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Original article

A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder

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Abstract

Objective:
Vortioxetine (Lu AA21004) is an investigational antidepressant. *In vitro* studies indicate that vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter. This trial assessed the efficacy and tolerability of 2.5 and 5 mg vortioxetine for the treatment of MDD.

Research design and methods:
Adults ($N = 611$) with MDD were randomized to 8 weeks of double-blind treatment with placebo, vortioxetine (2.5 or 5 mg) or active reference (duloxetine 60 mg). The primary measure was change from baseline in the 24-item Hamilton Depression Scale (HAM-D24). Secondary endpoints included responder rate, Clinical Global Impression Scale-Global Improvement scale (CGI-I), and remission rate. Participants were monitored for adverse events (AEs), and treatment-emergent sexual dysfunction using the Arizona Sexual Experiences (ASEX) scale.

Results:
Both doses of vortioxetine were associated with declines in HAM-D24 total scores compared to placebo but were not statistically significant. At 8 weeks, changes from baseline were [mean (SE)]: −10.50 (0.76) placebo, −12.04 (0.74) 2.5 mg vortioxetine, and −11.08 (0.74) 5 mg vortioxetine. Secondary outcome measures in the vortioxetine groups, including responder rate, CGI-I, and remission rate, were also not significantly different from placebo. Duloxetine treatment was associated with declines in HAM-D24 total score [−13.47(0.75); $p = 0.005$] as well as significant improvements in secondary outcome measures versus placebo ($p \leq 0.05$). The most common AEs for vortioxetine were nausea, dry mouth, and headache. Rates of sexual dysfunction (ASEX) were 51.0%, 37.5%, 46.9%, and 33.3% in the vortioxetine 2.5 mg, vortioxetine 5 mg, duloxetine, and placebo groups, respectively.

Conclusions:
In this study of adults with MDD treated for 8 weeks with vortioxetine 2.5 mg or 5 mg per day, reductions in depression symptoms were not statistically significant compared with placebo. Study limitations are discussed, including patient characteristics, MDD severity, drug dosing, and aspects of trial design. Both doses of vortioxetine were well tolerated.
This trial has been registered at clinicaltrials.gov #NCT00672620

Introduction

Major depressive disorder (MDD) is a leading cause of disability and is associated with significant reductions in quality of life, impaired productivity, reduced

overall health, and substantial economic costs[1,2–5]. Among patients who have MDD and receive one of the currently available first-line pharmacologic therapies, about 30–40% achieve a full remission and another one-third respond to therapy but have residual symptoms[6–9]. Fewer than half of patients with MDD adhere to their antidepressant regimen for the recommended duration, in part because of side-effects such as sleep disturbances, sexual dysfunction, and weight gain[10–13]. Thus, there is a strong need for improved therapies that have better tolerability and effectiveness[14].

The mechanism of action of vortioxetine is thought to be related to its multimodal activity, which is a combination of two pharmacological modes of action: direct modulation of receptor activity and inhibition of the serotonin transporter. *In vitro* studies indicate that vortioxetine is a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the 5-HT transporter. The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear. However, data from serotonergic receptor and transporter occupancy studies coupled with neuronal firing and microdialysis studies in rats suggest that the targets interact in a complex fashion, leading to modulation of neurotransmission in several systems, including serotonin, norepinephrine, dopamine, histamine and acetylcholine systems within the rat forebrain. These multimodal pharmacological actions are thought to be responsible for the antidepressant effects of vortioxetine[15,16]. Vortioxetine is in clinical development for the treatment of MDD.

To date, the majority of clinical trials of vortioxetine have demonstrated efficacy in patients with MDD; however, there have been inconsistent results seen across doses and geographic regions. Several multinational, non-US trials have found evidence for efficacy of vortioxetine in patients with MDD. A 6-week trial of vortioxetine (5 or 10 mg per day) found that both doses were associated with significant improvement in Montgomery–Åsberg Depression Rating Scale (MADRS) total scores compared with placebo[17].

In an 8-week trial there was no statistically significant difference between vortioxetine 5 mg or vortioxetine10 mg and placebo in the primary efficacy analysis of the mean change from baseline in MADRS total score at week 8[18]. As the active reference duloxetine also did not separate from placebo, it failed to validate the study. However, based on the results from the secondary efficacy analyses (MMRM), where vortioxetine 5 mg and 10 mg and duloxetine separated from placebo in the majority of the analyses, this study is considered supportive. Another trial compared three doses of vortioxetine (1 mg, 5 mg, and 10 mg) with placebo for 8 weeks[19]. That trial found that all doses of vortioxetine were associated with improvements in Hamilton Depression Scale 24-item version (HAM-D24) total score versus placebo (only the primary endpoint of 10 mg was considered statistically significant because of the testing strategy). A fourth trial studied vortioxetine (5 mg or 10 mg) versus placebo for prevention of relapse in MDD patients who achieved remission during 12 weeks of treatment with open-label vortioxetine (5 or 10 mg)[20]. This trial found that double-blind Lu AA 21004 maintenance therapy was associated with significantly longer time to relapse compared with placebo.

Trials conducted in the US have obtained less consistent evidence for the efficacy of vortioxetine. A 6-week trial conducted entirely in the US found no significant improvement in HAM-D24 total scores in patients with MDD treated with 5 mg vortioxetine[21]. However, this trial did not contain an active reference arm in which the responsiveness of the enrolled population could be assessed. A multinational trial in elderly patients (mean age70.6 years), in which one-third of the patients were enrolled at US sites, found that patients receiving 5 mg vortioxetine had significantly greater declines in HAM-D24 scores at 8 weeks compared with patients receiving placebo[22].

The current trial was undertaken to assess the efficacy and safety of vortioxetine for the treatment of MDD at the lower limit of its dose range (2.5 and 5 mg per day). Vortioxetine was compared with placebo, and an active reference arm was included, in which patients received duloxetine at the recommended starting and maintenance dose for treatment of MDD (60 mg per day). Exploratory analyses were also performed to evaluate the effects of vortioxetine on sexual function.

Patients and methods

Participants

Potential participants were recruited at each study site with the aid of advertisement posters, brochures, doctor-to-patient letters, and websites. Adults between 18 and 75 years of age were eligible for participation if they had a primary diagnosis of major depressive episode of at least 3 months' duration according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revised (DSM-IV-TR). In addition, eligible participants had to have a MADRS total score ≥22 and no other concurrent psychiatric disorders at screening and baseline. Patients were excluded from the study if they had a history of psychosis, recent history of substance abuse, or clinically significant neurological disorder; were using a prohibited medication during the study period; or were at significant risk of suicide according to the investigator's opinion, scored ≥5 on item 10 (suicidal thoughts) on the MADRS, or had made a suicide attempt in the preceding 6 months. Patients were also excluded if their depressive

symptoms had been resistant to two adequate antidepressant treatments of at least 6 weeks' duration each, or if they had received electroconvulsive therapy in the preceding 6 months.

The planned number of participants (sample size) was calculated on the basis of an estimated standard deviation of 9.5 for the primary endpoint and a difference to placebo in mean change from baseline in HAM-D24 total score of 3.5 points for the primary endpoint. Using a 2-sample *t*-test and 85% power to detect a statistical difference at the 0.05 significance level, it was determined that 560 evaluable patients were needed (140 per treatment group).

The study was conducted according to the World Medical Association Declaration of Helsinki, the ICH Harmonised Tripartite Guideline for GCP, and all applicable local or regional regulatory requirements. An institutional review board approved the protocol for each site, and written informed consent was obtained from each participant before any study procedures were performed.

Study design and procedures

The study was conducted at 47 centers in the United States from April to December 2008. Eligible participants were randomized in equal proportion to one of four treatment groups: placebo, 2.5 mg per day vortioxetine, 5 mg per day vortioxetine, or 60 mg per day duloxetine. The randomization schedule was generated by Takeda Global Research & Development, Inc., and investigators were informed of each patient's coded treatment allocation by an interactive voice-activated system. All study drugs were administered as identical-looking capsules and both participants and investigators were blinded to treatment allocation for the duration of the 8-week treatment period and 4-week safety follow-up period.

The primary efficacy measure was least-square mean change from baseline in HAM-D24 total score after 8 weeks of treatment with vortioxetine (2.5 or 5 mg) versus placebo. Secondary efficacy measures included response rate during each assessment (percentage of patients with ≥50% decrease from baseline in HAM-D24 total score), Clinical Global Impression-Global Improvement Scale (CGI-I) at week 8, change in HAM-D24 total score in patients with baseline HAM-A total score ≥20, change from baseline in Sheehan disability scale (SDS), and percentage of patients in remission (MADRS total score ≤10) at week 8. Exploratory analyses of sexual function were conducted using the Arizona Sexual Experiences Scale (ASEX)[23], and potential relationships between study drug and suicidality were assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). All patients were monitored for adverse events and by physical examination, measurement of vital signs, electrocardiogram, and clinical laboratory tests.

At day 0 (2–10 days after screening), eligible patients were re-evaluated for continued eligibility, randomized to treatment groups, and baseline values for each of the primary and secondary endpoints were obtained. Patients were instructed to start taking study drug on day 1, and returned for evaluations at weeks 1, 2, 4, 6, and 8. At the end of the treatment period, patients entered a 1-week double-blind discontinuation period during which those randomized to either vortioxetine group or placebo received placebo, and those randomized to the duloxetine (60 mg per day) group received 30 mg per day duloxetine. After the discontinuation period, all study drugs were stopped. Safety follow-up was conducted by telephone at week 12, or 4 weeks after discontinuation in patients who withdrew early.

Analysis

Data analyses and tabulations were performed using SAS System, Version 9.1.1. All means were calculated using the method of least squares (LS-mean). Primary and secondary endpoints were analyzed using analysis of covariance (ANCOVA) with treatment and center as fixed factors and baseline HAM-D24 total score as covariate. Study centers that had <8 participants were pooled with geographically adjacent centers to minimize artificial effects of imbalances. For the analyses reported here, missing data were imputed using the method of last observation carried forward (LOCF). Post-hoc sensitivity analyses using mixed-effect model repeated measures were also performed. The analysis cohort for efficacy endpoints was the full analysis set (FAS), defined as all randomized participants who received at least one dose of study drug and had at least one valid post-baseline value for the primary efficacy measure. All participants were analyzed according to the treatment group into which they were randomized.

All statistical tests of efficacy were 2-sided with a significance level of 0.05. To control type I error associated with multiple statistical tests, a hierarchical testing procedure was applied, in which all subsequent tests were stopped at the first occurrence of a nonsignificant endpoint. The testing sequence was (all 5 mg Lu AA 21004 versus placebo at week 8, unless otherwise indicated): change from baseline in HAM-D24 total score, HAM-D24 response rate, CGI-I, change from baseline in HAM-D24 total score in participants with baseline HAM-A total score ≥20, change from baseline in SDS total score, MADRS remission rate, and change from baseline in HAM-D24 total score at week 8 for 2.5 mg vortioxetine versus placebo. For endpoints that occurred after the pre-specified statistical testing sequence was stopped or were outside the sequence, nominal *p*-values with no adjustment for multiplicity are reported.

Safety analyses included all participants who received at least one dose of study drug. Participants who received at least one dose of study medication were also eligible to be included in the ASEX analysis. The main analysis of the ASEX data was performed to assess the number of participants who were normal at baseline but developed sexual dysfunction during the study period. Sexual dysfunction was defined as an ASEX total score $\geq$19, a score $\geq$5 on any item, or a score $\geq$4 on any 3 items[24]. Analysis of ASEX data was performed by logistic regression using a model that included treatment, baseline sexual dysfunction status, baseline sexual dysfunction status by treatment interaction, and baseline score.

Results

The disposition of the 961 screened patients and 611 randomized participants is shown in Figure 1. Among the randomized participants, 603 received at least one dose of study medication and are included in the safety analysis, and 597 of these had at least one valid post-baseline assessment for HAM-D24 total score and are included in the full analysis set (FAS) used for efficacy analyses. In all, 451 participants (73.8% of randomized participants) completed the study. Demographic and key baseline characteristics of randomized participants are shown in Table 1. Treatment groups were similar except for a significant difference in baseline body mass index (BMI; $p = 0.035$).

Efficacy outcomes

Figure 2 shows the primary outcome measure, HAM-D24 mean change from baseline, for each clinic visit during the 8-week double-blind treatment period. Values at the primary endpoint of 8 weeks are shown in Table 2. Both doses of vortioxetine were associated with mean declines from baseline HAM-D24 total score that were numerically greater than the placebo group, but the differences were not statistically significant. Likewise, vortioxetine was associated with improvements in most secondary outcome measures that were numerically greater than placebo, but none were statistically significant. Patients in the duloxetine group exhibited improvements in mean HAM-D24 total score and secondary endpoints ($p < 0.05$) that were significantly greater than the improvements observed among patients in the placebo group.

A subgroup analysis was performed to determine if any groups of patients defined according to age (younger or older than 55 years), sex, or race (white including Hispanic or black) had evidence of greater responsiveness to vortioxetine. No subgroup receiving vortioxetine exhibited change from baseline in HAM-D24 total score that was significantly different than the corresponding subgroup receiving placebo. Furthermore, analyses using mixed-effect model repeated measures for incomplete data found results that were similar to the LOCF method (not shown).

Safety

Treatment-emergent adverse events occurring in at least 5% of patients in any treatment group are shown in Table 3. The most common adverse events across all treatment groups were nausea (24.4%), dry mouth (13.8%), and headache (13.8%). The only adverse events that increased in frequency with increasing dose of vortioxetine were nausea and vomiting. Vomiting occurred in 0.7% of patients in the placebo and 2.5 mg vortioxetine groups, but 4.6% in the 5 mg vortioxetine group, and 3.3% in the duloxetine group. Except for headache, which occurred at similar rates in all groups, most adverse events occurred at higher rates in the duloxetine group compared to either the placebo or vortioxetine groups.

Most adverse events were of mild or moderate intensity, but 50 (8.3%) participants had 68 adverse events of severe intensity. These occurred in 9.3%, 6.0%, 7.2%, and 10.7% of patients in the placebo, 2.5 mg vortioxetine, 5 mg vortioxetine, and duloxetine groups, respectively. Adverse events leading to early withdrawal occurred in 5.3%, 5.4%, 8.5%, and 10.7% of patients in these same groups, respectively. Seven (1.2%) participants had eight serious adverse events: two in the placebo group (elective abortion, worsening of depression), four in the 5 mg vortioxetine group (coronary artery disease, head trauma, seizure, atrial fibrillation), and two in the duloxetine group (myocardial infarction, panic attacks). One serious adverse event in the 5 mg vortioxetine group (atrial fibrillation) and one in the duloxetine group (panic attacks) were judged by the investigator to be possibly related to study drug. No patients died during the study.

No clinically meaningful differences between groups were found for clinical laboratory values, vital signs, physical examination findings, or electrocardiograms.

Suicidality

Two patients in the 2.5 mg vortioxetine group and two patients in the duloxetine group had adverse events of suicidal ideation. The two patients in the vortioxetine group discontinued study drug and all patients recovered. According to results of the C-SSRS, the percentage of patients reporting suicidal ideation – with or without intent to act – was small, and there were no significant differences noted between any active treatment group and the placebo group.

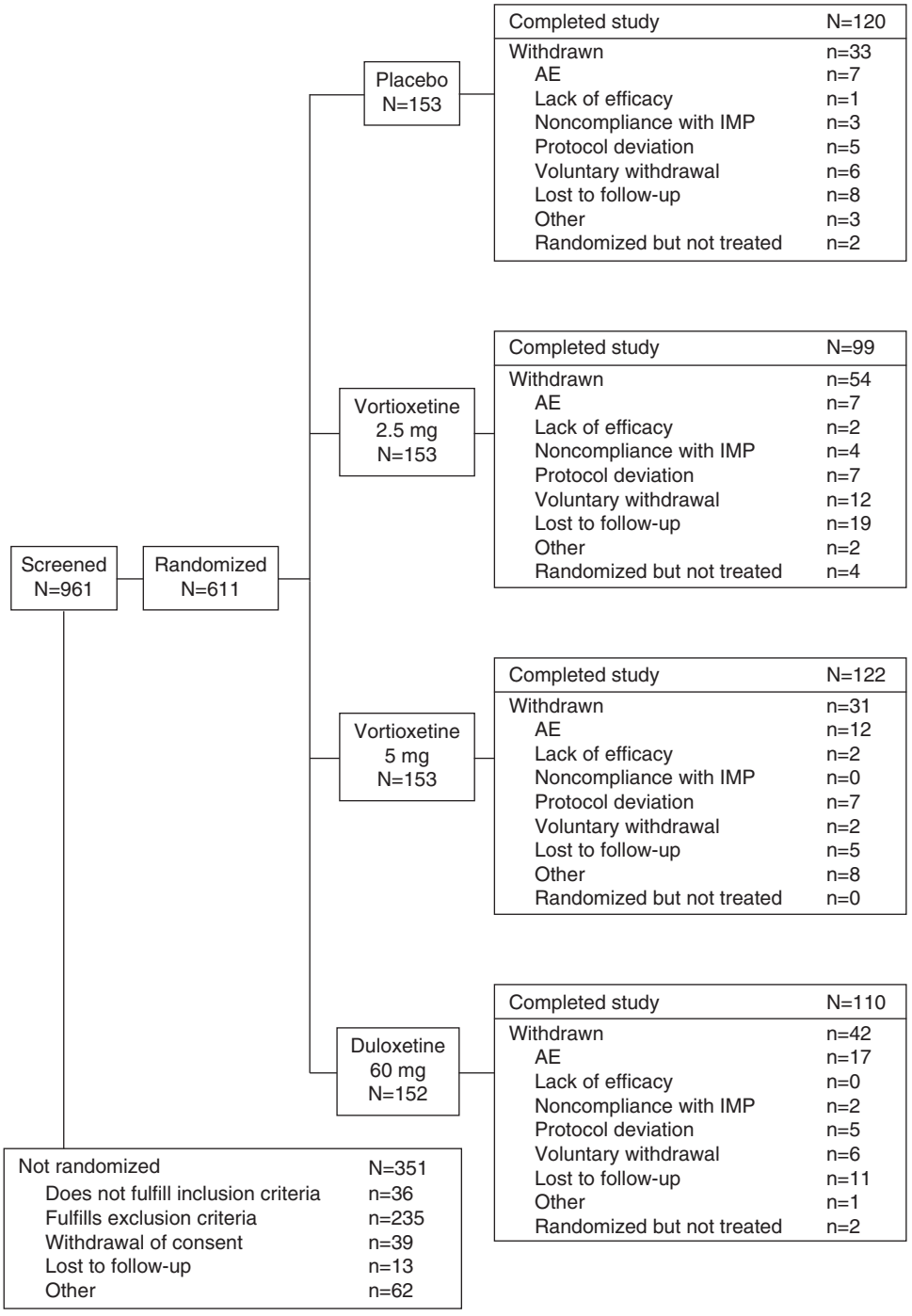

Figure 1. Disposition of screened patients and randomized participants. One patient was inappropriately recorded as both randomized and a screen failure, and is not included here.

Sexual function

Table 4 shows adverse events related to sexual dysfunction during the study, as well as an analysis of data from the ASEX. Most participants in the trial (64.5–71.2%) had sexual dysfunction at baseline. Among those who did not, sexual dysfunction emerged during double-blind treatment in 33–51%, with the highest rate occurring in the 2.5 mg vortioxetine and duloxetine groups. There were no significant (versus placebo) changes from baseline in ASEX total score in either vortioxetine group at any clinic visit. There were small but significant (versus placebo) increases from baseline in the duloxetine group at weeks 1, 2, and 4 ($p < 0.006$), but no significant changes at weeks 6 or 8.

Table 1. Demographic and baseline characteristics of randomized participants.

Characteristic	Placebo $n=153$	Vortioxetine 2.5 mg $n=153$	Vortioxetine 5 mg $n=153$	Duloxetine 60 mg $n=152$
Sex, *n* (%)				
Male	60 (39.2)	55 (35.9)	47 (30.7)	61 (40.1)
Female	93 (60.8)	98 (64.1)	106 (69.3)	91 (59.9)
Mean age, years (SD)	42.6 (13.8)	42.6 (12.9)	43.1 (13.9)	42.7 (14.4)
Race, *n* (%)				
White	121 (79.1)	112 (73.2)	108 (70.6)	111 (73.0)
Black	28 (18.3)	35 (22.9)	40 (26.1)	36 (23.7)
Asian	3 (2.0)	3 (2.0)	3 (2.0)	3 (2.0)
American Indian/Alaskan	1 (0.7)	2 (1.3)	0	0
Pacific Islander	0	1 (0.7)	0	1 (0.7)
Mean BMI, kg/m^2 (SD)*	29.6 (7.3)	29.5 (7.5)	31.4 (8.8)	30.1 (6.8)
Mean baseline HAM-D24 total score (SD)	29.5 (6.1)	29.8 (5.4)	29.8 (5.6)	28.7 (5.1)
Mean baseline MADRS total score (SD)	30.0 (4.4)	29.8 (4.6)	30.1 (4.5)	29.4 (4.3)
Mean baseline HAM-A score (SD)	18.8 (5.5)	19.3 (5.2)	18.7 (5.7)	17.4 (5.5)
Mean baseline CGI-I score (SD)	4.5 (0.62)	4.6 (0.62)	4.6 (0.65)	4.5 (0.67)
Median duration of current major depressive episode, weeks	28.0	24.0	24.0	26.0
Prior pharmacotherapy for MDD, *n* (%)	83 (55.0)	79 (53.0)	90 (58.8)	83 (55.3)

SD, standard deviation; *$p=0.035$.

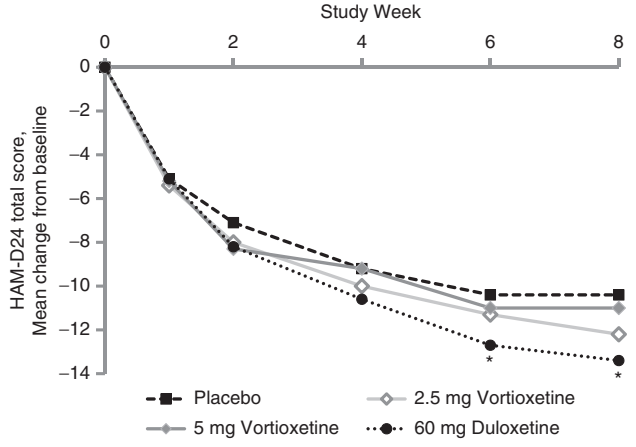

Figure 2. Mean (least-square mean) change from baseline in HAM-D24 total score during the 8-week double-blind treatment period. *$p<0.05$ versus placebo.

Discussion

In two previous short term clinical trials of patients with MDD conducted outside the US, patients receiving 5 mg per day vortioxetine had improved depression symptoms (as assessed by MADRS or HAM-D24 total score) after 6 or 8 weeks[17,19]. A third trial found evidence of efficacy on secondary analyses[18]. The current study evaluated 2.5 mg and 5 mg doses of vortioxetine in patients with MDD using change in HAM-D24 total score as the primary outcome measure. After 8 weeks of double-blind treatment, patients in both vortioxetine groups had declines in HAM-D24 scores that were larger than those in the placebo group, but the differences from placebo were not statistically significant. Another recent trial of 5 mg vortioxetine conducted in the US failed to demonstrate antidepressant efficacy, but the interpretation of that result was confounded by the lack of an active reference arm[21]. The current trial included a fourth group of patients randomized to duloxetine (60 mg per day) as active reference; these patients exhibited statistically significant improvements in HAM-D24 total scores compared to patients in the placebo group ($p=0.005$). A sixth trial, conducted in elderly patients with MDD, found significant separation from placebo for 5 mg vortioxetine ($p=0.0011$)[22]. It has been suggested that efficacy of an antidepressant can be more fully evaluated using a relapse-prevention study design (randomized withdrawal) and vortioxetine has shown maintenance of improvement and prevention of relapse in adults with MDD[20,25].

The reasons for the discrepancies between clinical trials of vortioxetine are not well understood. In the previous trials that found significant separation between vortioxetine and placebo, participants had higher average scores than the current trial on either the HAM-D24 or MADRS scale at baseline[17,19] but the differences from the current trial were neither large nor consistent. It is possible that the current trial had insufficient power to detect a difference between vortioxetine and placebo, as suggested by the trend toward separation seen in Figure 2. The sample size calculation used for the current trial was based on an anticipated treatment effect of 3.5 point decline in HAM-D24 total score, which is less than the effect size observed in the previous positive trials[17,19]. Therefore, it seems unlikely that the criteria for efficacy were too stringent or the sample size too small in the current trial. One criterion for inclusion in the current trial was MADRS score ≥ 22, which may have led to some score inflation at initial assessment, possibly contributing to a stronger placebo effect. However, the other positive trials of vortioxetine required

Table 2. Primary and secondary outcome measures at week 8 (LOCF).

Outcome measure	Placebo $n=149$	Vortioxetine 2.5 mg $n=146$	Vortioxetine 5 mg $n=153$	Duloxetine 60 mg $n=149$
HAM-D24 total score				
LS mean change from baseline (SE)	−10.50 (0.76)	−12.04 (0.74)	−11.08 (0.74)	−13.47 (0.75)
P value (vs. placebo)		0.138	0.577	0.005
HAM-D24 responder rate*				
Number (%) of responders	48 (32.2)	60 (41.1)	58 (37.9)	76 (51.0)
Odds ratio (vs. placebo)		1.473	1.288	2.179
P-value (vs. placebo)		0.111	0.296	0.001
CGI-I score				
LS mean change from baseline (SE)	2.79 (0.1)	2.73 (0.1)	2.63 (0.1)	2.39 (0.1)
P-value (vs. placebo)		0.680	0.230	0.003
HAM-D24 total score in participants with baseline HAM-A ≥20				
n	85	74	96	100
LS mean change from baseline (SE)	−10.46 (0.99)	−12.17 (1.06)	−10.63 (0.95)	−13.50 (0.93)
P-value (vs. placebo)		0.215	0.892	0.019
SDS total score				
n	130	122	123	114
LS mean change from baseline (SE)	−6.83 (0.64)	−6.46 (0.64)	−6.59 (0.64)	−8.91 (0.67)
P-value (vs. placebo)		0.672	0.790	0.021
MADRS remission†				
n	119	100	120	110
Number (%)	33 (27.7)	33 (33.0)	32 (26.7)	51 (46.4)

*≥50% decrease from baseline HAM-D24 total score. †MADRS total score <10. SE, standard error.

Table 3. Treatment-emergent adverse events occurring in at least 5% of participants in any treatment group.

Adverse event	Number of participants (%)			
	Placebo	Vortioxetine 2.5 mg	Vortioxetine 5 mg	Duloxetine 60 mg
Any	96 (63.6)	96 (64.4)	108 (70.6)	128 (85.3)
Fatigue	5 (3.3)	3 (2.0)	3 (2.0)	13 (8.7)
Nausea	16 (10.6)	24 (16.1)	44 (28.8)	63 (42.0)
Dry mouth	11 (7.3)	16 (10.7)	16 (10.5)	40 (26.7)
Diarrhea	13 (8.6)	7 (4.7)	14 (9.2)	19 (12.7)
Constipation	11 (7.3)	6 (4.0)	6 (3.9)	18 (12.0)
Decreased appetite	1 (0.7)	1 (0.7)	2 (1.3)	8 (5.3)
Headache	18 (11.9)	20 (13.4)	24 (15.7)	21 (14.0)
Dizziness	7 (4.6)	10 (6.7)	9 (5.9)	22 (14.7)
Somnolence	6 (4.0)	3 (2.0)	9 (5.9)	20 (13.3)
Insomnia	6 (4.0)	6 (4.0)	6 (3.9)	11 (7.3)
Hyperhidrosis	4 (2.6)	4 (2.7)	4 (2.6)	11 (7.3)

even higher MADRS scores for inclusion. Furthermore, an exploratory analysis of baseline score distributions in the current trial did not reveal conclusive evidence of score inflation. Thus, inflation of scores at baseline is unlikely to account for the strong placebo effect or the lack of separation between vortioxetine and placebo in the current trial. It should also be noted that the active reference duloxetine arm separated from placebo in this trial. The duloxetine arm was associated with a higher rate of AEs than the placebo or vortioxetine arms, which may have led to functional unblinding of duloxetine and an increase in response to a perceived active drug. AE rates in the vortioxetine arms were lower than duloxetine and similar to placebo levels, which may have led to a perception of not being on active drug. This possibility was not examined during the trial but should be kept in mind for future studies.

Other exploratory analyses were performed in an attempt to understand the results of the current trial (not shown). These analyses included studies of subgroups defined by demographic characteristics, BMI, level of anxiety, number of prior MDD episodes, duration of current episode, presence of melancholia, and site characteristics (e.g., use of a single rater or multiple raters per study participant). No single factor changed the results of the trial or provided a clear explanation of the results. When similar analyses were performed using data pooled from several trials of vortioxetine in MDD, some trends were observed.

Table 4. Adverse events related to sexual dysfunction and results of the ASEX.

Outcome measure	Number of participants (%)			
	Placebo $n=151$	Vortioxetine 2.5 mg $n=149$	Vortioxetine 5 mg $n=153$	Duloxetine 60 mg $n=150$
Adverse events related to sexual dysfunction				
Libido decreased	3 (2.0)	3 (2.0)	3 (2.0)	4 (2.7)
Orgasm abnormal	0	0	3 (2.0)	3 (2.0)
Disturbance in sexual arousal	0	1 (0.7)	1 (0.7)	0
Loss of libido	0	0	2 (1.3)	0
ASEX results				
Number of respondents	146	138	149	142
Sexual dysfunction at baseline	104 (71.2)	89 (64.5)	101 (67.8)	93 (65.5)
No sexual dysfunction at baseline	42	49	48	49
Treatment-emergent sexual dysfunction	14 (33.3)	25 (51.0)	18 (37.5)	23 (46.9)
Odds ratio (vs. placebo)		3.282	1.662	2.419
95% CI		1.265–8.515	0.652–4.237	0.964–6.071
P-value		0.015	0.288	0.060
Odds ratio (vs. duloxetine)		1.356	0.687	
95% CI		0.558–3.295	0.286–1.648	
P-value		0.501		

Sexual dysfunction defined as ASEX total score ≥19, score >4 on any 3 items, or score >5 on any item. Odds ratios, 95% CIs, and *p*-values are from logistic regression with explanatory variables for treatment, baseline sexual dysfunction, status, baseline sexual dysfunction status by treatment interaction, and baseline score.

For example, participants who had no prior episodes of depression tended to have greater placebo responses than participants who had multiple prior episodes, participants with melancholia tended to respond better to vortioxetine than those without melancholia, and placebo participants who had a single rater throughout the study tended to have smaller responses than participants who had multiple raters. Further analyses of pooled data are required before these trends can be confirmed.

Vortioxetine is being evaluated for the treatment of MDD and its magnitude and mode of action, as well as optimal dosing, are not yet established. The current trial utilized doses considered to be at the lower end of its dose range, although the 5 mg daily dose overlaps with doses found to produce significant separation from placebo in the two previous positive trials. One notable difference between vortioxetine trials is that the previous trials were conducted outside of the US in Europe, North America, Asia and Australia, whereas the current trial and the previous failed trial were conducted in the United States. Previous studies of antidepressants have noted differences in the ability to detect efficacy in clinical trials conducted in different countries. These differences may be related to regional differences in patient and disease characteristics as well as diagnostic and clinical practices[26].

It is widely recognized that many clinical trials of effective antidepressant agents are negative. In a recent overview of trials submitted for regulatory approval in the United States – in which only drugs, doses, and treatment durations known to be effective for the treatment of MDD were included – only 53% of trials were positive (drug therapy significantly better than placebo)[26]. Prior analyses had reached similar conclusions[27–29]. One explanation that has been offered is that patients in the placebo arms of antidepressant trials commonly have strong placebo responses. Furthermore, the magnitude of placebo responses has increased in recent years, making it more difficult to detect a drug effect[29,30]. Patients in the current trial who received placebo also exhibited a strong decline in HAM-D24 total score during the treatment period, and this strong placebo response likely contributed to the difficulty in detecting an effect of vortioxetine. Although there was a significant difference detected with the active reference, the overall treatment effect was weak compared to previous studies of duloxetine[31].

Several design features of the current trial have been associated with low signal detection in previous trials of antidepressants. For example, it has been noted that trials with multiple treatment arms and fixed dosing (versus flexible dosing) are less likely to detect antidepressant efficacy versus placebo[30,32]. Trials with a low proportion of patients randomized to the placebo arm have been associated with strong placebo responses, possibly because of expectations of efficacy on the part of patients and raters[33,34]. As discussed by Mallinckrodt and colleagues[33], greater statistical power could be achieved by allocating more patients to the placebo arm in trials with multiple active-treatment arms. It has also been noted that the process of patient assessment itself can have a therapeutic benefit, possibly contributing to larger placebo responses[35]. Other aspects of the trial design or analysis may have reduced the ability of the trial to detect a drug effect, including the methods of recruitment, low doses of vortioxetine, use of

de-centralized raters[36,37], and use of the LOCF method for imputing values for discontinued participants[38,39]. Future trials of vortioxetine may utilize different methods of recruitment or depression scoring. Finally, regional differences in patients or disease characteristics, diagnostic criteria, or clinical care[26] may necessitate the use of higher drug doses to demonstrate efficacy in US-based trials versus non-US-based trials.

Although the current trial did not show a statistically significant antidepressant effect of vortioxetine, it did provide information about the tolerability of the drug, including effects on sexual function. Overall, the 2.5 mg and 5 mg doses of vortioxetine were well tolerated and associated with fewer adverse events than duloxetine. Treatment-emergent sexual dysfunction occurred at higher rates in the low-dose (2.5 mg) vortioxetine group than in the higher-dose (5 mg) group, but neither group experienced treatment-emergent sexual dysfunction at a rate that was significantly higher than that in the duloxetine group.

Conclusion

In this study of patients with MDD of at least 3 months' duration, 8 weeks of treatment with low doses of vortioxetine (2.5 and 5 mg) was associated with declines in HAM-D24 total score that were numerically greater, but not statistically different, than placebo. Vortioxetine was well tolerated in this population.

Transparency

Declaration of funding

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Declaration of financial/other relationships

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