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A randomized, double-blind, fixed-dose study comparing the efficacy and tolerability of vortioxetine 2.5 and 10 mg in acute treatment of adults with generalized anxiety disorder

Atul R. Mahableshwarkar*, Paula L. Jacobsen, Michael Serenko and Yinzhong Chen

Takeda Development Center Americas, Deerfield, Illinois, USA

Background Vortioxetine is a recently approved multimodal antidepressant with anxiolytic properties in preclinical studies.
Objective This double-blind, placebo-controlled study assessed the efficacy and tolerability of vortioxetine in subjects with a primary diagnosis of generalized anxiety disorder.
Methods Subjects ($n = 457$) were randomized 1:1:1 to treatment with placebo or vortioxetine 2.5 or 10 mg once daily. The primary efficacy endpoint was reduction in Hamilton Anxiety Scale (HAM-A) total scores from baseline after 8 weeks of treatment. Key secondary outcomes were changes from baseline in HAM-A total scores for the 2.5 and 10 mg dose, Hospital Anxiety and Depression anxiety subscore, 36-Item Short-Form Health Survey, Sheehan Disability Scale, and Clinical Global Impression-Improvement Scale score, as well as HAM-A response rate at week 8.
Results Neither vortioxetine dose achieved a statistically significant improvement over placebo on the primary endpoint (least-squares mean difference ± standard error from placebo: -0.87 ± 0.803 [$p = 0.279$] for 2.5 mg and -0.81 ± 0.791 [$p = 0.306$] for 10 mg vortioxetine) or on any secondary efficacy endpoints. Common adverse events (≥5% in either vortioxetine group) were nausea, dry mouth, headache, diarrhea, constipation, and vomiting.
Conclusions Vortioxetine 2.5 and 10 mg treatment did not significantly improve generalized anxiety disorder symptoms versus placebo. Vortioxetine was safe and well tolerated in this patient population. Copyright © 2014 John Wiley & Sons, Ltd.

KEY WORDS—general anxiety disorder; multimodal therapy; vortioxetine

INTRODUCTION

Vortioxetine is a recently approved, multimodal antidepressant believed to work through a combination of two pharmacologic modes of action, inhibition of serotonin (5-HT) reuptake and activity at 5-HT receptors. *In vitro* studies indicate that vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} receptor partial agonist, a 5-HT_{1A} receptor agonist, and an inhibitor of the 5-HT transporter (Bang-Andersen *et al*., 2011; Westrich *et al*., 2012). The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear. However, data from serotonin receptor and transporter occupancy studies, coupled with neuronal firing and microdialysis studies in rats, suggest that the targets interact in a complex fashion that leads to the modulation of neurotransmission in several systems. These include the serotonin, norepinephrine, dopamine, histamine, and acetylcholine systems within the rat forebrain (Mork *et al*., 2012; Pehrson *et al*., 2013). These multimodal pharmacological actions are thought to be responsible for the antidepressant effects of vortioxetine. In addition, treatment with vortioxetine (2.0, 4.0, or 8.0 mg/kg) exerted anxiolytic-like effects in social interaction and conditioned fear animal models (Mork *et al*., 2011).

Generalized anxiety disorder (GAD) is a chronic condition characterized by fluctuations in symptom severity. Although some subjects respond to treatment with selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors, between 25% and 40% of subjects in clinical trials remain symptomatic (Baldwin *et al*., 2011). Among those who do respond, functional impairment remains a problem for a substantial percentage of individuals (Bobes *et al*., 2011). Benzodiazepines and atypical antipsychotic medications may also be effective in treating GAD, but all treatment options carry some risk of

*Correspondence to: Atul R. Mahableshwarkar, MD, Senior Medical Director, Takeda Development Center Americas, One Takeda Parkway, Deerfield, Illinois 60015, USA. Tel: +1-224-554-2805; Fax: +1-224-554-1058
E-mail: atul@tgrd.com
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unwanted side effects (Baldwin *et al*., 2011). Therefore, new therapies are needed to address the potential for incomplete response and tolerability concerns associated with current GAD treatments.

The phase 3 clinical development program to evaluate the efficacy and safety/tolerability of vortioxetine in subjects with a primary GAD diagnosis consisted of four 8-week short-term studies (NCT00731120, NCT00730691, NCT00734071, and NCT00744627) and one long-term relapse-prevention study (NCT00788034). Data from two short-term, identically designed, randomized, double-blind, parallel-group, placebo-controlled studies in the program have been reported (Bidzan *et al*., 2012; Rothschild *et al*., 2012). In one study ($n = 301$) (Bidzan *et al*., 2012), vortioxetine 5mg treatment provided significantly greater improvement versus placebo on the primary efficacy endpoint (change in baseline Hamilton Anxiety Scale [HAM-A] total score at week 8) and all secondary efficacy endpoints. In the other study ($n = 304$) (Rothschild *et al*., 2012), no difference between vortioxetine 5mg and placebo was observed for the primary efficacy endpoint. Vortioxetine 5 mg was safe and well tolerated in both studies. The second study was conducted exclusively in the United States, whereas the trial showing significant benefit with vortioxetine 5 mg was conducted outside the United States. In the relapse-prevention study, subjects ($n = 459$) who responded ($\geq$50% reduction from baseline in HAM-A total score) to treatment during a 20-week, open-label, flexible-dose period entered a randomized, double-blind, placebo-controlled phase. During the double-blind phase, vortioxetine treatment reduced the relapse risk almost three-fold (HAM-A ≥ 15; hazard ratio, 2.71; $p < 0.001$) compared with placebo over 24–56 weeks (Baldwin *et al*., 2012).

The present phase 3 trial was designed to assess a wider dosage range of vortioxetine than evaluated in the aforementioned studies. The vortioxetine 10 mg dose was based on prior data demonstrating efficacy in subjects with major depressive disorder (MDD) with high anxiety levels (Alvarez *et al*., 2012), whereas the 2.5 mg dose was selected to establish a minimally efficacious dose.

MATERIALS AND METHODS

Study design

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study was conducted at 41 sites in the United States (see acknowledgements for full list of investigators and study sites). The trial started in June 2008 and was completed in February 2009. The study was approved by individual institutional review boards where applicable and by a central review board for the remaining sites. The study was conducted in compliance with the US Food and Drug Administration code of Federal Regulations Part 21, the International Conference on Harmonisation Tripartite Guidelines for Good Clinical Practice, and the World Medical Association Declaration of Helsinki. The study sponsor provided all relevant documents for submission to each respective institutional review board for review and approval, including study protocol, investigator's brochure, informed consent form, subject recruitment materials, and/or advertisements. Each individual study site was responsible for the recruitment, screening, and final approval of each subject prior to entry into the study. After providing signed informed consent, subjects entered a 2-day to 10-day screening period, and, if eligible, they were randomized (1:1:1) to receive placebo, vortioxetine 2.5 mg, or vortioxetine 10 mg once daily during the 8-week double-blind treatment period using an interactive voice-response system (Figure 1). Vortioxetine tablets (2.5 or 10 mg) were enclosed in brownish-orange capsules; identical capsules containing lactose monohydrate/magnesium stearate filler were used for placebo.

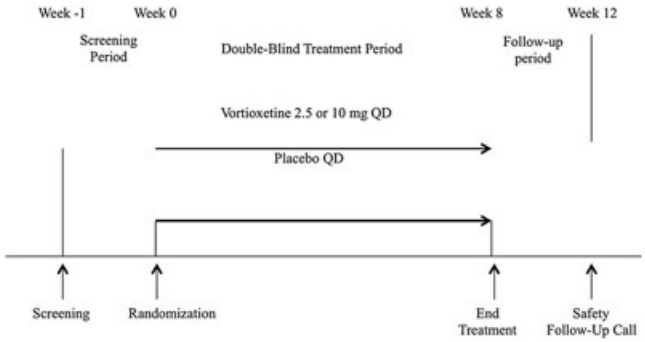

Figure 1. Study design. QD, once daily

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Raters

Each study site was required to identify and provide skilled raters who met appropriate pre-specified qualifications. The rater training and certification process consisted of verifying rater qualification via completion of a Rater Experience Survey and completion of certification training on key scales (i.e., HAM-A) and finally interview skills training. Upon enrollment of the first two subjects for each rater at a given site, sites were required to send the source documents within two working days of visits 1, 2, 3, and final visit for the completed HAM-A assessments. This requirement was designed to increase the precision and validity of clinician ratings.

Subjects

Adult men and non-pregnant women (aged $\geq$18 years) were included if they had a primary diagnosis of GAD as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision classification (American Psychiatric Association, 2000) code 300.02. Subjects were required to have a HAM-A total score of $\geq$20, a HAM-A score $\geq$2 on both item 1 (anxious mood) and item 2 (tension), and a Montgomery–Åsberg Depression Rating Scale total score $<$16 at screening and baseline visits. Subjects were not eligible if they had received any investigational compound $<$ 30 days before screening or five half-lives prior to screening; received vortioxetine in a previous clinical study; had any concurrent psychiatric disorder other than GAD or prior history of psychiatric disorders, such as a manic or hypomanic episode, schizophrenia, or substance abuse disorder; had a significant suicide risk in the opinion of the investigator or a score of $\geq$5 on item 10 of the Montgomery–Åsberg Depression Rating Scale; or had previously failed to respond to treatment with an adequate dose of a selective serotonin reuptake inhibitor or a serotonin–norepinephrine reuptake inhibitor for the current GAD episode. In addition, subjects who had clinically significant unstable medical conditions, such as hepatic impairment, cardiovascular, respiratory, or gastrointestinal disorders, were excluded.

Study treatments

Efficacy measures. Baseline measurements of the HAM-A, Clinical Global Impression-Severity (CGI-S) Scale (Guy, 1976), patient-reported Hospital Anxiety and Depression (HAD) Scale (Zigmond and Snaith, 1983), the 36-Item Short-Form Health Survey (SF-36) (Ware Jr. and Sherbourne, 1992), and the Sheehan Disability Scale (SDS) (Sheehan and Sheehan, 2008) were obtained prior to randomization. HAM-A, CGI-S, and CGI-Improvement of Illness (CGI-I) Scale (Guy, 1976) scores were assessed at every evaluation visit. Other measures were evaluated at baseline and on the following schedule: HAD at weeks 1, 4, and 8; SF-36 at weeks 2, 4, and 8; and SDS at weeks 1, 2, 4, and 8.

Safety assessments. Adverse events (AEs) were documented at weeks 0, 1, 2, 4, 6, and 8 and follow-up and coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities* version 11.1. Vital signs were assessed at all visits. Clinical laboratory values and weight were determined at weeks 0, 4, and 8. Electrocardiograms and physical examinations were conducted at weeks 0 and 8. Suicidal ideation and behavior was assessed as an exploratory outcome using the Columbia Suicide-Severity Rating Scale (C-SSRS) (Posner *et al*., 2007) at all visits.

Statistical analysis

Analysis sets. The safety set included all randomized subjects who received at least one dose of study medication. The full analysis set was composed of all randomized subjects who received at least one dose of study medication and had at least one valid post-baseline value for the primary efficacy assessment. Data analysis and descriptive and inferential statistical tabulations were performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

Statistical methods

Primary efficacy analysis. Comparisons of change from baseline in HAM-A total score at week 8 between vortioxetine treatment groups and placebo were performed using an analysis of covariance model, with treatment and center as fixed factors, baseline HAM-A as a covariate, and using last observation carried forward (LOCF). Tests were two-sided with a 5% level of significance comparing the 10 mg dose and then the 2.5 mg dose with placebo. Ninety-five percent confidence limits are presented together with the estimated p values.

Key secondary efficacy analyses. HAM-A total scores, CGI-I, CGI-S, and HAD scores were analyzed by an analysis of covariance adjusting for baseline score, center, and treatment using the methods as described for the primary efficacy analysis. Response (defined as a $\geq$50% decrease from baseline in HAM-A total score) was assessed at all time points by logistic regression.

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

- Change from baseline in HAM-A total score at week 8 (vortioxetine 10 mg vs. placebo, LOCF)
- Change from baseline in HAD anxiety subscore at week 8 (vortioxetine 10 mg vs. placebo, LOCF)
- CGI-I at week 8 (vortioxetine 10 mg vs. placebo, LOCF)
- Change from baseline in SDS total score at week 8 (vortioxetine 10 mg vs. placebo, LOCF)
- HAM-A response rate at week 8 (vortioxetine 10 mg vs. placebo, LOCF)
- Change from baseline in HAM-A total score at week 8 in subjects with baseline HAM-A total score ≥ 25 (vortioxetine 10 mg vs. placebo, LOCF)
- Change from baseline in SF-36 social functioning subscore at week 8 (vortioxetine 10 mg vs. placebo, LOCF)
- Change from baseline in HAM-A total score at week 8 (vortioxetine 2.5 mg vs. placebo, LOCF)

As soon as a test was not significant at the level of 0.05, the testing procedure stopped for all subsequent endpoints. Nominal p values with no adjustment for multiplicity were reported for all comparisons between vortioxetine and placebo.

Safety

Adverse events and C-SSRS scores were summarized using descriptive statistics. AEs that were reported more than once by a subject during the same period were counted only once for that subject and at the period of maximum severity.

Absolute values and changes from screening/baseline in clinical safety laboratory tests, vital signs, electrocardiogram parameters, and weight/body mass index were summarized for each treatment group using descriptive techniques. Values outside normal ranges and potentially clinically significant values were flagged and tabulated.

RESULTS

Subjects

As shown in Figure 2, of the 677 individuals screened, 457 were randomized to receive placebo ($n = 153$) and to each of the vortioxetine groups ($n = 152$ each). Of the 221 individuals who were excluded, most ($n = 153$) met ≥ 1 exclusion criteria. Approximately 12% of each group had ≥ 1 major protocol violation. Nine randomized subjects had been enrolled in a previous vortioxetine trial.

Demographics and baseline clinical characteristics were similar across treatment groups except that subjects randomized to receive placebo were somewhat younger than subjects randomized to the active-treatment groups (Table 1). The median GAD duration was 12 months in all groups.

Similar proportions of subjects in each treatment group had been treated for the current GAD episode prior to study enrollment (29.4% in the placebo group, 33.8% in the vortioxetine 2.5 mg group, and 31.6% in the vortioxetine 10 mg group) as were previous drug treatment rates (28.1% in the placebo group, 31.8% in the vortioxetine 2.5 mg group, and 29.6% in the vortioxetine 10 mg group).

Primary efficacy endpoint

The difference in change from baseline in HAM-A total score was not statistically significantly different in the vortioxetine 10 mg group compared with placebo (least-squares mean difference ± standard error from placebo was -0.81 ± 0.791 [$p = 0.306$] for vortioxetine 10 mg) (Table 2). Similarly, vortioxetine 2.5 mg did not show significant difference from placebo (-0.87 ± 0.803; $p = 0.279$).

Secondary efficacy outcomes

Vortioxetine treatment did not result in differences with nominal p values < 0.05 versus placebo for any of the key secondary efficacy endpoints (Table 2). HAM-A response rates at week 8 were 41.9% in the placebo group, 46.5% in the vortioxetine 2.5 mg group, and 41.8% in the vortioxetine 10 mg group.

Safety

Common AEs reported in $\geq 5\%$ of subjects in any vortioxetine treatment group were nausea, dry mouth, headache, diarrhea, constipation, and vomiting. Most of the common AEs were of mild to moderate intensity (Table 3). There were higher nausea, diarrhea, constipation, vomiting, and headache rates in the vortioxetine treatment groups compared with placebo.

In the placebo group, six (3.9%) subjects withdrew from the study because of AEs, as did six (4.0%) subjects in the vortioxetine 2.5 mg group and eight (5.3%) in the vortioxetine 10 mg group. The events that led to early termination in more than one subject were nausea ($n = 2$), diarrhea ($n = 3$), and vomiting ($n = 2$)—all in the vortioxetine 10 mg group. There were four serious AEs, of which one (pyrexia of unknown origin), occurring in the vortioxetine 2.5 mg group, was considered possibly related to the study

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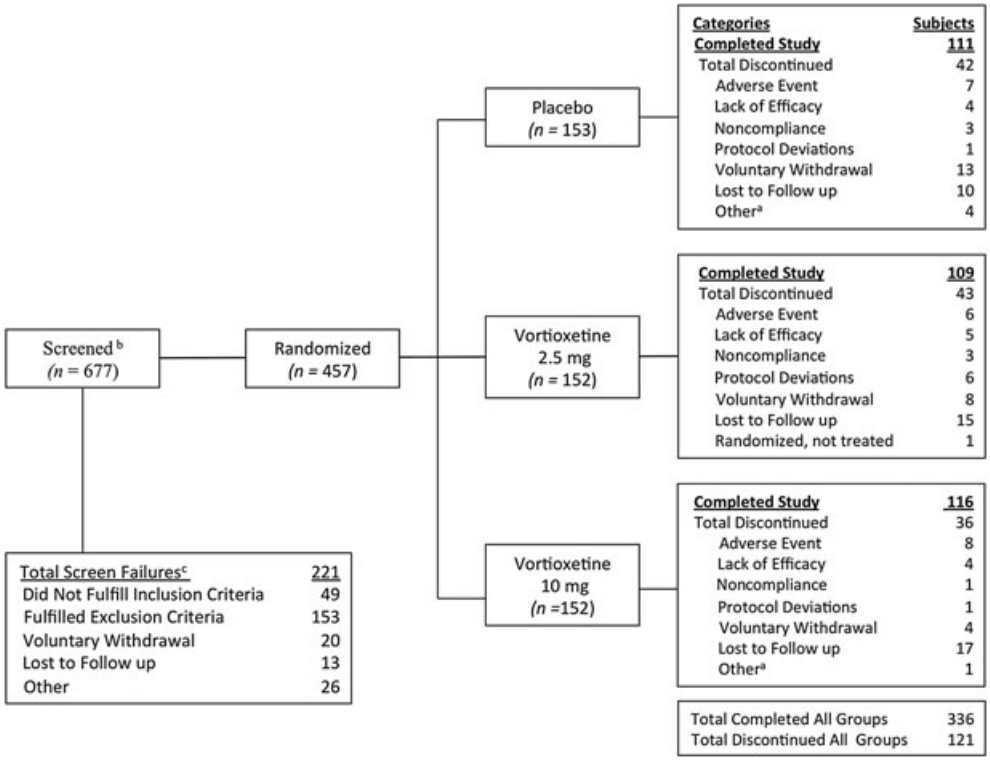

Figure 2. Subject disposition. [a]Other reasons for early termination were family obligations, moved out of state, personal choice, and new job schedule. [b]Subject 0047–906 had both a randomized and screen fail status in the database. Therefore, the number screened is shown as 677 instead of 678 as the table counts only discrete subjects. [c]More than one reason for screen failure may have been reported for a subject

drug; the subject was treated with intravenous antibiotics and recovered from the event. The three other serious AEs were judged unrelated by the investigator and were composed of positional vertigo in a placebo-treated subject, left inguinal hernia in a subject receiving vortioxetine 2.5 mg, and a spontaneous abortion in a subject receiving vortioxetine 10 mg. No deaths occurred.

No differences among treatment groups and no trends warranting safety concerns were observed for clinical laboratory values, vital signs, electrocardiograms, or physical examination findings.

Analysis of the C-SSRS data showed that no subjects reported suicidal behavior during the study; the incidence of treatment-emergent suicidal ideation was low and equally distributed among the vortioxetine and placebo groups (1–2 subjects per treatment group).

DISCUSSION

Antidepressant agents are considered first-line treatments for individuals with GAD (Swinson *et al*., 2006; Bandelow *et al*., 2008). The rationale for investigating vortioxetine in subjects with GAD was based on positive results in a study (Alvarez *et al*., 2012) conducted in subjects with MDD with high levels of anxiety symptoms (mean baseline HAM-A total scores = 22.2). In this study, treatment with vortioxetine significantly reduced anxiety symptoms in this patient group.

The results of the current study found no statistically significant differences between the vortioxetine 2.5 or 10 mg treatment groups and placebo group in the primary efficacy endpoint (change from baseline in HAM-A total score at week 8) or in any clinical and functional outcomes assessed as secondary endpoints.

Adverse events reported were consistent with those expected from the vortioxetine safety profile observed in other clinical trials. No increased rates of suicide-related events as assessed by the C-SSRS were reported during the study. These results support previous findings that vortioxetine is not associated with increased suicidal ideation and behavior in subjects with GAD or MDD (Bidzan *et al*., 2012; Henigsberg *et al*., 2012; Jain *et al*., 2013)

This is the third study to evaluate the efficacy and safety/tolerability of vortioxetine in subjects with a primary diagnosis of GAD. The two previously published studies used an identical study design. In the first study, vortioxetine 5 mg was superior to placebo in

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Table 1. Demographics and other baseline characteristics

	Treatment group		
Characteristic	Placebo ($n = 153$)	Vortioxetine 2.5 mg ($n = 152$)	Vortioxetine 10 mg ($n = 152$)
Sex			
Male, *n* (%)	48 (31.4)	49 (32.2)	56 (36.8)
Age[a] (years), mean (SD)	39.5 (13.5)	40.8 (13.8)	43.3 (15.0)
Age category,[b] *n* (%)			
≤55 years	136 (88.9)	127 (83.5)	120 (78.9)
>55 years	17 (11.1)	25 (16.4)	32 (21.1)
Race, *n* (%)			
White, including Hispanic	105 (68.5)	110 (72.4)	112 (73.7)
Black	46 (30.1)	38 (25.0)	38 (25.0)
Asian	2 (1.3)	3 (2.0)	2 (1.3)
American Indian/Alaskan Native	0 (0.0)	1 (0.7)	0 (0.0)
Ethnicity, *n* (%)			
Hispanic/Latino	13 (8.3)	18 (11.8)	15 (9.9)
Non-Hispanic/non-Latino	140 (91.5)	134 (88.2)	137 (90.1)
Duration of current GAD (months)			
Mean (SD)	40.9 (97.5)	36.7 (88.5)	57.4 (107.7)
Median (range)	12 (1 to 840)	12 (1 to 828)	12 (1 to 520)
Previously treated for current GAD, *n* (%)	45 (29.4)	51 (33.8)	48 (31.6)
Previously treated with medication, *n* (%)	43 (28.1)	48 (31.8)	45 (29.6)
Previously treated with an SSRI, *n* (%)	24 (15.7)	32 (21.2)	31 (20.4)
HAM-A total score, *n*	153	152	152
Mean (SD)	25.2 (3.9)	25.0 (3.6)	24.5 (3.7)

GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Scale; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor.
[a]$p = 0.007$.
[b]$p = 0.018$.

the primary efficacy endpoint and across all secondary outcomes (Bidzan *et al*., 2012). In the second study, vortioxetine 5 mg did not separate from placebo (Rothschild *et al*., 2012). In an additional study, a relapse-prevention study comparing vortioxetine 5 or 10 mg versus placebo, vortioxetine significantly reduced the relapse risk (hazard ratio, 2.71) compared with placebo (Baldwin and Nutt, 2012). Given the robust positive outcomes with vortioxetine 5 mg in one short-term study and vortioxetine 5 and 10 mg in the long-term relapse-prevention trial, it is unlikely that the current trial failed because vortioxetine is not efficacious in treating GAD or that the 10 mg dose is subtherapeutic. Failed or unsuccessful trials are commonly seen in depression studies conducted in the United States as shown by the recent analysis of the Food and Drug Administration database by Khin *et al*. (Khin *et al*., 2011), where approximately 50% of trials with antidepressants at approved doses had failed to separate from placebo. In the clinical development program for vortioxetine in MDD, efficacy has been replicated at the 5, 10, and 20mg doses, with variable results across clinical trials. Of the 10 short-term trials with vortioxetine, seven have shown clinically relevant response to treatment. There has been a tendency across studies to see increasing efficacy at higher doses (Henigsberg *et al*., 2012; Boulenger *et al*., 2012, 2013). Vortioxetine was consistently well tolerated across different study populations when measured by various objective scales in addition to spontaneously reported AEs.

Variable results are common in clinical trials involving depression and anxiety disorders, and in recent years, effect sizes have decreased. Less than one-half (48%) of all clinical anxiolytic trials approved in the United States showed superiority over placebo (Khan *et al*., 2002). Numerous reasons for these outcomes have been hypothesized, but few explanations have been identified, and analysis of factors contributing to variable outcomes in GAD trials has not been well studied (Baldwin and Nutt, 2012). One meta-analysis (21 studies) of published clinical trial data for subjects with GAD (Hidalgo *et al*., 2007) showed no correlation between treatment effect size: study publication date, dosing schedule (fixed vs. flexible), number of study arms, or number of outcome measures. In contrast to vortioxetine GAD trials, in which the two positive trials were conducted outside of the United States and the failed trials were conducted in the United States, the meta-analysis found no significant correlation between study-site location (e.g., US vs. other) and treatment effect. Rater training and certification,

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Table 2. Primary efficacy endpoint and key secondary efficacy variables at week 8 (last observation carried forward, full analysis set)

	Placebo	Vortioxetine 2.5 mg[a]	Vortioxetine 10 mg[a]
	($n = 148$)	($n = 144$)	($n = 146$)
HAM-A total score			
Baseline, *n*	148	144	146
Baseline, LS mean (SE)	25.01 (0.277)	25.11 (0.270)	24.75 (0.275)
Change from baseline to week 8, LS mean (SE)	−9.87 (0.584)	−10.75 (0.569)	−10.68 (0.581)
LS mean difference from placebo (SE)		−0.87 (0.803)	−0.81 (0.791)
Nominal *p* value		0.279	0.306
HAD anxiety subscore			
Baseline, *n*	148	144	146
Baseline, LS mean (SE)	14.06 (0.290)	13.16 (0.282)	13.36 (0.231)
Change from baseline to week 8, LS mean (SE)	−3.63 (0.396)	−4.29 (0.354)	−4.20 (0.361)
LS mean difference from placebo (SE)		−0.66 (503)	−0.57 (0.493)
Nominal *p* value		0.187	0.249
CGI-I score			
Baseline, *n*	148	144	146
Score at week 8, LS mean (SE)	2.60 (0.095)	2.56 (0.093)	2.51 (0.096)
LS mean difference from placebo (SE)		−0.040 (0.131)	−0.08 (0.129)
Nominal *p* value		0.782	0.510
SDS total score			
Baseline, *n*	124	113	109
Baseline, LS mean (SE)	15.35 (0.662)	13.97 (0.668)	14.38 (0.705)
Change from baseline to week 8, LS mean (SE)	−4.26 (0.617)	−5.73 (0.623)	−5.24 (0.657)
LS mean difference from placebo (SE)		−1.47 (0.866)	−0.98 (0.863)
Nominal *p* value		0.090	0.257
HAM-A response[b] at week 8			
Subjects with response, *n* (%)	62 (41.9)	67 (46.5)	61 (41.8)
Odds ratio versus placebo		1.203	0.961
Nominal *p* value		0.436	0.868
HAM-A total score for subjects with baseline HAM-A ≥25	78	74	60
Baseline, *n*	27.62 (0.373)	27.36 (0.342)	27.36 (0.400)
Baseline, LS mean (SE)	−10.38	−11.21 (0.906)	−11.80 (1.060)
Change from baseline to week 8, LS mean (SE)	(0.983)	−0.83 (1.280)	−1.42 (1.347)
LS mean difference from placebo (SE)		0.516	0.294
Nominal *p* value			
SF-36 social functioning subscore			
Baseline, *n*	146	141	141
Baseline, LS mean (SE)	48.15 (2.189)	56.66 (2.138)	54.09 (2.195)
Change from baseline to week 8, LS mean (SE)	15.35 (2.075)	18.38 (2.025)	17.56 (2.070)
LS mean difference from placebo (SE)		3.03 (2.860)	2.21 (2.817)
Nominal *p* value		0.290	0.434

CGI-I, Clinical Global Impression–Improvement of Illness; HAD, Hospital Anxiety and Depression; HAM-A, Hamilton Anxiety Scale; LS, least-squares; SDS, Sheehan Disability Scale; SE, standard error; SF-36, 36-Item Short-Form Health Survey.

[a]In sequential testing procedures to control two-sided type I error, the vortioxetine 10 mg group was first in the testing hierarchy. Change from baseline in HAM-A total score for vortioxetine 2.5 mg was the last variable to be tested in this sequence and the only variable in the 2.5 mg group that was included in this sequential testing hierarchy.

[b]Responders were defined as subjects who had a ≥50% decrease from baseline in HAM-A total score.

including assessment of inter-rater reliability, were performed on all raters, with no clear pattern that would explain the failure of this study. It has also been speculated that reliance on commercial clinical research organizations to recruit subjects in the United States may have compromised the quality of results. Incentives for rapid recruitment may reduce the stringency with which subjects are screened and enrolled, possibly resulting in recruitment of subjects who may be unsuitable for clinical trials. An important consideration in this study is the relatively high rates of protocol violations (12%). An

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Table 3. Incidence of common treatment-emergent adverse events in ≥5% of subjects in any treatment group (safety set)

	Placebo	Vortioxetine 2.5 mg	Vortioxetine 10 mg
TEAE, *n* (%)	(*n* = 153)	(*n* = 151)	(*n* = 152)
Any TEAE	102 (66.7)	94 (62.3)	105 (69.1)
Gastrointestinal disorders			
Nausea	13 (8.5)	24 (15.9)	37 (24.3)
Dry mouth	17 (11.1)	14 (9.3)	12 (7.9)
Diarrhea	11 (7.2)	13 (8.6)	17 (11.2)
Constipation	6 (3.9)	4 (2.6)	9 (5.9)
Vomiting	4 (2.6)	3 (2.0)	8 (5.3)
Infections and infestations			
Nasopharyngitis	8 (5.2)	5 (3.3)	4 (2.6)
Nervous system disorders			
Headache	17 (11.1)	20 (13.2)	18 (11.8)

TEAE, treatment-emergent adverse event.

example of inappropriate participant screening is the enrollment of nine subjects in this study who were subsequently found to be randomized to more than one vortioxetine trial. Although it is difficult to determine the role that such study conduct issues may have in trial results, greater attention to ensuring that suitable subjects are screened is likely to increase the possibility of efficacy signal detection. Inflated baseline HAM-A total scores is one possible consequence of less stringent screening practices. Evidence suggests that severity of symptoms at baseline is negatively correlated with placebo response in MDD trials (Khin *et al*., 2011). Although this correlation has not been established in GAD, it is reasonable to speculate that an elevated placebo response could reduce the treatment effect. In the current study, the change from baseline in HAM-A total score in the placebo group was −9.87, compared with −9.59 in the positive trial (Bidzan *et al*., 2012) and −13.6 in the other failed trial (Rothschild *et al*., 2012), suggesting that the small treatment effect in this study cannot be attributed to inflated baseline scores. It is unlikely that any single factor can explain the inconsistent results observed in the vortioxetine GAD trials.

CONCLUSION

The results of this large, randomized, double-blind, placebo-controlled, phase 3 trial did not show any clinical benefit of vortioxetine over placebo for the treatment of GAD. The favorable safety profile of vortioxetine 2.5 and 10 mg in the current study adds to the growing evidence supporting vortioxetine as safe and well tolerated in a broad patient population.

CONFLICT OF INTEREST

Drs. Atul R. Mahableshwarkar, Yinzhong Chen and Ms. Paula L. Jacobsen are employees of Takeda Development Center Americas. At the time of this study, Michael Serenko was an employee of Takeda Development Center Americas.

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STUDY INVESTIGATORS

DL Anderson, MD, Redlands, CA; BS Bortnick, MD, Comprehensive Neuroscience, Inc., Atlanta, GA; O Brawman-Mintzer, MD, Medical University of South Carolina, North Charleston, SC; R Buynak, MD, FACP, Northwest Indiana Center for Clinical Research, Valparaiso, IN; M DiBuono, MD, Richmond Behavioral Associates, Staten Island, NY; N Dubin, MD, Cincinnati, OH; BW Dunlop, MD, Emory University Department of Psychiatry and Behavioral Sciences, Atlanta, GA; AC Fedyszen, MD, Midlothian, VA; C Goldstein, MD, Rush University Medical Center, Chicago, IL; MS Greenbaum, MD, Capstone Clinical Research, Libertyville, IL; D Gruener, MD, CRI Worldwide, LLC, Philadelphia, PA; C Guerra, Jr, MD, Houston, TX; S Gupta, MD, Olean, NY; JR Hart, MD, Nashville, TN; JM Joyce, MD, Clinical Neurosciences Solutions, Inc., Jacksonville, FL; ZE Kayatekin, MD, Berkshire Medical Center, Pittsfield, MA; NS Kaye, MD, Hockessin, DE; DJ Kelsh, MD, Vince and Associates Clinical Research, Overland Park, KS; RD Knapp, DO, Florida Clinical Research Center, LLC, Fruitland Park, FL; CJ Kohlenberg, MD, Independent Psychiatric Consultants, SC, Waukesha, WI; MR Liebowitz, MD, The Medical Research Network, LLC, New York, NY; M Marandi, MD, Comprehensive NeuroScience, Inc., Cerritos, CA; JA Mattes, MD, Psychopharmacology Research Association of Princeton, Princeton, NJ; W McNeel, MD, Omega Clinical Trials, LLC, Anaheim, CA; I Mezhebovsky, MD, Boston Clinical Trials, Boston, MA; CB Montano, MD, Connecticut Clinical Research, Cromwell, CT; CR Morin, MD, Coastal Research

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Associates, Inc., Braintree, MA; AE Mulroy, MD, Clinical Trials of Texas, Inc., San Antonio, TX; WR Murphy, MD, Psychiatric Associates, Overland Park, KS; MS Okasha, MD, Comprehensive Psychiatric Care, Norwich, CT; WM Patterson, MD, Birmingham Research Group, Inc., Birmingham, AL; JF Prater, DO, Fort Myers, FL; RA Riesenberg, MD, Atlanta, GA; LI Rosenberg, MD, Center for Emotional Fitness, Cherry Hill, NJ; V Sebastian, MD, Sooner Clinical Research, Oklahoma City, OK; CI Semeniuk, MD, Pacific Clinical Research Medical Group, Orange, CA; F Sicuro, MD, Millennium Psychiatric Associates, LLC, St. Louis, MO; KN Sokolski, MD, MS, Costa Mesa, CA; JG Sonnenberg, PhD, Uptown Research Institute, Chicago, IL; HM Thomas, MD, Clinical Trials Technology, Inc., Prairie Village, KS; AJ Vallanat, MD, Comprehensive NeuroScience, Inc, Fresh Meadows, NY; S Virk, MD, Department of Psychiatry, The Ohio State University, Columbus, OH; MW Warren, MD, Research Across America, Reading, PA; TR Weiss, MD, Radiant Research San Antonio, San Antonio, TX; MJ Woyshville, MD, Middleburg Height, OH.

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