

Relapse prevention in adults with major depressive disorder treated with vilazodone: a randomized, double-blind, placebo-controlled trial

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This randomized withdrawal study assessed relapse prevention with vilazodone in adults with major depressive disorder. After 20 weeks of open-label treatment with vilazodone 40 mg/day, responders were randomized (1 : 1 : 1) to 28 weeks of double-blind, fixed-dose treatment with vilazodone 20 mg/day, vilazodone 40 mg/day, or placebo. The primary efficacy endpoint was time to first relapse, defined as Montgomery-Åsberg Depression Rating Scale total score of at least 18 and meeting major depressive episode criteria, Montgomery-Åsberg Depression Rating Scale total score of at least 18 at two consecutive visits, or discontinuation for an insufficient therapeutic response. Of 1204 patients who received open-label treatment, 564 completed treatment and were randomized (placebo = 192, vilazodone 20 mg/day = 185, vilazodone 40 mg/day = 187). No significant difference was detected in time to relapse during the double-blind period ($P > 0.05$). The crude percentage of patients that relapsed was similar between treatment groups (placebo = 12.6%; vilazodone 20 mg/day = 11.4%; vilazodone 40 mg/day = 13.4%). The most common treatment-emergent

adverse events were diarrhea (29.6%), nausea (24.0%), and headache (14.0%) during open-label treatment and headache (8.9%), nasopharyngitis (8.4%), and diarrhea (7.5%) during double-blind treatment in the combined vilazodone groups (20 and 40 mg/day). In conclusion, time to relapse with vilazodone was not statistically different from placebo. Vilazodone was generally well tolerated in adults with major depressive disorder. *Int Clin Psychopharmacol* 33:304–311 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Relapse in major depressive disorder (MDD) is defined as a return of depressive symptoms after effective acute treatment with an antidepressant therapy (Segal *et al.*, 2003). Factors associated with a greater risk of relapse include discontinuation of treatment too soon following initial response, multiple courses of acute antidepressant therapy, and residual symptoms and/or functional impairment after treatment (Shelton, 2001; Rush *et al.*, 2006; Sheehan *et al.*, 2011; Judd *et al.*, 2015). It has been suggested that focusing efforts on relapse prevention may be more beneficial than trying to manage active relapse episodes (Nierenberg *et al.*, 2003), and studies have shown that patients who achieve treatment response with antidepressants have lower rates of relapse (Thase *et al.*, 1992). Risk of relapse may also be

further reduced if patients continue antidepressant treatment for 4–9 months after the response is achieved (American Psychiatric Association, 2010).

Vilazodone is a selective serotonin reuptake inhibitor (SSRI) and 5-HT_{1A} receptor partial agonist that is approved in the USA, Mexico, Brazil, and Canada for the treatment of MDD in adults. The efficacy of vilazodone in reducing depression symptoms was established in four large clinical trials in which patients were randomized to receive 8 or 10 weeks of double-blind treatment with placebo or vilazodone (20 or 40 mg/day) (Rickels *et al.*, 2009; Khan *et al.*, 2011; Croft *et al.*, 2014; Mathews *et al.*, 2015). In these studies, treatment with vilazodone versus placebo resulted in significantly greater improvements in Montgomery-Åsberg Depression Rating Scale (MADRS) total score (Rickels *et al.*, 2009; Khan *et al.*, 2011; Croft *et al.*, 2014; Mathews *et al.*, 2015) and Hamilton Depression Rating Scale total score (Rickels *et al.*, 2009; Khan *et al.*, 2011). Although these studies demonstrated the acute effects of vilazodone on depressive symptoms, they did not provide information about longer-term treatment or the ability of vilazodone to prevent relapse. Therefore, a randomized,

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double-blind, withdrawal study was conducted to evaluate vilazodone relative to placebo in the prevention of relapse in adults with MDD who responded to 20 weeks of open-label vilazodone treatment.

Participants and methods

Study design and participants

This randomized, double-blind, parallel-group, placebo-controlled, fixed-dose, withdrawal study (NCT01573598) was conducted from 2012 to 2014 at 64 sites (USA, Bulgaria, Finland, Germany, Romania, Serbia, Ukraine) in full compliance with the International Conference on Harmonization Guidelines on General Considerations for Clinical Trials and the Declaration of Helsinki. The protocol and amendments were approved by an institutional review board at each study center. All patients provided written informed consent.

The study comprised a 1–2-week no-drug screening period, an 8-week open-label run-in phase, a 12-week open-label stabilization phase, a 28-week double-blind phase in which eligible patients were randomized to placebo or vilazodone, and a 2-week down-taper phase (Supplementary Fig., Supplemental digital content 1, <http://links.lww.com/ICP/A47>). Men and women (18–70 years, inclusive) with a *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (DSM-IV-TR) diagnosis of MDD (American Psychiatric Association, 2000) were included in the study. Patients had an ongoing major depressive episode (≥ 8 weeks to ≤ 18 months); at least three lifetime depressive episodes (including current episode) and two episodes within 5 years before screening (including the current episode); MADRS total score of at least 26; and BMI of at least 18 and up to 40 kg/m².

Patients were excluded if they had a current DSM-IV-TR Axis I disorder other than MDD within 6 months before screening (comorbid generalized anxiety disorder, social anxiety disorder, and/or specific phobias were allowed); history of manic, psychotic, obsessive–compulsive, personality, and/or cognitive disorder(s); substance abuse or dependence within 6 months before screening; suicide risk, based on investigator judgment, suicide attempt within the past year, MADRS suicidal thoughts item score of at least 5, and/or Columbia-Suicide Severity Rating Scale (C-SSRS) findings; nonresponse to at least two antidepressants after at least 8 weeks of treatment at approved recommended doses; and any condition that could interfere with study conduct, confound interpretation of study results, or endanger patient well-being. Concomitant use of medications with psychoactive effects or strong cytochrome P450 effects was prohibited; medications for insomnia (e.g. eszopiclone, zopiclone, zaleplon, zolpidem) were allowed as needed.

Randomization, blinding, and treatment

Computerized randomization codes were generated by an administrator who was not otherwise involved in the study. Patients, investigators, and study site personnel

were blinded to the patient group, and blinding was managed and maintained through the use of an interactive web response system. No breaking of the blind occurred during the study. All study medications (vilazodone 10- and 20-mg tablets, matching placebo tablets) were identical in appearance and packaging.

During the 8-week open-label run-in phase, vilazodone was titrated to 40 mg/day (Supplementary Fig., Supplemental digital content 1, <http://links.lww.com/ICP/A47>). Patients could continue to the 12-week open-label stabilization phase if they completed the 8-week run-in phase, had MADRS total score of 12 or less at the final visit of the run-in phase, and had no significant tolerability issues as judged by the investigator at the final visit of the run-in phase. Patients received vilazodone 40 mg/day for the stabilization phase. Eligible patients from the open-label period who demonstrated stable response continued into the 28-week double-blind period and were randomized (1 : 1 : 1) to placebo, vilazodone 20 mg/day, or vilazodone 40 mg/day. Criteria for randomization included completion of the 20-week open-label period; MADRS total score of 12 or less at the final three study visits of this period (weeks 16, 18, and 20); no greater than 2 MADRS total score excursions of greater than 12 and 16 or less (weeks 10, 12, and 14); and no significant tolerability issues as judged by the investigator.

Patients who completed the double-blind period or discontinued from the study for any reason entered a 2-week down-taper period; patients randomized to vilazodone had dose reductions during the first week (40 to 20 to 10 mg/day), unless deemed medically inappropriate by the study investigator, and no medication during the second week.

Efficacy and safety parameters

The primary efficacy parameter was the time to first relapse during the double-blind period, defined as the number of days from randomization to the date of relapse. Relapse was defined as MADRS total score of at least 18 and presence of a major depressive episode (per DSM-IV-TR criteria) at any visit; MADRS total score of at least 18 at any two consecutive visits; discontinuation for insufficient therapeutic response, defined as worsening of depression requiring medication switch and at least a two-point increase from randomization in Clinical Global Impressions-Severity (CGI-S) score; or worsening of depression requiring hospitalization. Patients who did not meet relapse criteria were censored at the time of completion or discontinuation.

Additional efficacy parameters assessed during the open-label and double-blind periods included changes from baseline in MADRS total score and CGI-S score, and mean CGI-Improvement (CGI-I) score. Open-label baseline was defined as the last available assessment before the first dose of open-label vilazodone treatment. Double-blind baseline was defined as the last available assessment before randomization.

Safety parameters included adverse events (AEs), clinical laboratory tests, vital signs and physical examinations, ECG findings, and C-SSRS assessments. An AE that occurred during the open-label or double-blind period was considered a treatment-emergent AE (TEAE) if it was not present before the first dose of open-label treatment or if it was present but increased in severity during the respective period. A newly emergent AE was defined as an AE that was not present before the first dose of the double-blind period or was present but increased in severity.

Statistical methods

Sample size and power calculations were based on analysis of time to relapse in the double-blind period. Assumptions, based on previous relapse studies with similar compounds (i.e. SSRIs), included relapse rate of 30 and 15% in the placebo and vilazodone 40 mg/day groups, respectively, and discontinuation rate of 15% in the double-blind period for reasons other than insufficient therapeutic response. It was estimated that 465 randomized patients (155/treatment group) would provide 87% power to detect a difference in the primary efficacy parameter using the log-rank test at the 0.05 significance level. On the basis of the assumption that response rates with vilazodone during the dose-titration and stable-dose phases of the open-label period would be 43 and 72%, respectively, it was estimated that ~1500 patients would need to be enrolled in the study.

Analyses were conducted in the open-label safety population (all patients who received ≥ 1 dose of open-label vilazodone), open-label intent-to-treat (ITT) population (open-label safety population with ≥ 1 postbaseline MADRS assessment during the open-label period), double-blind safety population (all patients who received ≥ 1 dose of double-blind treatment), and double-blind ITT population (double-blind safety population with ≥ 1 postbaseline MADRS assessment during the double-blind period or those who discontinued the double-blind period due to insufficient therapeutic response).

The primary efficacy parameter (time to relapse) was analyzed in the double-blind ITT population using a log-rank test; hazard ratio estimates and 95% confidence intervals were based on a Cox proportional hazard regression model with treatment group as explanatory variables and stratified by US/non-US category. The cumulative rate of relapse was characterized by Kaplan–Meier curves for double-blind treatment. Two sensitivity analyses were performed to assess the robustness of the primary analysis. The first sensitivity analysis assumed that patients who discontinued the double-blind period had relapsed and were not censored; the second sensitivity analysis was an extension of the placebo-based pattern mixture model, which assumed that vilazodone-treated patients who discontinued double-blind treatment would have had disease progression similar to the placebo group.

Additional efficacy parameters were analyzed descriptively in the open-label ITT population, with the last observation

carried forward to impute missing values. In the double-blind ITT population, additional efficacy parameters were analyzed using a mixed-effects model for repeated measures with treatment group, study center, visit, and treatment group-by-visit interaction as fixed effects and baseline and baseline-by-visit interaction as covariates. A post-hoc analysis was conducted to determine the percentage of patients (open-label ITT population) achieving MADRS response ($\geq 50\%$ total score reduction) and MADRS remission (total score ≤ 10). Patient demographics, baseline characteristics, and safety parameters were analyzed descriptively.

Results

Patients

Of the 1204 patients who entered the open-label period, 564 completed the 20-week open-label treatment period and met the criteria for randomization (Fig. 1). A total of 376 (66.8%) patients completed the double-blind period, not including the 68 patients who were discontinued because they met the relapse criteria. A greater proportion of placebo-treated patients (70.8%) than vilazodone-treated patients (64.7%) completed the double-blind period.

Patient baseline characteristics are presented in Table 1. Characteristics were similar between the open-label and double-blind safety populations and across treatment groups in the double-blind safety population. Mean MADRS total score was 31.7 at open-label baseline; at randomization, mean MADRS total scores were ~5 in all treatment groups (Table 1). Mean duration of vilazodone treatment in the open-label period was 105.5 days. Mean treatment duration in the double-blind period was 158.1 days for placebo, 152.7 days for vilazodone 20 mg/day, and 157.0 days for vilazodone 40 mg/day.

Efficacy outcomes

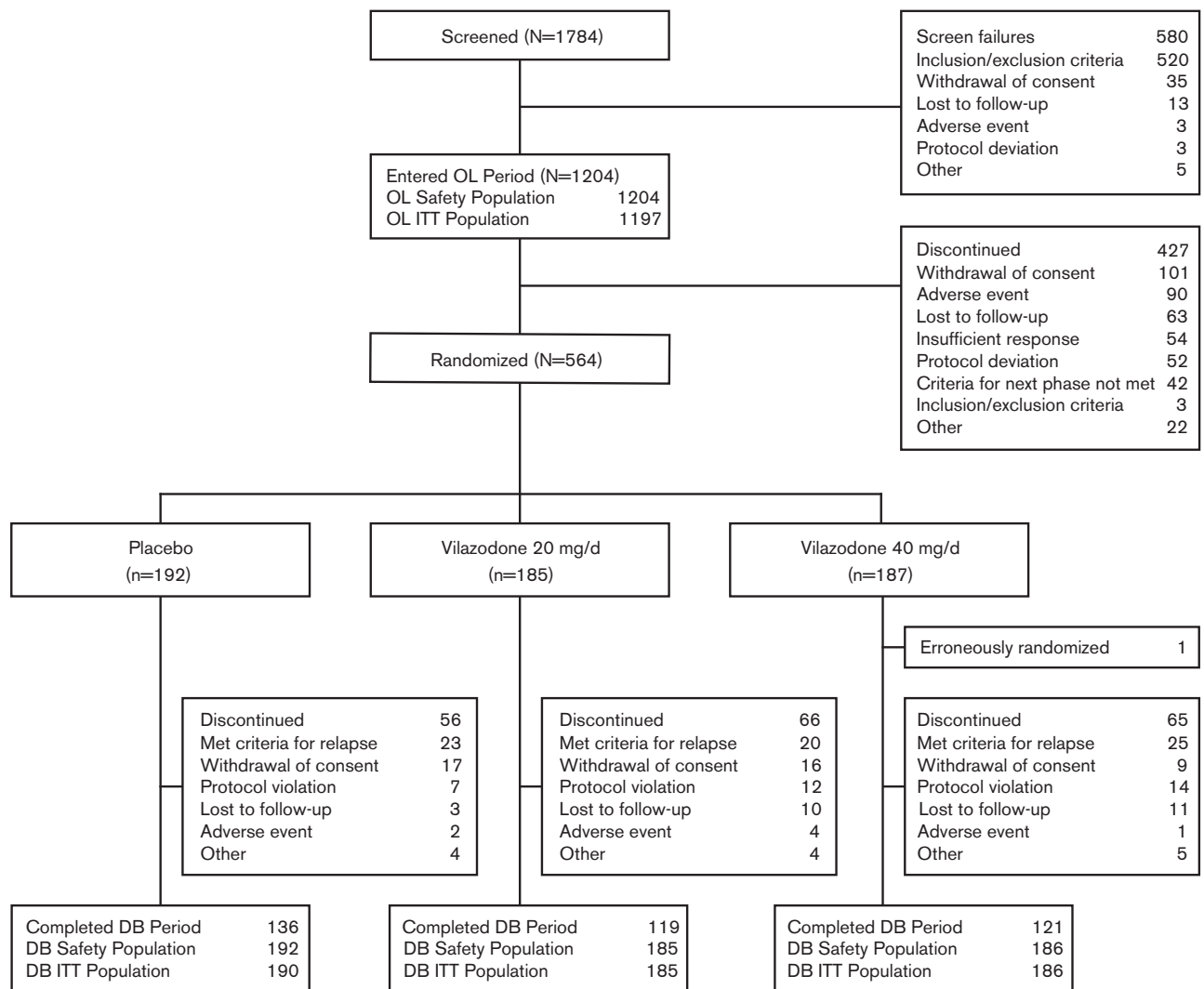
Open-label period

Mean MADRS total score decreased from baseline by ~20 points by week 8 of the open-label run-in treatment period and remained relatively stable thereafter. Post-hoc analysis of MADRS data showed that 77.6% of patients were responders ($\geq 50\%$ decrease in MADRS total score from baseline) at week 8 of the open-label treatment period (Supplementary Fig., Supplemental digital content 2A, <http://links.lww.com/ICP/A48>). At week 20, 72.8% of patients were treatment responders. Moreover, 63.9% of patients met remission criteria (MADRS total score ≤ 10) after receiving 20 weeks of open-label vilazodone treatment (Supplementary Fig., Supplemental digital content 2B, <http://links.lww.com/ICP/A48>). Mean change from baseline to week 20 in CGI-S score was -2.3 ; mean CGI-I score at week 20 was 1.9.

Double-blind period

There was no significant difference between either vilazodone group and placebo group for time to first relapse [hazard ratio (95% confidence interval): vilazodone 20 mg/day vs. placebo = 0.91 (0.51–1.63), vilazodone 40 mg/day vs.

Fig. 1



Patient disposition. One patient was erroneously randomized to vilazodone 40 mg/day and therefore not included in any double-blind safety or ITT analysis. DB, double-blind; ITT, intent-to-treat; OL, open-label.

placebo = 1.07 (0.61–1.87); Fig. 2]. The crude rate of patients who relapsed during the double-blind period was similar across treatment groups (placebo = 12.6%; vilazodone 20 mg/day = 11.4%; vilazodone 40 mg/day = 13.4%). Neither pre-defined sensitivity analysis for the primary efficacy endpoint demonstrated a significant difference between vilazodone (20 or 40 mg/day) and placebo. In addition, no significant differences were found between either dose of vilazodone and placebo for change from baseline in MADRS total score or CGI-S score, or in CGI-I score at the end of the double-blind period (Table 2).

Safety outcomes

Adverse events

An overall summary of AEs is presented in Table 3. During the open-label period, 79.1% of patients had at least one TEAE, and 8.1% of patients discontinued the study because

of an AE. The only TEAEs occurring in at least 10% of patients were diarrhea (29.6%), nausea (24.0%), and headache (14.0%). Most cases of diarrhea and nausea resolved within 2 weeks of onset (67.1 and 72.7%, respectively). During the double-blind period, the most common TEAEs in the vilazodone 20 and 40 mg/day groups were headache (8.1 and 9.7%, respectively), nasopharyngitis (8.6 and 8.1%), and diarrhea (7.0 and 8.1%); most cases of diarrhea resolved within 3 weeks of onset (placebo = 66.7%; vilazodone 20 mg/day = 84.6%; vilazodone 40 mg/day = 66.7%). During the double-blind treatment period, discontinuation because of AEs occurred more frequently in the vilazodone 20 mg/day group (3.2%) than in the placebo or vilazodone 40 mg/day groups (0.5%, each). No newly emergent AEs occurred in at least 10% of patients in any group (Table 3).

Table 1 Patient baseline characteristics (safety populations)

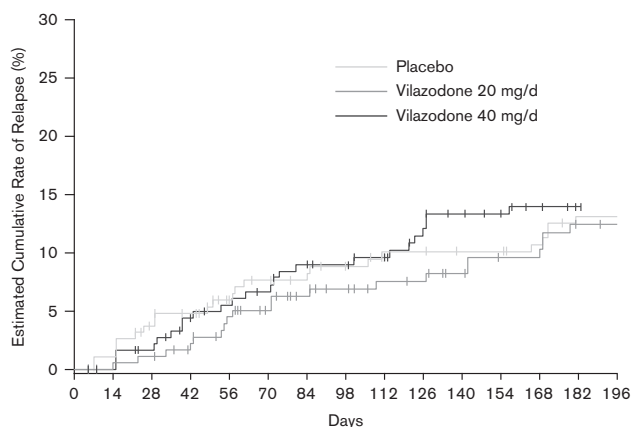
	Open-label Vilazodone 40 mg/day (n = 1204)	Double-blind		
		Placebo (n = 192)	Vilazodone 20 mg/day (n = 185)	Vilazodone 40 mg/ day (n = 186)
Demographics				
Age [mean (SD)] (years)	44.4 (12.7)	46.7 (11.9)	45.2 (12.6)	43.8 (12.0)
Female [n (%)]	767 (63.7)	116 (60.4)	113 (61.1)	126 (67.7)
White [n (%)]	938 (77.9)	149 (77.6)	147 (79.5)	155 (83.3)
BMI [mean (SD)] (kg/m ²)	28.1 (5.4)	28.6 (5.5)	27.7 (5.2)	28.5 (5.4)
MDD history				
MDD duration [mean (SD)] (years)	14.3 (10.4)	14.1 (10.6)	14.4 (10.8)	14.0 (10.3)
Recurrent episodes [n (%)] ^a	1200 (99.7)	192 (100.0)	184 (99.5)	183 (98.4)
Number of episodes [mean (SD)] ^b	4.7 (3.9)	4.8 (3.9)	4.6 (2.3)	4.4 (1.7)
Previous antidepressant treatment [n (%)]	244 (20.3)	44 (22.9)	42 (22.7)	38 (20.4)
MADRS total score [mean (SD)] ^c	31.7 (3.8)	4.6 (3.3)	4.8 (3.4)	5.0 (3.4)

DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision; ITT, intent-to-treat; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder.

^aDefined by DSM-IV-TR criteria for recurrent episode MDD.

^bIncluding the current major depressive episode.

^cAt baseline in the open-label ITT population (n = 1197); at randomization in the double-blind ITT population (placebo, n = 190; vilazodone 20 mg/day, n = 185; vilazodone 40 mg/day, n = 186).

Fig. 2

Kaplan-Meier curves of time to relapse in the double-blind period (ITT population). ITT, intent-to-treat.

Most TEAEs (>93%) that occurred during the study were judged as mild or moderate by the investigator. No deaths occurred during the study, and the only serious AE reported in more than patient was a suicide attempt (two patients during the open-label period). Neither case was judged by the investigator as related to treatment, and both patients were discontinued from the study (one each for suicide attempt and AE of abdominal pain upper/stomachache).

Laboratory tests, vital signs, and electrocardiograms

In the double-blind safety population, mean changes from baseline for liver enzyme/function, metabolic parameters, vital signs, or ECG parameters were similar across treatment groups and to the open-label safety population (Supplementary Table, Supplemental digital content 3, <http://links.lww.com/ICP/A49>). In both the open-label and double-blind treatment period there were few potentially clinically significant changes in laboratory parameters.

Table 2 Additional efficacy outcomes in the double-blind period (ITT population, MMRM)

Outcome at week 48	Placebo (n = 190)	Vilazodone 20 mg/day (n = 185)	Vilazodone 40 mg/day (n = 186)
MADRS total score (n)	135	118	120
LS change from DB baseline [mean (SE)] ^a	0.50 (0.40)	0.79 (0.42)	0.64 (0.41)
LSMD vs. placebo (95% CI)	–	0.29 (–0.83 to 1.42)	0.14 (–0.98 to 1.26)
P value	–	0.6104	0.8054
CGI-S score (n)	135	118	120
LS change from baseline [mean (SE)]	0.01 (0.06)	0.03 (0.06)	0.02 (0.06)
LSMD vs. placebo (95% CI)	–	0.01 (–0.15 to 0.17)	0.00 (–0.16 to 0.16)
P value	–	0.8667	0.9667
CGI-I score (n)	135	118	120
LS score [mean (SE)]	1.34 (0.05)	1.34 (0.06)	1.36 (0.06)
LSMD vs. placebo (95% CI)	–	0.00 (–0.15 to 0.15)	0.03 (–0.12 to 0.17)
P value	–	0.9892	0.7345

CGI, Clinical Global Impression of Improvement; CGI-S, Clinical Global Impression of Severity; CI, confidence interval; DB, double-blind; ITT, intent-to-treat; LS, least squares; LSMD, LS mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures; n, number of patients with available assessment at week 48.

^aBaseline was defined as the last nonmissing efficacy assessment before randomization.

Table 3 Adverse events (safety populations)

	Open-label Vilazodone 40 mg/day (n = 1204) [n (%)]	Double-blind		
		Placebo (n = 192) [n (%)]	Vilazodone 20 mg/day (n = 185) [n (%)]	Vilazodone 40 mg/day (n = 186) [n (%)]
Patients with any TEAE	952 (79.1)	103 (53.6)	101 (54.6)	115 (61.8)
Patients who discontinued because of AE ^a	97 (8.1)	1 (0.5)	6 (3.2)	1 (0.5)
Nausea	20 (1.7)	0	0	0
Diarrhea	15 (1.2)	0	0	0
Patients with any serious AE	13 (1.1)	4 (2.1)	5 (2.7)	1 (0.5)
Patients with NEAE ^b	NA	92 (47.9)	85 (45.9)	107 (57.5)
Deaths	0	0	0	0
Common TEAEs ^c				
Diarrhea	356 (29.6)	9 (4.7)	13 (7.0)	15 (8.1)
Nausea	289 (24.0)	7 (3.6)	6 (3.2)	9 (4.8)
Headache	169 (14.0)	9 (4.7)	15 (8.1)	18 (9.7)
Dizziness	115 (9.6)	6 (3.1)	2 (1.1)	2 (1.1)
Somnolence	59 (4.9)	3 (1.6)	0	5 (2.7)
Nasopharyngitis	88 (7.3)	14 (7.3)	16 (8.6)	15 (8.1)
Insomnia	72 (6.0)	7 (3.6)	7 (3.8)	1 (0.5)
Upper respiratory tract infection	70 (5.8)	12 (6.3)	12 (6.5)	10 (5.4)
Dry mouth	58 (4.8)	0	2 (1.1)	2 (1.1)
Fatigue	55 (4.6)	1 (0.5)	3 (1.6)	3 (1.6)
Vomiting	48 (4.0)	2 (1.0)	1 (0.5)	3 (1.6)
Weight increased	47 (3.9)	4 (2.1)	7 (3.8)	10 (5.4)
Abnormal dreams	46 (3.8)	2 (1.0)	2 (1.1)	3 (1.6)
Common NEAEs ^d				
Headache	NA	6 (3.1)	11 (5.9)	14 (7.5)
Nasopharyngitis	NA	10 (5.2)	10 (5.4)	10 (5.4)
Weight increased	NA	4 (2.1)	6 (3.2)	10 (5.4)
Upper respiratory tract infection	NA	7 (3.6)	8 (4.3)	7 (3.8)
Diarrhea	NA	2 (1.0)	6 (3.2)	7 (3.8)
Dizziness	NA	6 (3.1)	1 (0.5)	2 (1.1)
Insomnia	NA	6 (3.1)	5 (2.7)	1 (0.5)

AE, adverse event; NA, not applicable; NEAE, newly emergent AE; TEAE, treatment-emergent AE.

^aAEs associated with discontinuation reported in $\geq 1\%$ of patients in any group during any phase.

^bAn NEAE was a TEAE that occurred during the double-blind phase that was either not present before the start of the double-blind phase or was present but increased in severity during the double-blind phase.

^cTEAEs reported in $\geq 3\%$ of patients in any treatment group.

^dNEAEs reported in $\geq 3\%$ of patients in any treatment group.

Columbia-Suicide Severity Rating Scale suicidal ideation and behavior

Based on C-SSRS monitoring, suicidal ideation during the open-label treatment period occurred in 214 (17.8%) of 1204 patients [132/214 (61.7%) in the least severe category, 'wish to be dead']; suicidal behavior occurred in 10 (0.8%) of 1204 patients. During the double-blind period, suicidal ideation for placebo, vilazodone 20 mg/day, and vilazodone 40 mg/day occurred in 14 (7.3%) of 192, 16 (8.6%) of 185, and 22 (11.8%) of 186 patients, respectively; most instances (65.4%) were in the least severe category. No patients had suicidal ideation in the most severe category ('active suicidal ideation with specific plan and intent'), and two (3.8%) patients (one each, placebo and vilazodone 40 mg/day) had active suicidal ideation with some intent to act but without specific plan. During the open-label period,

suicidal ideation was reported as an AE in four (0.3%) patients, and suicide attempt was reported in two (0.2%) patients. During the double-blind period, suicidal ideation was reported as an AE in one patient, and there were no reports of AEs of a suicide attempt.

Discussion

The randomized withdrawal design of this study is considered a standard for demonstrating the effectiveness of long-term antidepressant treatment, following the precedent set by other drugs that have been approved by the US Food and Drug Administration for maintenance treatment in patients with MDD (Kornstein *et al.*, 2006; Perahia *et al.*, 2009). In this study, there was no significant difference in time to the first relapse between patients who had received 20 weeks of open-label vilazodone and were withdrawn from active treatment (i.e. randomized to placebo) and those who continued receiving active treatment (randomized to vilazodone 20 or 40 mg/day). This lack of worsening in patients who were withdrawn from active treatment was somewhat surprising, as it was expected that a significantly greater number of placebo-treated patients would relapse.

Although no direct comparisons can be made, relapse rates in this study were notably lower than in other relapse studies (Supplementary Table, Supplemental digital content 4, <http://links.lww.com/ICP/A50>), including a review of 15 maintenance trials (mean relapse, placebo = 37%; drug = 18%) (Borges *et al.*, 2014). One important factor that may have contributed to low relapse rates and lack of significant difference in the primary efficacy parameter was the high magnitude of response to vilazodone during open-label treatment. Inclusion in this study required a MADRS total score of at least 26, and the mean score at baseline of the open-label period was 31.7. At randomization, however, the mean MADRS total score was ~ 5 in all treatment groups, representing a considerably lower score than that used to determine eligibility for randomization. A post-hoc analysis of MADRS data from the open-label period showed that over three-quarters of patients achieved predefined response criteria after 8 weeks of treatment. This response rate is substantially higher than the roughly 50% response rate seen in other antidepressant maintenance trials (Borges *et al.*, 2014) and may be because of the high percentage of patients ($\sim 80\%$) that entered this study as treatment naive.

Study design factors, including duration of the open-label and double-blind periods, stabilization criteria, and relapse criteria, may have additionally contributed to the failure to detect a significant difference in relapse rates between placebo-treated and vilazodone-treated patients. Although a previous analysis of maintenance trials found no relationship between the length of open-label periods and relapse rate, most of the studies (12 of 15) had an open-label phase less than or equal to 12 weeks leading to little

opportunity to detect a difference (Borges *et al.*, 2014). Further, only eight studies included a stabilization phase; of these, symptomatic stability was present for more than 3 weeks in only one study. Recently, the Food and Drug Administration began recommending that maintenance studies of antidepressants include a 12-week stabilization period after patients achieve treatment response (Borges *et al.*, 2014). As a result, the present study consisted of an 8-week run-in followed by a 12-week stabilization phase before randomization. This extended open-label period led to longer exposures at effective therapeutic doses, which is especially noteworthy considering longer exposure to antidepressant agents after the initial therapeutic response has been associated with lower rates of relapse (Thase *et al.*, 1992; American Psychiatric Association, 2010). Given the high response rate at the end of the open-label treatment period, a longer double-blind phase may have been required to see separation in relapse rates between placebo-treated and vilazodone-treated patients. The long stabilization period may have also increased the risk of losing some patients to early relapse. However, this stabilization period also ensured that randomized patients were true responders and were not just experiencing a transient response. In addition, varying relapse criteria used in maintenance studies can influence time to and rates of relapse. As investigator's judgement was not a criterion for relapse in this study, it is possible that patients who would have been considered to have relapsed in a real-world setting were not characterized as relapsed within this study.

The incidence and types of TEAEs seen in the open-label period were consistent with results from previous randomized, placebo-controlled trials of vilazodone in patients with MDD (Rickels *et al.*, 2009; Khan *et al.*, 2011; Croft *et al.*, 2014; Mathews *et al.*, 2015). The most commonly reported TEAEs in the open-label period (i.e. diarrhea, nausea, headache, dizziness) occurred in less than 5% of placebo-treated patients in the double-blind period. Patients who remained on vilazodone continued to experience these TEAEs, although at a lower incidence than in the open-label period (except for a headache in the vilazodone 20 mg/day group). Providing information about TEAEs commonly associated with vilazodone, along with appropriate management of these side effects as needed, may help patients adhere to treatment, which is an important component of any long-term treatment strategy.

Overall, the data in this study suggest that responsiveness to treatment during the open-label phase had an impact on outcomes in the double-blind period. Although no definitive conclusions can be drawn from the double-blind period about the effects of vilazodone on relapse prevention, results from the open-label period suggest that treatment with an effective antidepressant for an adequate length of time may be an important strategy in reducing the risk of relapse.

Limitations of this study included generalizability to a broader patient population because of eligibility criteria, including the exclusion of patients with comorbid psychiatric disorders or a history of a nonresponse to antidepressant treatment. The inclusion of a 12-week stabilization phase likely helped identify patients who were true responders to vilazodone; however, it may have also censored patients who relapsed early and were not randomized. Additional study design factors such as stabilization criteria and relapse criteria may have also limited the ability to detect efficacy in this study. Moreover, since ~35% of patients did not continue from the open-label treatment period, efficacy and safety outcomes could have been affected by attrition. In addition, without an SSRI-only active comparator during the open-label period, it is difficult to elucidate whether the response to treatment was specific to vilazodone or simply due to the relatively long duration of treatment. Further, given the suppression of MADRS total scores to ~5 during open-label treatment, the withdrawal period of 28 weeks may not have been long enough to detect differences in time to relapse, and the study may have been underpowered based on the substantially lower-than-expected relapse rates. Indeed, this may be considered more of a failed study than a negative study.

Conclusion

No conclusions can be drawn regarding the effect of vilazodone on relapse prevention in adults with MDD. Following randomization, patients who continued on vilazodone failed to separate from patients who were randomized to placebo. Long-term treatment with vilazodone was well tolerated, and no new safety signals were noted.

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Conflicts of interest

Suresh Durgam, Carl Gommoll, Raffaele Migliore, Changzheng Chen, and Michelle Aguirre acknowledge a potential conflict of interest as full-time employees of Allergan plc. Michael E. Thase declares a potential conflict of interest in his role as advisor or consultant for the following companies: Alkermes Inc.; Allergan plc; AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Cerecor Inc.; Fabre-Kramer Pharmaceuticals Inc.; Forest Laboratories Inc. (an Allergan affiliate); Gerson Lehrman Group; GlaxoSmithKline; Guidepoint Global, LLC; Eli Lilly and Company; H. Lundbeck A/S; MedAvante Inc.; Merck & Co. Inc.; moksha8 Pharmaceuticals Inc.;

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References

- American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision. Washington, DC: American Psychiatric Association.
- American Psychiatric Association (2010). *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*, 3rd ed. Arlington, VA: American Psychiatric Association.
- Borges S, Chen YF, Laughren TP, Temple R, Patel HD, David PA, *et al.* (2014). Review of maintenance trials for major depressive disorder: a 25-year perspective from the US Food and Drug Administration. *J Clin Psychiatry* **75**:205–214.
- Croft HA, Pomara N, Gommoll C, Chen D, Nunez R, Mathews M (2014). Efficacy and safety of vilazodone in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* **75**:e1291–e1298.
- Judd LL, Schettler PJ, Rush AJ, Coryell WH, Fiedorowicz JG, Solomon DA (2015). A new empirical definition of major depressive episode recovery and its positive impact on future course of illness. *J Clin Psychiatry* **77**:1065–1073.
- Khan A, Cutler AJ, Kajdasz DK, Gallipoli S, Athanasiou M, Robinson DS, *et al.* (2011). A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. *J Clin Psychiatry* **72**:441–447.
- Kornstein SG, Bose A, Li D, Saikali KG, Gandhi C (2006). Escitalopram maintenance treatment for prevention of recurrent depression: a randomized, placebo-controlled trial. *J Clin Psychiatry* **67**:1767–1775.
- Mathews M, Gommoll C, Chen D, Nunez R, Khan A (2015). Efficacy and safety of vilazodone 20 and 40 mg in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *Int Clin Psychopharmacol* **30**:67–74.
- Nierenberg AA, Petersen TJ, Alpert JE (2003). Prevention of relapse and recurrence in depression: the role of long-term pharmacotherapy and psychotherapy. *J Clin Psychiatry* **64** (Suppl 15):13–17.
- Perahia DG, Maina G, Thase ME, Spann ME, Wang F, Walker DJ, Detke MJ (2009). Duloxetine in the prevention of depressive recurrences: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* **70**:706–716.
- Rickels K, Athanasiou M, Robinson DS, Gibertini M, Whalen H, Reed CR (2009). Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* **70**:326–333.
- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, *et al.* (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* **163**:1905–1917.
- Segal ZV, Pearson JL, Thase ME (2003). Challenges in preventing relapse in major depression. Report of a National Institute of Mental Health Workshop on state of the science of relapse prevention in major depression. *J Affect Disord* **77**:97–108.
- Sheehan DV, Harnett-Sheehan K, Spann ME, Thompson HF, Prakash A (2011). Assessing remission in major depressive disorder and generalized anxiety disorder clinical trials with the discan metric of the Sheehan disability scale. *Int Clin Psychopharmacol* **26**:75–83.
- Shelton RC (2001). Steps following attainment of remission: discontinuation of antidepressant therapy. *Prim Care Companion J Clin Psychiatry* **3**:168–174.
- Thase ME, Simons AD, Mcgeary J, Cahalane JF, Hughes C, Harden T, Friedman E (1992). Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. *Am J Psychiatry* **149**:1046–1052.