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Vortioxetine (Lu AA21004) 5 mg in generalized anxiety disorder: Results of an 8-week randomized, double-blind, placebo-controlled clinical trial in the United States

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Abstract
The goal of the current clinical study, conducted in the United States (US), was to evaluate the efficacy and tolerability of vortioxetine 5 mg vs placebo in adults with a primary diagnosis of generalized anxiety disorder (GAD; HAM-A total score $\geq$20 and MADRS score $\leq$16). Subjects were randomized (1:1) to receive vortioxetine 5 mg (n=152) or placebo (n=152) for 8 weeks. Efficacy was assessed using change from baseline in HAM-A total scores after 8 weeks of treatment compared with placebo, using mixed-model repeated measures (MMRM) analyses. Adverse events (AEs) were assessed throughout the study. A total of 304 subjects were randomized (mean age, 41.2 years). After 8 weeks of treatment, there was no statistically significant difference in the reduction in HAM-A total score from baseline between the Vortioxetine (n=145) and placebo (n=145) groups. There were no statistically significant differences in any key secondary efficacy outcome between vortioxetine and placebo. Factors potentially contributing to the differences between the results of this study and those of one of identical design conducted outside the US are discussed. The most common treatment-emergent AEs were nausea, headache, dizziness, and dry mouth. Nausea was more frequently reported in the vortioxetine group (25% vs 4.6% for the placebo group). Most AEs were mild to moderate in severity. In conclusion, in this trial, vortioxetine did not improve symptoms of GAD (compared with placebo) over 8 weeks of treatment. Vortioxetine was well tolerated in this study.

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1. Introduction

The symptoms of depression and anxiety respond to treatment with similar agents, suggesting that some shared neuropathology exists between the two conditions. Selective serotonin (5-HT) reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are indicated for the treatment of generalized anxiety disorder (GAD) and social anxiety disorder, as well as major depressive disorder (MDD). Vortioxetine is a member of a new, structurally and functionally distinct chemical class of psychotropics, the bis-aryl-sulfanylamines. This investigational multimodal antidepressant is believed to work through a combination of two pharmacological modes of action: reuptake inhibition and receptor activity. Preclinical data show that vortioxetine functions as a 5-HT_3 and 5-HT_7 receptor antagonist, a 5-HT_{1A} receptor agonist, a 5-HT_{1B} receptor partial agonist, and an inhibitor of the 5-HT transporter in vitro. In vivo nonclinical studies have demonstrated that vortioxetine enhances levels of the neurotransmitters serotonin, noradrenaline, dopamine, acetylcholine, and histamine in the ventral hippocampus and the medial prefrontal cortex of the brain (Bang-Andersen et al., 2011; Mørk et al., 2011).

The effects of vortioxetine have been studied in MDD and GAD patients. A proof-of-concept trial conducted in 11 countries outside the United States (US) evaluated the efficacy of vortioxetine 5 mg and 10 mg in subjects with MDD (Alvarez et al., 2011). Compared with placebo, both doses produced significant reductions from baseline on the Montgomery Åsberg Depression Scale (MADRS) (Montgomery and Åsberg, 1979) total scores at Week 6 ($P<0.0001$ for both comparisons). In an 8-week active-referenced trial evaluating 2.5, 5, and 10 mg vortioxetine in MDD subjects, also conducted outside the US (Baldwin et al., 2011b), there was no significant reduction from baseline in MADRS total score for any of the vortioxetine arms or the duloxetine-reference arm on the primary analysis of last observation carried forward (LOCF). However, the secondary analysis, using mixed-model repeated measures (MMRM) of the primary endpoint (mean change from baseline in MADRS total score), and most secondary endpoints suggested likely efficacy for vortioxetine 5 mg and 10 mg. In another 8-week MDD non-US trial, treatment with vortioxetine resulted in significant reductions from baseline in the 24-Item Hamilton Depression scale (HAM-D24) total score compared with placebo (-15.42 ± 0.743 with vortioxetine 5 mg and -16.23 ± 0.755 with vortioxetine 10 mg vs -11.30 ± 0.738 with placebo; $P<0.001$) (Henigsberg et al., 2011). In a 6-week MDD study conducted in the US, vortioxetine 5 mg did not differ significantly from placebo in reducing depression symptoms (Jain et al., submitted for publication). The reasons for the different outcomes are not clear. However, as reported in the Food and Drug Administration database, there has been a decline in the proportion of positive-outcome MDD trials in recent years (Khin et al., 2011).

In all four of these MDD trials, including the studies that failed on the primary efficacy measure, vortioxetine 5 mg and 10 mg improved HAM-D24 total scores in the subgroup of subjects with high baseline anxiety (HAM-A $\geq$20) (Alvarez et al., 2011; Baldwin et al., 2011b; Jain et al., submitted for publication; Henigsberg et al., 2011). In the initial proof-of-concept trial, vortioxetine significantly improved HAM-A scores ($P<0.01$ for both doses) after 6 weeks (Alvarez et al., 2011). In both 8-week trials, all doses of vortioxetine significantly reduced HAM-A total scores at end of treatment on the MMRM analysis. At the end of the second 6-week trial, the changes in HAM-A scores (vs baseline) were statistically similar for vortioxetine 5 mg and placebo (Jain et al., submitted for publication). Preclinical studies have shown that, in addition to efficacy in models of depression, vortioxetine exerts anxiolytic-like effects in models of conditioned fear (Mørk et al., 2011).

Based on these preliminary data, the present phase 3 trial was conducted in the US to evaluate the safety and efficacy of a fixed dose of 5 mg vortioxetine in subjects with a primary diagnosis of GAD. A second study of identical design, also part of the development program for vortioxetine, was performed in parallel with the current trial in several countries outside the US. The results of the second GAD trial are reported in a paper by Bidzan et al. (in preparation). Herein we present the results of the US trial and discuss the different outcomes of the two studies.

2. Experimental procedures

2.1. Study design

Study 310 was a phase 3, multicenter, double-blind, placebo-controlled, parallel-group study of vortioxetine 5 mg, fixed-dose, once-daily treatment in adults with GAD. The 8-week trial was conducted at 36 sites in the US. The study was conducted in accordance with the principles of the United States Food and Drug Administration (FDA) Code of Federal Regulations (CFR) Part 2, Good Clinical Practice (ICH, 1996) and the Declaration of Helsinki (World Medical Association (WMA), 2008). Local research Ethics Committees approved the trial design, and eligible patients provided written informed consent before participating in the trial.

Men and non-pregnant women $\geq$18 years of age were included if they met all of the following criteria: primary diagnosis of GAD according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition Text Revision (DSM-IV-TR) (classification code 300.02) (American Psychiatric Association, 2000); Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959) total score $\geq$20, HAM-A score $\geq$2 on both Item 1 (anxious mood) and Item 2 (tension); and MADRS (Montgomery and Åsberg, 1979) total score $\leq$16 at screening and baseline.

Subjects were excluded from the trial if they had any current psychiatric disorder other than GAD, or had a presence or history of a clinically significant neurological disorder (e.g., epilepsy) or neurodegenerative disorder (e.g., Alzheimer's disease, Parkinson's disease). Also excluded were subjects who were considered by the investigator to pose a significant risk of suicide; those who had a score $>$5 on Item 10 (suicidal thoughts) of the MADRS or had made a suicide attempt in the previous 6 months; and those whose GAD had previously failed to respond to adequate treatment with SSRIs and/or serotonin-norepinephrine reuptake inhibitors (SNRIs).

Eligible subjects entered a screening period (lasting from 2 to 10 day) before randomization. At the screening visit, subjects underwent a physical examination, clinical laboratory testing, a 12-lead electrocardiogram (ECG), and psychological assessments including the MINI International Neuropsychiatric Interview (Sheehan et al., 1998), the 24-Item Hamilton Depression Scale (HAM-D24) (Hamilton, 1959), MADRS (Montgomery and Åsberg, 1979), and the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2007). Evaluation visits occurred every week for the first 2 weeks of treatment, and then every 2 weeks until the end of the study.

2.2. Study treatments

Eligible subjects were randomized (1:1) to receive 5 mg of vortioxetine or placebo, orally, once daily, during the 8-week double-blind treatment period. The 5-mg dose was selected based on its favorable efficacy and safety outcomes in subjects with MDD (Alvarez et al., 2011). Placebo consisted of lactose monohydrate and magnesium stearate encapsulated in oval brownish-orange capsules identical to those containing the active study drug. An interactive voice-response system (IVRS) was used to manage the dispensation of study medication, and all participants were blinded to treatment assignment throughout the study.

2.3. Efficacy and outcomes measures

Prior to randomization, baseline measurements were obtained for HAM-A (Hamilton, 1959), Clinical Global Impression-Severity (CGI-S) (Guy, 1976), patient-reported Hospital Anxiety and Depression (HAD) scale (Zigmond and Snaith, 1983), the 36-Item Short-Form Health Survey (SF-36) (Ware and Sherbourne, 1992), and the Sheehan Disability Scale (SDS) (Sheehan et al., 1996; Sheehan and Sheehan, 2008). HAM-A, CGI-S, and CGI-I (Clinical Global Impression-Improvement of illness scale) (Bech et al., 1986) were measured at every evaluation visit. Other measures were assessed as follows: HAD at Weeks 1, 4, and 8; SF-36 at Weeks 2, 4, and 8; and SDS at Weeks 1, 2, 4, and 8.

2.4. Safety measures

Spontaneously reported adverse events (AEs) were recorded at each visit, with investigators determining severity and relationship to the study drug. Physical examinations were performed at screening and Week 8. Weight was measured at screening, baseline, Week 4, and Week 8 (or study completion/withdrawal). Vital signs were monitored at every visit. Clinical laboratory tests (hematology, serum chemistry, and urinalysis) and 12-lead ECGs were performed at Week 4 and Week 8 (or study completion/withdrawal), in addition to the screening visit. The C-SSRS was administered at every visit.

2.5. Statistical analysis

2.5.1. Analysis sets

The safety set comprised all individuals who were randomized and received at least one dose of study medication. The full analysis set (FAS) included all individuals who were randomized, received at least one dose of study medication, and had at least one valid post-baseline efficacy value for assessment of the primary efficacy endpoint.

2.5.2. Statistical methods

The primary efficacy endpoint was the change from baseline in HAM-A total score at 8 weeks of treatment. Comparisons between vortioxetine 5 mg and placebo were performed on the FAS at all assessment points, using MMRM. To confirm results of the primary analysis (MMRM), the change from baseline in HAM-A total score after 8 weeks (primary endpoint) was also analyzed using analysis of covariance (ANCOVA), with treatment and center as fixed factors and baseline HAM-A total score as covariate, and based on the LOCF and the observed case (OC; i.e., only values actually measured at that time point) data sets.

Serving as secondary endpoints, change from baseline in HAD anxiety and HAD Depression subscales and SF-36 domain subscores were analyzed as continuous variables (MMRM on OC; ANCOVA on LOCF and OC). This was done in a manner similar to that used to evaluate the primary endpoint, where the relevant baseline value was used as the covariate adjustment in the MMRM and ANCOVA analyses.

CGI-S and CGI-I were also analyzed as continuous variables (MMRM on OC; ANCOVA on LOCF and OC), as described for the primary variable, with baseline CGI-S used as the covariate adjustment in the MMRM and ANCOVA analyses of CGI-I.

HAM-A response (defined as a decrease of $\geq$50% from baseline in HAM-A total score) and remission (defined as a HAM-A total score of $\leq$7) rates were analyzed at all time points by logistic regression, adjusting for baseline score and treatment using both LOCF and OC data.

To control the overall type I error at the level of 0.05, the primary endpoint and the six key secondary endpoints were tested in a prespecified sequential order, as follows:

1. Change from baseline in HAM-A total score at Week 8 (MMRM).
2. Change from baseline in HAD anxiety subscore at Week 8 (MMRM).
3. CGI-I at Week 8 (MMRM).
4. Change from baseline in SDS total score at Week 8 (MMRM).
5. HAM-A response rate at Week 8 (LOCF).
6. Change from baseline in HAM-A total score at Week 8 in the subgroup of subjects with HAM-A total score $\geq$25 (MMRM) at baseline.
7. Change from baseline in SF-36 social functioning subscore at Week 8 (MMRM).

As soon as the test with an endpoint was not significant at 0.05, the testing procedure was stopped for all subsequent endpoints. The nominal *P* values, with no adjustment for multiplicity, were reported for all comparisons of vortioxetine and placebo. The phrase "separation from placebo" was used to describe findings with nominal *P* values $\leq$ 0.05.

AEs were coded by system organ class (SOC) and preferred term (PT) using the *Medical Dictionary for Regulatory Activities* (MedDRA) Version 11.1.

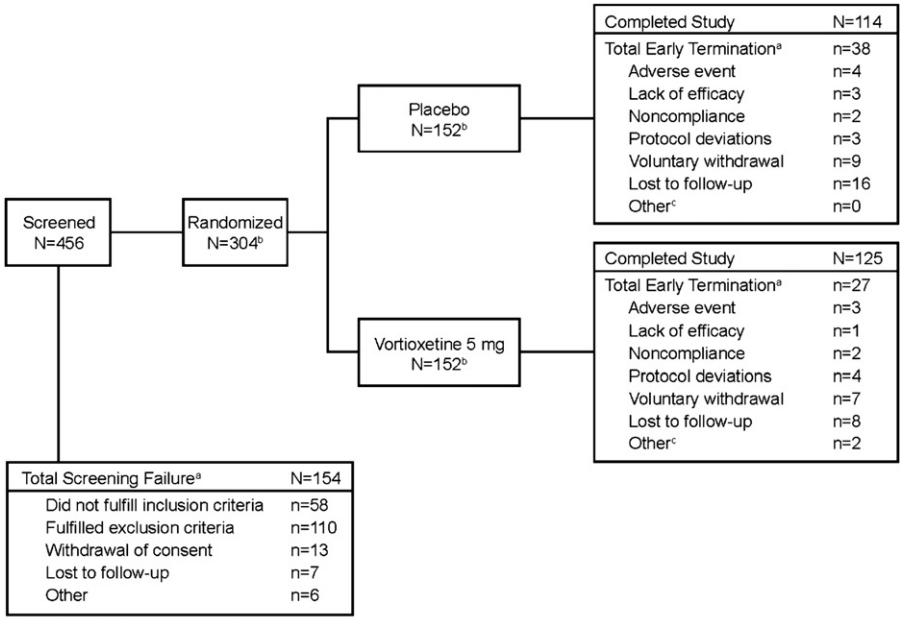
3. Results

3.1. Subjects

The study began in June 2008 and concluded in February 2009. Of the 456 subjects who were screened, 304 were randomized (Figure 1). The safety set comprised 299 subjects who received at least one dose of study drug. (One patient in the placebo group and four in the vortioxetine group did not receive study medication.) As shown in Table 1, demographics and baseline characteristics were similar for the two study groups. Most subjects were female (65.8%) and white (83.6%), and the mean age was 41.2 years. The mean baseline HAM-A score was 24.7. Mean baseline HAD Depression subscale and MADRS scores confirmed that the overall population had an acceptably low level of depressive symptoms. Only 25% of the subjects had been treated previously for GAD. Almost all of the previously treated subjects had received medication for treatment of GAD (32 of 37 subjects in each treatment group).

3.2. Primary efficacy outcomes

The mean decrease from baseline HAM-A total score at Week 8 was 13.16 ($\pm$0.655) in the placebo group and 12.57



[a] More than one reason for screening failure or early termination may have been reported per subject.
[b] N=304 includes 5 subjects who were randomized but not treated.
[c] Other reasons for early termination: pregnancy, new job schedule.

Figure 1 Subject disposition.

($\pm$0.646) in the vortioxetine group (Figure 2). The difference was not significant (0.59$\pm$0.911; 95% CI, from $-$1.20 to 2.38; P=.518). This finding was confirmed by the ANCOVA analyses.

3.3. Secondary efficacy outcomes

No statistically significant differences were observed for any secondary endpoint (Table 2). HAM-A response rates at Week 8 were 50% in the placebo group and 53% in the vortioxetine group (nominal P=0.602). HAM-A remission rates at Week 8 were 22% in the placebo group and 26% in the vortioxetine group (nominal P=0.517).

3.4. Subgroup analysis

To determine whether previous experience with drug treatment for GAD may affect response to treatment with vortioxetine, a post-hoc analysis was conducted. Among this subgroup of previously treated patients, the mean change from baseline in HAM-A score was $-$13.1 for those who received vortioxetine (n=37) and $-$10.1 for those who received placebo (n=37; P=.091). Among the treatment-naïve subjects, the mean change from baseline in HAM-A score was $-$13.0 for subjects who received vortioxetine (n=108) and $-$13.4 for the placebo group (n=107; P=.712).

3.5. Safety outcomes

Treatment-emergent AEs that occurred in $\geq$5% of either treatment group are shown in Table 3. The most frequently reported were nausea, headache, dizziness, and dry mouth. The majority of AEs were considered by the investigators to be mild or moderate in intensity.

Three serious AEs (SAEs) were reported among placebo recipients. Two of these were spontaneous abortions; both were considered by the investigators to be related to the study drug. The third was a prostate infection deemed unrelated to the study drug. The only SAE in the vortioxetine group was death (n=1) from morphine toxicity, which was determined to be unrelated to study treatment.

There were no differences between study groups in any of the CSSR-S items.

Of the 65 (21.4%) subjects who discontinued early from the study (including five who were randomized but not treated), six subjects (two on placebo, four on vortioxetine 5 mg) discontinued because of AEs (total of nine AEs). The AEs resulting in discontinuation were moderate to severe in intensity; two of the nine events (both in the active-treatment group) were considered unrelated to the study medication. No clinically important trends in physical findings, weight, or vital signs were observed between the two groups, nor were there any clinically significant differences in laboratory or ECG results.

4. Discussion

This trial did not show any clinical advantage for the 5-mg dose of vortioxetine, relative to placebo, for the treatment of subjects with GAD. It is possible that the 5-mg dose, which was based on experience in treating MDD, was too low to be effective for treatment of GAD or that the drug is not effective in treating symptoms of GAD. However, these explanations may not be applicable because the results of the current trial differ from those of a non-US trial of identical design that involved 301 subjects with GAD (Bidzan, in preparation). In the non-US trial, statistically significant improvement in the primary and secondary efficacy endpoints was attained with vortioxetine 5 mg vs

Table 1 Demographics and baseline characteristics.

Characteristic	Study group	
	Placebo ($n=152$)	Vortioxetine 5 mg ($n=152$)
Gender		
Male, *n* (%)	55 (36.2)	49 (32.2)
Age (year), mean (SD)	41.4 (12.81)	41.0 (14.05)
Race, *n* (%)		
Caucasian (White, including Hispanic)	131 (86.2)	123 (80.9)
Black	17 (11.2)	24 (15.8)
Asian	2 (1.3)	3 (2.0)
American Indian or Alaska native	0	2 (1.3)
Native Hawaiian/ Other Pacific Islander	2 (1.3)	0
Ethnicity		
Hispanic/Latino, *n* (%)	24 (15.8)	26 (17.1)
Duration of GAD[a] (mo), median (range)	12.0 (1–806)	12.5 (1–600)
Previously treated for GAD[a], *n* (%)	37 (24.5)	37 (25.0)
Previously treated with medication[a], *n* (%)	32 (21.2)	32 (21.6)
Previously treated with an SSRI[a], *n* (%)	21 (13.9)	25 (16.9)
HAM-A total score		
Mean (SD)	24.6 (3.6)	24.7 (3.8)
HAM-A $\geq$25, *n* (%)	73 (48.0)	71 (46.7)
CGI-S, mean (SD)	4.3 (0.5)	4.3 (0.5)
HAD Anxiety subscale, mean (SD)	13.5 (3.1)	13.8 (3.4)
HAD Depression subscale, mean (SD)	8.5 (3.8)	8.1 (3.9)
MADRS total score, mean (SD)	11.8 (3.0)	12.1 (2.9)
SF social functioning scale	50.92 (2.30)	49.48 (2.34)

Abbreviations: GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Scale; CGI-S, Clinical Global Impression-Severity of illness scale; HAD, Hospital Anxiety and Depression Scale; MADRS, Montgomery Åsberg Depression Rating Scale; SF, Short Form.

[a]Based on the safety set: placebo n=151, vortioxetine n=148.

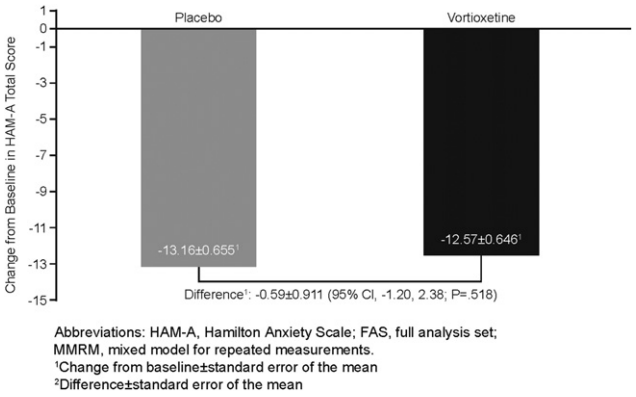


Figure 2 Least-squares mean change from baseline in HAM-A total score at week 8 (full-analysis set, MMRM).

placebo. In contrast, the results of the present study did not show a positive trend for any of the efficacy endpoints. Thus, increasing the sample size several folds would not have changed the outcome of the study. Moreover, both this and the non-US studies randomized the sample number ($N \geq 300$) calculated to achieve at least 85% power detect a difference of 2.5 between the vortioxetine 5 mg dose vs placebo by a 2-sample t-test with a 0.05 2-sided significance level. These factors also argue against that the larger placebo response in the US study population obscuring a statistically significant difference. However, because no positive control was included in the present trial, it is impossible to determine whether the lack of treatment effect is attributable to the study drug or to issues inherent in the trial itself.

We investigated several clinical factors that may have contributed to the failure of the current trial. The mean baseline HAM-A total scores in the present study were slightly lower than those of the companion non-US trial (24.7 ± 3.69 in the US trial; 26.6 ± 3.94 in the non-US trial), and fewer subjects in the US trial had a baseline HAM-A score $\geq$25 (47% vs 54%). If the overall lack of efficacy were due simply to a smaller proportion of subjects having severe symptoms of anxiety in the current study, one would still expect significant improvement with Lu AA21004 in the subset of severely ill individuals. A prespecified analysis of outcomes in the group with baseline HAM-A $\geq$25 in the US trial did not show a treatment effect for vortioxetine. As was observed in the vortioxetine MDD trials,

Studies with venlafaxine and fluoxetine suggest that the probability of response correlates inversely with the duration of GAD (Baldwin et al., 2011a). Even though the duration of GAD was longer in the US population (median, 12.3 months [range, 1–806 months]) than in the non-US population (median, <8 months [range, 1–120 months]), it seems unlikely that this difference contributed to the dissimilar outcomes. Moreover, we found no evidence that use of concomitant medications or differences in dose titration schedules were contributing factors.

A smaller percentage of subjects in the US trial had been treated previously for GAD (25% vs 43%). In a post-hoc analysis of data from this study, no significant difference was found in the mean change-from-baseline HAM-A scores between vortioxetine and placebo, regardless of whether GAD had been treated previously. A similar analysis of results in the non-US subjects showed significantly greater improvement in HAM-A scores with vortioxetine vs placebo in the treatment-naïve population, but not in the subjects treated previously (Bidzan, in preparation). The relevance of this result to the overall difference in outcomes between the two trials is not clear.

The discontinuation rate was higher in the US study than in the non-US study. However, if a higher dropout rate is considered a reason for study failure, the MMRM method of

Table 2 Secondary efficacy variables at Week 8 (MRMM).

Key secondary efficacy variables	Study group	
	Placebo ($n=144$)	Vortioxetine 5 mg ($n=145$)
HAD anxiety subscore		
Baseline (n)	140	144
LS mean (SE)	13.60 (0.291)	14.06 (0.294)
Change from baseline at Week 8 (n)	111	124
LS mean (SE) (MMRM)[a]	−4.84 (0.392)	−5.06 (0.384)
P value (active vs placebo)		0.685
CGI-I score		
Baseline (n)[b]	144	145
LS mean (SE)	4.36 (0.041)	4.37 (0.042)
Mean at week 8 (N)	113	124
LS mean (SE) (MMRM)	2.25 (0.101)	2.25 (0.099)
P value (active vs placebo)		0.984
SDS total score:		
Baseline (n)	124	121
LS mean (SE)	15.04 (0.668)	16.10 (0.691)
Change from baseline at Week 8 (n)	91	97
LS mean (SE) (MMRM)	−6.68 (0.618)	−6.35 (0.616)
P value (active vs placebo)		0.703
HAM-A response[c] rate		
Week 8 (n)	144	145
Subjects with response (response rate [%]) (LOCF)	72 (50.0)	77 (53.1)
Odds ratio (active vs placebo)		1.131
P value (active vs placebo)		0.602
HAM-A total score in subgroup with HAM-A total score $\geq$25 at baseline		
Baseline (n)	73	71
LS mean (SE)	27.22 (0.343)	27.59 (0.333)
Change from baseline at week 8 (n)	59	63
LS mean (SE) in subgroup (MMRM)	−14.04 (1.104)	−14.05 (1.080)
P value (active vs placebo subgroup)		0.995
SF-36 social functioning subscore		
Baseline (N)	139	143
LS mean (SE)	50.92 (2.295)	49.48 (2.337)
Change from baseline at Week 8 (n)	113	125
LS mean (SE) (MMRM)	17.43 (2.133)	18.44 (2.091)
P value (active vs placebo)		0.731

[a]Analysis used.
[b]CGI-S score used as baseline value.
[c]Response was defined as a HAM-A total score decrease from baseline of >50%.

analysis would adjust for changes in scores due to subjects who discontinued, and this is not seen in the results.

Other demographic characteristics may have contributed to the different outcomes. The study population of the US trial was racially diverse, whereas the population of the non-US trial was almost entirely Caucasian. The racial diversity may have introduced differences in response and remission rates due to genetic differences that were not assessed. For example, in the STAR*D study, non-Caucasians were significantly less likely to achieve remission (Trivedi et al., 2006). Moreover, a recent study showed that single nucleotide polymorphisms (SNPs) in the *BDNF* and *HTR2A*

Table 3 Adverse events (AEs) reported in ≥5% of subjects in either treatment group (safety set).

SOC term/preferred term[a]	Study group			
	Placebo (n=151)		Vortioxetine 5 mg (n=148)	
	Events	Subjects (%)	Events	Subjects (%)
Total no. of AEs	209	93 (61.6)	296	109 (73.6)
Gastrointestinal disorders				
Nausea	7	7 (4.6)	40	37 (25.0)
Dry mouth	5	5 (3.3)	12	12 (8.1)
Diarrhea	8	7 (4.6)	8	8 (5.4)
Infections and infestations				
Nasopharyngitis	6	6 (4.0)	8	8 (5.4)
Nervous system disorders				
Headache	13	13 (8.6)	19	15 (10.1)
Dizziness	5	5 (3.3)	13	12 (8.1)
Somnolence	3	3 (2.0)	9	9 (6.1)

Abbreviation: SOC, system organ class.
[a]SOC terms are listed in alphabetical order. Preferred terms appear in descending order, according to the overall number of AEs.

genes predict delayed response to citalopram in a diverse population, suggesting that genetic factors may influence response to treatment (Schatzberg et al., 2011).

Subjects in the US trial were, on average, about 30 lb heavier and had a higher body mass index (BMI; 29 kg/m^2) than those in the multinational study (26 kg/m^2). These characteristics lead to the possibility of decreased systemic exposure to the drug, which may result in lower efficacy. Unfortunately, no pharmacokinetic data are available to determine whether these disparities resulted in clinically important differences in blood levels of vortioxetine. Rates of cigarette smoking and alcohol consumption were similar for the two studies.

The contradictory outcomes observed between the two studies, however, are not unprecedented. It is widely recognized that clinical trials in patients with mood disorders conducted in recent years have produced smaller effect sizes, variable outcomes, and higher placebo response rates than those conducted in the past (Undurraga and Baldessarini, 2012; Khin et al., 2011; Hidalgo et al., 2007; Brunoni et al., 2009; Khan et al., 2002, 2010; Kirsch et al., 2008). Since 1995, 50% of antidepressant trials have failed to show efficacy in at least one treatment arm (Khin et al., 2011). An earlier analysis found that US Food and Drug Administration-approved anxiolytics showed statistical superiority to placebo in only 48% (36/93) of clinical trials (Khan et al., 2002). A meta-analysis (21 studies) of published clinical trial data for subjects with GAD (Hidalgo et al., 2007) showed no correlation between treatment effect size and any of the following: study publication date, study-site location (e.g., US vs other), dosing schedule (fixed vs flexible), number of study arms, or number of outcome measures. However, an exploratory analysis of data found that MDD studies with mean baseline HAM-D total scores <20 were less likely to show a positive treatment effect than studies of more severely depressed subjects (Khin et al., 2011). Moreover, the analysis showed an overall lower drug response for US trials compared with non-US trials, but placebo response also was lower in the US trials. Whether these observations would apply to studies of GAD is not known.

The results of the present study emphasize the need to optimize study design to demonstrate efficacy and safety of antidepressant agents for treatment of GAD and other mood disorders. As mentioned, the lack of a positive control makes it impossible to discriminate between a true lack of efficacy and a flawed trial. Investigators may wish to include a positive control in future studies. However, the inability to identify a reason or reasons that one trial showed consistent benefit while the other showed a consistent lack of benefit fits an emerging pattern and raises fundamental questions about contemporary clinical trial designs. The growing reliance on large multisite trials may indicate that more participants had been previously involved in multiple clinical trials, and this experience may bias their treatment response (Bridge et al., 2009; Mundt et al., 2007). These trials often recruit participants through advertisements rather than through physician referral. The baseline characteristics of thus recruited "symptomatic volunteers" differ from those of patients referred to trials after seeking treatment (Rapaport et al., 1996), bringing into question the validity of generalizing the results obtained in symptomatic volunteers to the clinical population of individuals with anxiety or mood disorders. Another consideration is the requirement for relatively high baseline scores for study inclusion. As a consequence, there may be a tendency (either intentional or unintentional) to inflate the baseline scores to permit enrollment (Mundt et al., 2007). In addition, complications with rater consistency and unintentional bias may arise when multiple raters are used for a single subject (Bridge et al., 2009; Mundt et al., 2007).

In conclusion, vortioxetine 5 mg did not significantly improve HAM-A total scores (vs placebo) in the current US trial of subjects with GAD, despite the demonstration of its efficacy for GAD in a similar study of the same dose. Although it appears that no single factor is responsible for failure of the present trial, a number of disparities have been identified that, in aggregate, may help to explain the results. Further studies are needed to fully define the efficacy and optimal doses of vortioxetine in the treatment of GAD.

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Contributors

Author Anthony J. Rothschild was the signatory investigator of the study, at the University of Massachusetts Medical School, and was involved in planning, writing, and reviewing the manuscript.

Author Atul R. Mahableshwarkar was involved in providing medical oversight to the study; data cleaning and interpretation; and planning, writing, reviewing, and revising the manuscript.

Author Paula Jacobsen was involved in protocol development; study oversight; data cleaning and interpretation; and planning, writing, reviewing, and revising the manuscript.

Author Mingjin Yan performed the statistical analysis and participated in reviewing and revising the manuscript.

Author David V. Sheehan participated in planning, reviewing, and revising the manuscript.

Conflict of interest

In the past 3 years, Dr. Rothschild has received grant support from the National Institute of Mental Health, Cyberonics, Takeda, and St. Jude Medical. He has served as a consultant to Eisai Medical, GlaxoSmithKline, Eli Lilly, Noven Pharmaceuticals, Pfizer, Shire, Sunovian, and Takeda. He has also received royalties for books published by American Psychiatric Press, Inc.

Drs. Mahableshwarkar, Jacobsen, and Yan are employees of Takeda Global Research & Development Inc.

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