25.8	29.4
Other	4.6	3.5	3.8	5.3
Weight [mean (SD)] (kg)	82.3 (17.0)	82.6 (18.2)	82.5 (17.9)	82.4 (18.3)
MDD history (safety population)				
Age at onset [mean (SD)] (years)	31.1 (14.2)	30.9 (13.3)	30.4 (12.9)	32.3 (13.9)
Duration of MDD [mean (SD)] (years)	10.9 (10.7)	10.8 (10.9)	10.4 (11.0)	10.3 (10.1)
Number of major depressive episodes (mean)	3.7	3.9	3.7	3.7
Duration of current episode [mean (SD)] (months)	6.4 (3.4)	6.0 (3.3)	6.3 (3.4)	6.6 (4.8)

MDD, major depressive disorder.

\* $P < 0.05$  versus placebo (Fisher exact test).

<sup>a</sup>Two citalopram patients in the safety population discontinued due to AEs during week 1 and were not part of the ITT population; three patients in the vilazodone 40 mg/day group withdrew consent or were lost to follow-up during week 1.

<sup>b</sup>Patients who completed or prematurely discontinued from the study were eligible to enter the down-taper period.

Table 2 Summary of efficacy assessments

	Placebo (n = 281)	Vilazodone 20 mg/day (n = 288)	Vilazodone 40 mg/day (n = 284)	Citalopram 40 mg/day (n = 280)
Primary and secondary efficacy				
MADRS total score				
MMRM				
Baseline score [mean (SE)]	31.3 (0.3)	31.0 (0.3)	30.8 (0.3)	31.1 (0.3)
Week 10 score [mean (SE)]	16.1 (0.7)	13.8 (0.7)	13.2 (0.7)	13.5 (0.7)
Change from baseline at week 10, [LS mean (SE)]	-14.8 (0.6)	-17.3 (0.6)	-17.6 (0.7)	-17.5 (0.6)
LSMD (95% CI)	-	-2.57 (-4.30 to -0.84)	-2.82 (-4.57 to -1.06)	-2.74 (-4.48 to -1.00)
P-value <sup>a</sup>	-	0.0073	0.0034	0.0020
LOCF <sup>b</sup>				
Baseline [mean (SE)]	31.4 (0.2)	31.3 (0.2)	31.2 (0.2)	31.2 (0.2)
Week 10 score [mean (SE)]	18.2 (0.6)	15.8 (0.6)	16.0 (0.6)	15.6 (0.6)
Change from baseline at week 10, [LS mean (SE)]	-13.6 (0.6)	-15.8 (0.6)	-15.4 (0.6)	-15.9 (0.6)
LSMD (95% CI)	-	-2.24 (-3.84 to -0.63)	-1.96 (-3.57 to -0.35)	-2.28 (-3.90 to -0.67)
P-value	-	0.0063	0.0170	0.0057
CGI-S total score				
MMRM				
Baseline [mean (SE)]	4.5 (0.0)	4.5 (0.0)	4.4 (0.0)	4.5 (0.0)
Week 10 score [mean (SE)]	3.0 (0.1)	2.6 (0.1)	2.6 (0.1)	2.6 (0.1)
Change from baseline at week 10, [LS mean (SE)]	-1.5 (0.1)	-1.9 (0.1)	-1.9 (0.1)	-1.9 (0.1)
LSMD (95% CI)	-	-0.35 (-0.58 to -0.13)	-0.33 (-0.55 to -0.10)	-0.35 (-0.57 to -0.12)
P-value <sup>a</sup>	-	0.0073	0.0097	0.0025
LOCF <sup>b</sup>				
Baseline [mean (SE)]	4.5 (0.0)	4.5 (0.0)	4.5 (0.0)	4.5 (0.0)
Week 10 score [mean (SE)]	3.2 (0.1)	2.9 (0.1)	2.9 (0.1)	2.8 (0.1)
Change from baseline at week 10, [LS mean (SE)]	-1.4 (0.1)	-1.7 (0.1)	-1.6 (0.1)	-1.7 (0.1)
LSMD (95% CI)	-	-0.29 (-0.49 to -0.09)	-0.20 (-0.41 to 0.00)	-0.28 (-0.49 to -0.08)
P-value	-	0.0049	0.0521	0.0071
MADRS sustained response				
Total score ≤ 12 for at least the last 2 consecutive visits during double-blind treatment (%) <sup>c</sup>	26.3	29.9	33.5	31.1
P-value <sup>a</sup>	-	0.3563	0.1611	0.2672
RR (95% CI)	-	1.130 (0.871-1.466)	1.253 (0.973-1.612)	1.157 (0.891-1.503)
Additional efficacy				
HAMA <sup>d</sup>				
Baseline [mean (SE)]	15.7 (0.3)	15.8 (0.3)	15.7 (0.3)	14.8 (0.3)
Week 10 score [mean (SE)]	8.6 (0.4)	7.7 (0.4)	7.7 (0.4)	7.1 (0.4)
Change from baseline at week 10, [LS mean (SE)]	-6.7 (0.4)	-7.4 (0.4)	-7.5 (0.4)	-7.9 (0.4)
P-value	-	0.1412	0.1229	0.0138
CGI-I <sup>d</sup>				
Score at week 10, [LS mean (SE)]	2.4 (0.1)	2.2 (0.1)	2.1 (0.1)	2.1 (0.1)
P-value	-	0.0390	0.0086	0.0091
CGI-I response at week 10 <sup>e</sup>				
Score ≤ 2 at week 10 (%)	55.2	63.2	71.9	68.3
OR (95% CI)	-	1.745 (0.947-3.216)	3.009 (1.585-5.712)	2.315 (1.249-4.293)
P-value	-	0.0743	0.0008	0.0077
MADRS response at week 10 <sup>e</sup>				
≥ 50% improvement from total baseline score at week 10 (%)	50.5	64.2	64.6	62.9
OR (95% CI)	-	2.363 (1.292-4.319)	2.410 (1.293-4.494)	2.202 (1.207-4.015)
P-value	-	0.0052	0.0056	0.0100

Statistical testing on additional endpoints was performed without adjustment for multiple comparisons.

ANCOVA, analysis of covariance; CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; CI, confidence interval; HAMA, Hamilton Rating Scale for Anxiety; LOCF, last observation carried forward; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures; OR, odds ratio; RR, relative risk.

<sup>a</sup>P-values for vilazodone 20 and 40 mg/day were adjusted using a matched parallel gatekeeping procedure to control for multiple dose-group comparisons.

<sup>b</sup>ANCOVA.

<sup>c</sup>Cochran-Mantel-Haenszel test.

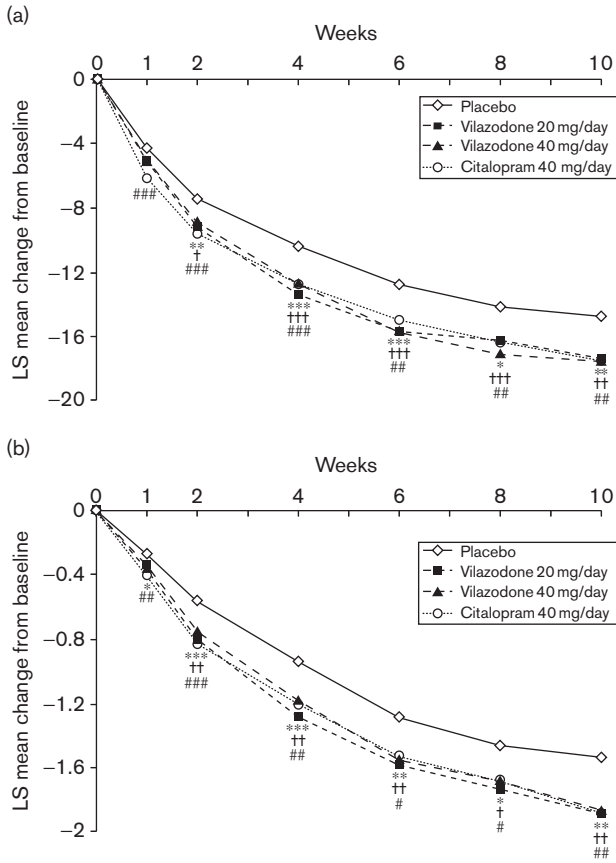
<sup>d</sup>MMRM analysis.

<sup>e</sup>Generalized linear mixed model.

scores (Fig. 1 and Table 2). Similar to the primary efficacy measure, significance was achieved in week 2 and was maintained throughout the double-blind period. Sustained MADRS response (MADRS ≤ 12 for at least

the last two consecutive visits during double-blind treatment) rates were numerically higher for all active treatment groups compared with placebo, although the differences did not reach statistical significance (Table 2).

Fig. 1



(a) MADRS and (b) CGI-S total score change from baseline to week 10 (ITT Population, MMRM). \**P* < 0.05 VLZ 20 vs. placebo; \*\**P* < 0.01 VLZ 20 vs. placebo; \*\*\**P* < 0.001 VLZ 20 vs. placebo; †*P* < 0.05 VLZ 40 vs. placebo; ††*P* < 0.01 VLZ 40 vs. placebo; †††*P* < 0.001 VLZ 40 vs. placebo; #*P* < 0.05 CIT vs. placebo; ##*P* < 0.01 CIT vs. placebo; ###*P* < 0.001 CIT vs. placebo. CGI-S, Clinical Global Impressions-Severity; CIT, citalopram; ITT, intent-to-treat; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures; VLZ, vilazodone.

Statistically significant differences for vilazodone 20 mg/day versus placebo were seen for CGI-I score and MADRS response rates at week 10 (Table 2). Significant advantage for vilazodone 40 mg/day versus placebo was seen for all additional efficacy outcomes except change from baseline to week 10 in HAMA scores. Statistical significance was seen for citalopram versus placebo on the CGI-S and on all additional efficacy measures demonstrating assay sensitivity across outcome measures.

**Safety and tolerability**

**Extent of exposure**

The median duration of exposure was ~70 days for all treatment groups. The mean (SD) daily dose was 17.8 (2.3) mg for vilazodone 20 mg/day, 30.1 (8.1) mg for vilazodone 40 mg/day, and 33.0 (5.3) mg/day for citalopram.

**Adverse events**

Treatment-emergent adverse events (TEAEs) are summarized in Table 3. The most commonly reported AE leading to discontinuation was nausea (placebo, *n* = 1; vilazodone 20 mg/day, *n* = 6; vilazodone 40 mg/day, *n* = 3, citalopram, *n* = 4). AEs that occurred in at least 5% of patients in either vilazodone group and at twice the rate of placebo were diarrhea, nausea, insomnia, and vomiting (40 mg/day group only). The incidence of vomiting and somnolence was greater in the vilazodone 40 mg/day group relative to the vilazodone 20 mg/day group. The majority of TEAEs in all treatment groups were mild or moderate in severity.

During double-blind treatment, the incidence of serious AEs (SAEs) was low in all treatment groups. There was one death in the vilazodone 20 mg/day group [accidental overdose (alcohol and hydrocodone)]; this death was not considered treatment related. SAEs were reported for two placebo patients, four vilazodone 20 mg/day patients,

Table 3 Summary of adverse events

Adverse events	<i>n</i> (%)			
	Placebo ( <i>n</i> = 281)	Vilazodone 20 mg/day ( <i>n</i> = 288)	Vilazodone 40 mg/day ( <i>n</i> = 287)	Citalopram 40 mg/day ( <i>n</i> = 282)
<b>Double-blind treatment summary</b>				
Deaths	0	1 (0.3)	0	0
Patients with ≥ 1 TEAE	178 (63.3)	208 (72.2)	222 (77.4)	217 (77.0)
Patients who discontinued due to AE	7 (2.5)	20 (6.9)	25 (8.7)	18 (6.4)
Patients with SAE	2 (0.7)	4 (1.4)	4 (1.4)	6 (2.1)
<b>Common double-blind AEs (≥5% in any treatment group)</b>				
Diarrhea	26 (9.3)	75 (26.0)	76 (26.5)	30 (10.6)
Nausea	23 (8.2)	62 (21.5)	69 (24.0)	55 (19.5)
Vomiting	7 (2.5)	11 (3.8)	19 (6.6)	5 (1.8)
Headache	39 (13.9)	42 (14.6)	41 (14.3)	42 (14.9)
Dizziness	20 (7.1)	18 (6.3)	18 (6.3)	19 (6.7)
Dry mouth	14 (5.0)	22 (7.6)	19 (6.6)	18 (6.4)
Insomnia	8 (2.8)	19 (6.6)	16 (5.6)	12 (4.3)
Fatigue	9 (3.2)	11 (3.8)	11 (3.8)	20 (7.1)
Somnolence	10 (3.6)	11 (3.8)	18 (6.3)	22 (7.8)
Upper respiratory tract infection	13 (4.6)	14 (4.9)	15 (5.2)	14 (5.0)
Nasopharyngitis	11 (3.9)	12 (4.2)	13 (4.5)	15 (5.3)
<b>Incidence of AEs related to sexual function</b>				
Libido decreased	3 (1.1)	6 (2.1)	5 (1.7)	4 (1.4)
Loss of libido	0	0	0	3 (1.1)
Libido increased	0	1 (0.3)	0	0
Anorgasmia	0	1 (0.3)	1 (0.3)	4 (1.4)
Orgasm abnormal	0	2 (0.7)	0	1 (0.4)
Premature ejaculation <sup>a</sup>	0	0	0	1 (0.9)
Erectile dysfunction <sup>a</sup>	3 (2.4)	0	3 (2.4)	3 (2.6)
Ejaculation delayed <sup>a</sup>	0	1 (0.8)	2 (1.6)	2 (1.7)
Sexual dysfunction	0	0	1 (0.3)	0
Ejaculation failure <sup>a</sup>	0	0	0	1 (0.9)

AEs were coded by MedDRA, version 15.1.

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

<sup>a</sup>Sex-specific TEAS for which the percentages are based on the number of males only.

four vilazodone 40 mg/day patients, and six citalopram patients. The only SAEs that occurred in more than one patient were suicidal ideation (placebo,  $n=1$ ; citalopram,  $n=1$ ) and diverticulitis (vilazodone 40 mg/day,  $n=1$ ; citalopram,  $n=1$ ). Of the SAEs, only two were considered related to treatment [vilazodone 20 mg/day,  $n=1$  (dizziness); citalopram,  $n=1$  (migraine with aura)]. During double-blind down-taper, SAEs were only reported for one placebo patient (abscess neck, oral abscess, and obstructive airways disorder).

#### **Clinical laboratory, vital signs, electrocardiogram evaluation**

The incidence of potentially clinically significant (PCS) changes in laboratory parameters was low and similar across treatment groups; no patient met Hy's law criteria (Watkins *et al.*, 2008). PCS changes in vital signs were infrequent, similar across groups, and were not associated with clinically significant TEAEs. The incidence of orthostatic hypotension ( $\geq 20$  mmHg reduction in systolic blood pressure or  $\geq 10$  mmHg reduction in diastolic blood pressure while changing from a supine to standing position) was similar in the placebo (10.3%) and vilazodone 20 mg/day (7.0%) and 40 mg/day (8.5%) groups, and slightly higher in the citalopram group (12.1%). No patient in any group had a QTcB or QTcF value greater than 500 ms; two patients had PCS ECG findings [vilazodone 40 mg/day,  $n=1$  (QRS  $\geq 150$  ms); citalopram,  $n=1$  (PR  $\geq 250$  ms)].

#### **C-SSRS suicidality and suicide-related adverse events**

The incidence of suicidal ideation during double-blind treatment, as determined by the C-SSRS, was higher in the placebo group (24.2%) relative to the active treatment groups (vilazodone 20 mg/day, 17.4%; vilazodone 40 mg/day, 18.1%; citalopram, 16.3%). There were no incidences of C-SSRS-rated suicidal behavior in either vilazodone group; there was one patient each in the placebo and citalopram groups with C-SSRS-rated suicidal behavior. During double-blind treatment, there was one patient in the vilazodone 40 mg/day group who attempted suicide (reported as an SAE; patient discontinued from the study).

#### **Sexual functioning**

Overall, the incidence of AEs related to sexual functioning was higher in the active treatment groups relative to placebo and most frequent in the citalopram group (Table 3). No patient in the vilazodone groups withdrew because of a sexual function AE. One patient in the citalopram group discontinued because of premature ejaculation and one patient in the placebo group discontinued because of erectile dysfunction.

CSFQ scores increased from baseline to week 10 in all treatment groups in both men and women (Table 4). Improvement in CSFQ scores was numerically greater for

vilazodone (both doses) and placebo relative to citalopram, but the differences between treatment groups were not statistically significant.

#### **Discussion**

In this multicenter, randomized, placebo-controlled and active-controlled, double-blind, fixed-dose study, vilazodone 20 and 40 mg/day were significantly superior to placebo on the primary efficacy measure, MADRS total score change from baseline to week 10. The LSMDs versus placebo for vilazodone 20 and 40 mg/day were  $-2.57$  and  $-2.82$ , respectively. In short-term clinical trials, a mean drug-placebo difference of at least two points on the MADRS has been suggested to indicate clinically relevant treatment effects (Melander *et al.*, 2008; Montgomery and Möller, 2009). For both vilazodone doses, mean drug-placebo differences exceeded this two-point threshold suggesting that the improvements in vilazodone-treated patients were clinically relevant. These results were supported by PMM and LOCF analyses. The SSRI citalopram was also associated with significant and clinically relevant improvements on the MADRS, supporting the validity and assay sensitivity of this trial.

The CGI-S can broadly capture additional dimensions that contribute to disease severity such as patient distress, functional impairment, and quality of life (Targum *et al.*, 2012). Significant improvement in CGI-S scores relative to placebo suggested that vilazodone treatment was associated with reduced global disease severity.

Sustained response (MADRS  $\leq 12$  for at least the last two consecutive visits during double-blind treatment) is a newly defined efficacy outcome that was developed with guidance from the FDA to show evidence of treatment benefits that are maintained beyond an individual time point in a short-term study. In this study, sustained response rates were higher in all active treatment groups compared with placebo but the differences did not reach statistical significance.

Results on additional efficacy measures supported the beneficial effects of vilazodone seen on the primary efficacy outcome. Vilazodone 20 mg/day was significantly superior to placebo on CGI-I scores and MADRS response rates at week 10. HAMA change from baseline and CGI-I response rates improved over time but did not achieve statistical significance relative to placebo. In the vilazodone 40 mg/day group, all additional efficacy measures except for HAMA total score were statistically significant versus placebo. Citalopram showed significant advantages to placebo on all additional efficacy measures.

Antidepressant side effects are common and can negatively impact patient outcomes. Intolerability to medication is one of the most common reasons patients discontinue antidepressant treatment (Demyttenaere *et al.*, 2001; Bull *et al.*, 2002; Hu *et al.*, 2004). In patients

**Table 4** Changes in Sexual Functioning Questionnaire scores (CSFQ analysis population)

	Placebo ( <i>n</i> = 212)	Vilazodone 20 mg/day ( <i>n</i> = 201)	Vilazodone 40 mg/day ( <i>n</i> = 192)	Citalopram 40 mg/day ( <i>n</i> = 205)
CSFQ total score				
Baseline score [mean (SE)]	42.0 (0.7)	42.2 (0.7)	41.3 (0.7)	41.0 (0.7)
Week 10 score [mean (SE)]	44.7 (0.8)	44.4 (0.7)	43.4 (0.8)	42.6 (0.8)
Change from baseline at week 10, [LS mean (SE)]	2.5 (0.5)	2.6 (0.5)	2.0 (0.6)	1.5 (0.5)
LSMD vs. citalopram (95% CI)	1.03 (−0.41 to 2.47)	1.19 (−0.25 to 2.64)	0.52 (−0.94 to 1.99)	–
LSMD vs. placebo (95% CI)	–	0.16 (−1.27 to 1.60)	−0.51 (−1.96 to 0.95)	−1.03 (−2.47 to 0.41)
Change in CSFQ by sex				
Men				
<i>n</i>	94	87	84	83
Baseline [mean (SE)]	46.9 (1.0)	46.5 (0.9)	46.3 (1.0)	46.3 (0.9)
Week 10 score [mean (SE)]	50.4 (1.0)	48.9 (1.0)	47.4 (1.0)	48.3 (1.0)
Change from baseline at week 10 [mean (SE)]	3.5 (0.8)	2.4 (0.8)	1.2 (0.8)	2.1 (0.8)
Women				
<i>n</i>	118	114	108	122
Baseline [mean (SE)]	38.2 (0.9)	39.0 (0.7)	37.4 (0.8)	37.4 (0.8)
Week 10 score [mean (SE)]	40.2 (1.0)	40.9 (0.9)	40.3 (1.0)	38.6 (1.0)
Change from baseline at week 10 [mean (SEM)]	2.0 (0.8)	1.9 (0.9)	3.0 (0.8)	1.2 (0.7)

CSFQ analysis population comprises all patients with a baseline and week 10 CSFQ score.

CI, confidence interval; CSFQ, Changes in Sexual Functioning Questionnaire; LS, least squares; LSMD, least squares mean difference.

that continue antidepressant treatment, adverse side effects can add to patient distress and diminish quality of life (Cassano and Fava, 2004; Papakostas, 2008). Some side effects, such as nausea and diarrhea, are usually short-term and resolve over time (Hu *et al.*, 2004) while others, such as swelling, blurred vision, sexual dysfunction, and weight gain, are considered chronic side effects that persist with continued treatment (Hu *et al.*, 2004). Vilazodone and citalopram were generally well tolerated in this study with most AEs considered to be of mild or moderate severity. Gastrointestinal-related AEs, particularly diarrhea, were higher in the vilazodone groups relative to citalopram and placebo; gastrointestinal-related events generally occurred during the early weeks of treatment and were transient in nature. Rates of fatigue and somnolence appeared to be higher with citalopram relative to vilazodone; conversely, insomnia was higher in the vilazodone groups compared with the citalopram group.

Sexual dysfunction is both a symptom of MDD and a common and persistent side effect associated with SSRIs. In this study, rates of sexual dysfunction-related AEs were lowest with placebo and slightly higher with citalopram compared with vilazodone. In addition, the CSFQ was used to assess sexual function throughout the study. All treatment groups showed improvements from baseline in mean CSFQ scores, with the greatest improvement occurring in the vilazodone 20 mg/day and placebo groups and smallest increases in the citalopram group. The differences between treatment groups were not statistically significant.

Weight gain is also a persistent treatment-related side effect and a common reason for antidepressant

nonadherence (Hu *et al.*, 2004). In this study, mean weight gain was low and similar across treatment groups. Changes in other vital signs and laboratory parameters were small and similar between treatment groups.

This study was not powered to detect differences between dose groups but inclusion of two vilazodone doses allowed evaluation of potential dose response. Improvements in most efficacy measures were comparable between vilazodone 20 and 40 mg/day groups. Vilazodone 40 mg/day showed higher rates of CGI-I response relative to vilazodone 20 mg/day. Vilazodone 20 mg/day was associated with slightly lower rates of somnolence and vomiting, and greater improvements in CSFQ scores.

Limitations of this study include inclusion and exclusion criteria, which may limit generalizability of the results, and the short duration of the study. The study included both an approved vilazodone 40 mg/day dose group and the active control citalopram 40 mg/day; however, this study was not powered to detect differences in efficacy and tolerability between active treatment groups.

## Conclusion

Treatment with vilazodone 20 and 40 mg/day compared with placebo was associated with significantly greater improvements in depression symptoms as measured by MADRS total score. The magnitude of changes on the primary, secondary, and additional efficacy parameters were generally comparable between active treatment groups. Both vilazodone doses were generally well tolerated in this study. These results support the efficacy, safety, and tolerability of vilazodone 20 and 40 mg/day in the treatment of MDD. Vilazodone 20 mg/day may represent an effective dose option for the treatment of MDD.

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## Conflicts of interest

Maju Mathews, Carl Gommoll, Dalei Chen, and Rene Nunez acknowledge a potential conflict of interest as employees of Forest Research Institute. Arif Khan, MD, Principal Investigator of over 380 clinical trials sponsored by over 65 pharmaceutical companies and 30 CROs, has done no compensated consulting or speaking on their behalf, nor does he own stock in any of these or other pharmaceutical companies. Dr Khan is not compensated for his role as author. The Northwest Clinical Research Center enrolled 56 patients in the vilazodone study (NCT01473381). In 2009, Dr Khan founded Columbia Northwest Pharmaceuticals LLC, and is Medical Director of the company. Columbia Northwest Pharmaceuticals owns intellectual property rights for potential therapies for Central Nervous System disorders and other medical conditions.

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