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Safety, tolerability, and efficacy of vortioxetine (Lu AA21004) in major depressive disorder: results of an open-label, flexible-dose, 52-week extension study

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Patients with major depressive disorder often experience relapse after responding to treatment; therefore, maintenance therapy with antidepressants is recommended for maintaining response or remission. This multicenter, open-label, flexible-dose, 52-week extension study evaluated the long-term safety, tolerability, and maintenance of efficacy in study participants who had completed one of two randomized, double-blind, placebo-controlled, 8-week dose-ranging vortioxetine trials in study participants with major depressive disorder. At the open-label baseline, all study participants were switched to vortioxetine 5 mg/day for the first week, with subsequent dose adjustments from 2.5 to 10 mg/day on the basis of response and tolerability. Treatment with vortioxetine for 52 weeks was well tolerated, with no new safety signals identified. Among the 834 evaluable study participants, treatment-emergent adverse events were reported in 70.6%, with the most common in the combined (all doses) population of nausea (15.2%), headache (12.4%), nasopharyngitis (9.8%), diarrhea (7.2%), and dizziness (6.8%). The rate of adverse events related to sexual dysfunction was low and weight gain was minimal. Laboratory values, vital signs, ECGs, physical examinations, and Columbia-Suicide Severity Rating Scale results showed no trends of clinical concern. The change in the severity of depressive and anxiety symptoms was maintained throughout the study as reflected by a 24-item Hamilton Depression Scale total score of 8.2 at week 52 (from 17.6 at open-label baseline) in the observed case data set. *Int Clin Psychopharmacol* 29:36–44 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Many effective treatments for major depressive disorder (MDD) are currently available, but response and remission rates are low or inconsistent. Approximately 50% of patients fail to respond adequately to initial treatment, and ~30% achieve the treatment goal of full remission (Warden *et al.*, 2007). Furthermore, among patients achieving remission, there is a considerable risk of relapse (Oestergaard and Moldrup, 2011). Thus, recent studies (Geddes *et al.*, 2003; Kornstein, 2008) and clinical guidelines (Davidson, 2010; National Guideline Clearinghouse, 2013; National Institute for Health and Clinical Excellence, 2010; Rodgers *et al.*, 2012) recommend long-term antidepressant therapy for maintaining response or remission of MDD. In addition, antidepressants may be associated with significant adverse effects that can affect patient acceptance of and adherence to therapy (Millan, 2006; Ginsberg, 2009). Newer effective antidepressive agents with better tolerability offer the potential to improve adherence to treatment and provide clinicians with improved therapeutic options for this debilitating condition (Ratner *et al.*, 2008; Spina *et al.*, 2008).

Vortioxetine (Lu AA21004) is an investigational antidepressant agent currently under development for the treatment of MDD. The mechanism of action of vortioxetine is considered 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-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 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 serotonergic receptor and transporter occupancy studies coupled with neuronal firing and microdialysis studies in rats suggest that the targets

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interact in a complex manner, leading to modulation of neurotransmission in several systems, including serotonin, norepinephrine, dopamine, histamine, and acetylcholine systems within the rat forebrain (Bang-Andersen *et al.*, 2011; Mork *et al.*, 2012). These multimodal pharmacological actions are considered to be responsible for the antidepressant effects of vortioxetine.

The efficacy and safety of vortioxetine has been evaluated in several clinical trials (Alvarez *et al.*, 2012; Baldwin *et al.*, 2012b; Henigsberg *et al.*, 2012; Katona *et al.*, 2012; Mahableshwarkar *et al.*, 2013) and an open-label extension study (Baldwin *et al.*, 2012a). Study participants who completed one of two short-term double-blind randomized trials (NCT00672620 and NCT00735709) (Henigsberg *et al.*, 2012; Mahableshwarkar *et al.*, 2013) were eligible to continue into this long-term study. In the dose-ranging lead-in studies, 45–60% of study participants with MDD responded to therapy after 8 weeks of treatment (with either 2.5, 5, 10 mg/day of vortioxetine, 60 mg of duloxetine, or placebo), defined as at least a 50% decrease from baseline in the 24-item Hamilton Depression Scale (HAM-D24) total score. The primary objective of the current study was to evaluate the long-term safety and tolerability of flexible doses of vortioxetine (2.5, 5, and 10 mg once daily) over a period of 52 weeks in study participants with MDD who completed one of the two acute double-blind studies.

Methods

Study design

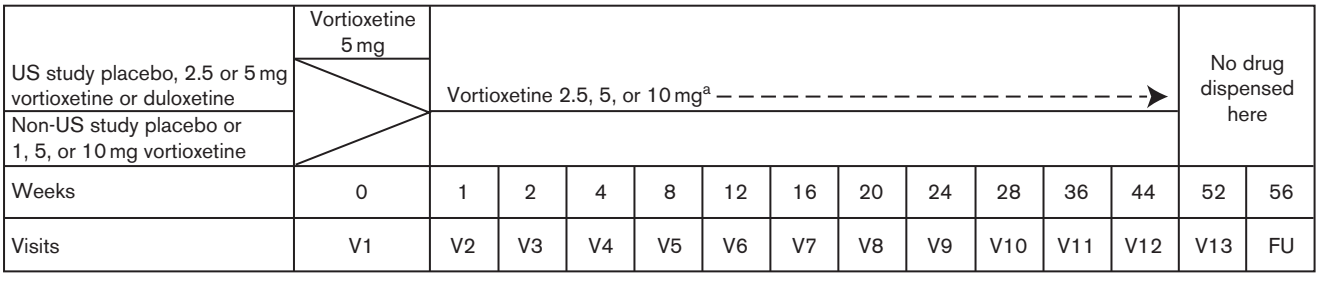
This was a multicenter, open-label, flexible-dose, 52-week extension study of study participants who had completed one of two previous acute double-blind efficacy and safety trials that were conducted at 88 sites in Asia, Australia, Europe (NCT00735709) (Henigsberg *et al.*, 2012), and the USA (NCT00672620) (Mahableshwarkar *et al.*, 2013). In the US study, study participants were originally randomized to receive vortioxetine 2.5 mg, vortioxetine 5 mg, duloxetine 60 mg, or placebo once daily; those in the non-US study were randomized to receive vortioxetine 1 mg, vortioxetine 5 mg, vortioxetine 10 mg, or placebo once daily. Study participants completing one of these acute double-blind studies were eligible to continue treatment for 52 weeks in this open-label extension study, irrespective of their response to treatment at the end of week 8 of the acute efficacy studies if they were considered by the investigator to benefit from 52 weeks of treatment with vortioxetine. After baseline screening, all study participants were switched to vortioxetine 5 mg/day for the first week of the extension study, irrespective of their treatment assignment at the completion of the acute double-blind trials. Thereafter, the vortioxetine dose could be maintained at 5 mg/day, increased to a maximum of 10 mg/day, or decreased to 2.5 mg/day, on the basis of patient response and tolerability as determined by the investigator.

The study was approved by the ethics committee of each site and was carried out in accordance with the ethical principles outlined in the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines. All enrolled study participants provided written informed consent before undergoing any study procedures.

Study visits

The visit schematic for the study is presented in Fig. 1. The baseline visit was the completion of the original lead-in study. At study visits during the treatment phase (weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 36, 44, and 52), assessments performed included physical examination (with measurement of vital signs and weight and 12-lead ECG), clinical laboratory tests, adverse event (AE) evaluation and concomitant medication use, and drug return assessment and accountability. Clinical assessments included the Columbia-Suicide Severity Rating Scale (C-SSRS), HAM-D24, Hamilton Anxiety Scale (HAM-A), Montgomery–Asberg Depression Rating Scale (MADRS), Clinical Global Impressions Scale – Severity of Illness Scale (CGI-S), 36-item Short-Form (SF-36), and the Sheehan Disability Scale (SDS). Assessments were repeated at the final study visit or the early termination visit. A follow-up safety call was made at least 4 weeks

Fig. 1



Study visit schematic. [a]Dose adjustment up or down as appropriate on the basis of response and tolerability. FU, follow-up safety call.

after the last dose of vortioxetine for any ongoing AEs, new AEs, new serious AEs, and concomitant medications.

Study participants

Inclusion criteria for the study included the completion of either of the lead-in trials immediately before enrollment in the extension study. The baseline visit must have been the same day as the completion of the preceding study. Study participants were required to have a primary diagnosis of MDD (classification code 296.xx) as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (American Psychiatric Association, 2000) at entry into the lead-in study and a clinical indication (in the opinion of the investigator) for 12 months of continued treatment. Study participants were required to be able to understand and comply with study instructions, and sexually active study participants of child-bearing potential had to agree to use appropriate contraception during the study and for 1 month afterward. Exclusion criteria included any concomitant diagnosis of other psychiatric disorders (e.g. mania, bipolar disorder, schizophrenia, etc.) before or during entry into either of the lead-in studies, risk for suicide, and/or a score of at least 5 points on item 10 (suicidal thoughts) on the MADRS. Study participants were also excluded if they experienced a continuing moderate or severe AE related to treatment from the original acute trial or were using disallowed medications.

Outcome variables

The primary objective was the safety and tolerability of vortioxetine, as assessed on the basis of AEs, vital signs and weight, ECGs, clinical laboratory values, and physical examination findings. AEs were assessed for severity (mild, moderate, or severe) and causal relationship with the study drug (probable, possible, or not related). Treatment-emergent adverse events (TEAEs) were defined as an AE with an onset that occurred after receiving the study drug and within 30 days after receiving the last dose of the study drug. Suicidal ideation and behavior were assessed as an exploratory variable utilizing the C-SSRS. Change in the severity of symptoms of depression and anxiety were assessed using the mean change from the open-label baseline in HAM-D24 total score (at all visits) and the mean change from baseline in the MADRS total score, HAM-A total score, and CGI-S at weeks 4, 24, and 52. Patient-reported outcomes included the SF-36 and the SDS.

Statistical analysis

The safety set included all study participants who received at least one dose of open-label study medication. The change in the severity of depressive symptoms was evaluated in study participants in the safety analysis who had been subjected to at least one post-open-label baseline evaluation [observed case (OC) data set]. Safety and efficacy data were summarized using descriptive statistics. The results were tabulated for all study participants enrolled in the open-label extension phase. Data were analyzed using the SAS System, version 9.1.3 (SAS Institute, Cary, North Carolina, USA).

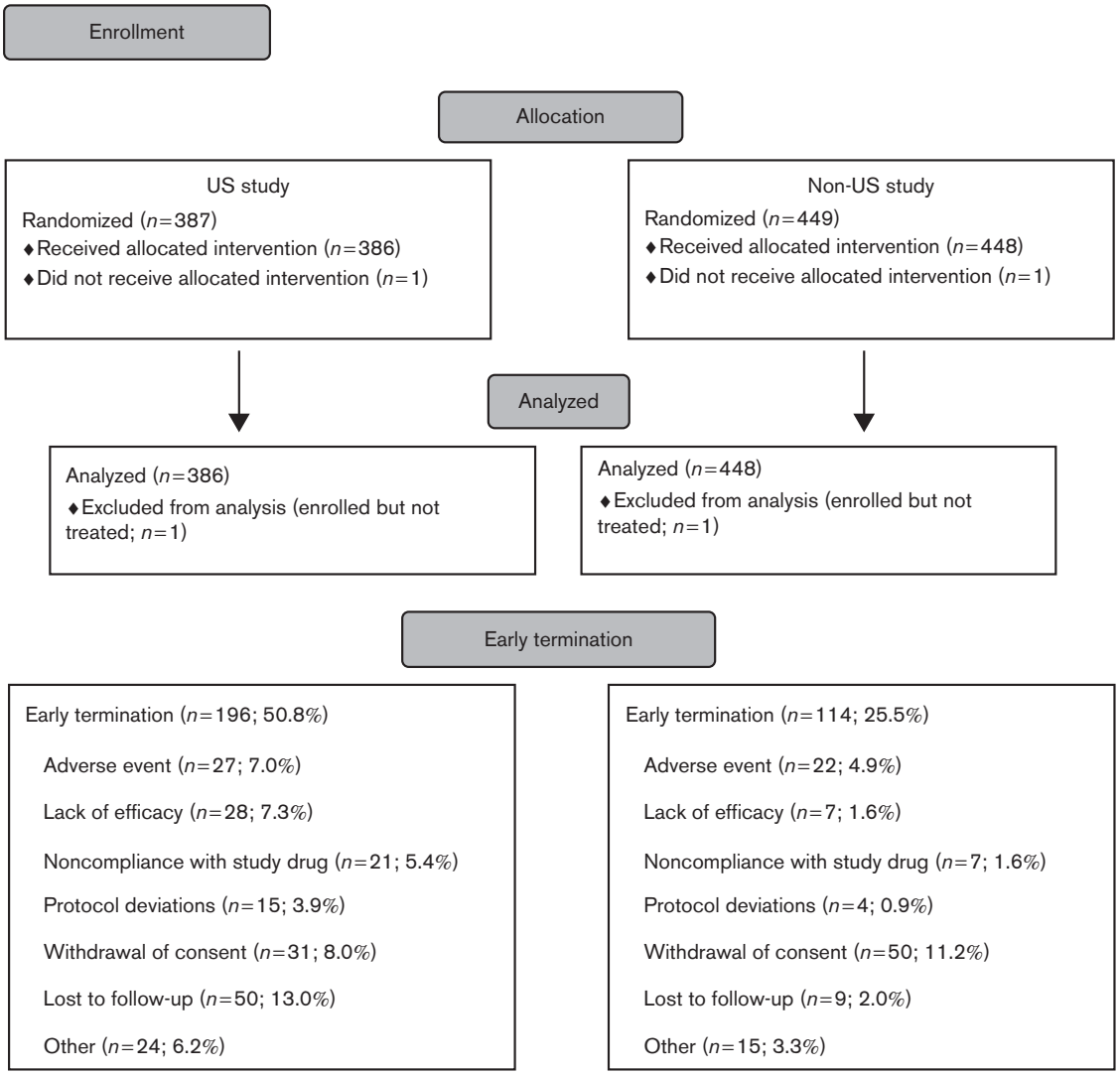
Results

A total of 836 study participants were enrolled: 387 from the US study and 449 from the non-US study. Two study participants did not receive study treatment and were not included in the analysis (Fig. 2). Study participants were predominantly women (63%) and White (83%), with a mean age of 45.5 years (Table 1). Mean compliance with study medication (([number of capsules dispensed – number of capsules returned]/[date of last dose – date of first dose + 1]) × 100) was ~100%, with the majority of study participants having a compliance rate of 80–120%. The mean exposure to the 2.5, 5, and 10 mg dose levels was 22.9, 15.5, and 31.1 weeks, respectively. Sixty-seven percent of the study participants received vortioxetine 10 mg for at least one week and 40% received vortioxetine 10 mg for at least 24 weeks. Medical histories from the acute efficacy trials were transcribed into the open-label extension subject database, with any ongoing AEs from the original studies recorded as concurrent conditions. The most common medical history/concurrent conditions (defined as occurring in ≥ 10% of the study participants in the overall population) included headache, hypertension, nausea, back pain, and insomnia. These conditions were more common in the US study than in the non-US study: headache (41.5 vs. 11.4%), hypertension (19.4 vs. 19.0%), nausea (22.0 vs. 8.5%), back pain (13.7 vs. 9.2%), and insomnia (17.4 vs. 4.0%).

Safety

Among the 834 evaluable study participants, the mean duration of vortioxetine exposure was 39.5 ± 18.1 (range, 0.1–56.9) weeks. TEAEs were reported by 589 (70.6%) of the 834 study participants, who experienced a total of 2117 events (Table 2). Most TEAEs were mild or moderate in severity. The most frequently reported TEAEs (incidence ≥ 5%) were nausea, headache, nasopharyngitis, diarrhea, dizziness, and upper respiratory tract infection (Table 3). There tended to be a higher TEAE rate in the study participants from the US study compared with the non-US study, with any TEAE reported in 79.3 and 63.2% of the study participants, from the two studies, respectively, although the rates of TEAE-related withdrawal (7.0 vs. 5.1%) and serious TEAEs (4.1 vs. 2.9%) were generally similar between studies. A total of 29 (3.5%) of the study participants experienced 38 serious AEs and five were considered by the investigator to be related to vortioxetine (left hemispheric ischemic stroke, depression, major depression, supraventricular tachycardia, and paroxysmal tachycardia). TEAEs leading to treatment discontinuation occurred in 50 study participants (6.0%), with nausea, somnolence, dizziness, and depression occurring in more

Fig. 2



CONSORT flow diagram.

Table 1 Baseline clinical and demographic characteristics

Characteristics	Total enrolled (*N*=836)	Rollover from US study (*n*=387)	Rollover from non-US study (*n*=449)
Male [*n* (%)]	310 (37.1)	138 (35.7)	172 (38.3)
Age			
Mean (SD)	45.5 (12.8)	43.8 (13.6)	47.0 (11.8)
>55 years [*n* (%)]	200 (23.9)	82 (21.2)	118 (26.3)
Race [*n* (%)]			
White	693 (82.9)	289 (74.7)	404 (90.0)
Black	86 (10.3)	86 (22.2)	0 (0.0)
Asian	54 (6.5)	9 (2.3)	45 (10.0)
American Indian/Alaskan Native	2 (0.2)	2 (0.5)	0 (0.0)
Native Hawaiian/other Pacific Islander	1 (0.1)	1 (0.3)	0 (0.0)
Ethnicity [*n* (%)]			
Hispanic/Latino	53 (6.3)	53 (13.7)	0 (0.0)
Non-Hispanic/non-Latino	782 (93.5)	333 (86.0)	449 (100.0)
Weight [mean (SD)] (kg)	81.2 (20.83)	87.3 (23.57)	75.88 (16.42)
Height [mean (SD)] (cm)	169.0 (9.78)	169.1 (10.39)	168.9 (9.78)
BMI [mean (SD)] (kg/m^2)	28.4 (7.07)	30.7 (8.44)	26.5 (4.92)

BMI, body mass index.

Table 2 Summary of treatment-emergent adverse events

TEAE	Number of events	Study participants (n=834) [n (%)]
Any TEAE	2117	589 (70.6)
Related[a]	1003	413 (49.5)
Not related	1114	176 (21.1)
Severity		
Mild	1068	187 (22.4)
Moderate	936	320 (38.4)
Severe	113	82 (9.8)
Leading to early termination	77	50 (6.0)
Nausea	–	8 (1.0)
Somnolence	–	4 (0.5)
Dizziness	–	3 (0.4)
Depression	–	3 (0.4)
Serious TEAEs	38	29 (3.5)
Related[a]	5	5 (0.6)
Deaths	0	0 (0.0)

TEAEs, treatment-emergent adverse events.
[a]Considered by the investigator to be possibly or probably related to vortioxetine.

Table 3 Treatment-emergent adverse events occurring in at least 5% of the study participants

	Number of study participants (n=834) [n (%)]
Any TEAE	589 (70.6)
Nausea	127 (15.2)
Headache	103 (12.4)
Nasopharyngitis	82 (9.8)
Diarrhea	60 (7.2)
Dizziness	57 (6.8)
Upper respiratory tract infection	53 (6.4)

TEAEs, treatment-emergent adverse events.

than two study participants (Table 2). Three of the study participants with serious related TEAEs withdrew from the study: participants with ischemic stroke, depression, and major depression. The other two study participants, with supraventricular tachycardia and paroxysmal tachycardia, recovered from the events and completed the study as scheduled. The study participant with ischemic stroke was a 78-year-old woman [body mass index (BMI)=33 kg/m^2] who had previously received duloxetine 60 mg during the double-blind phase. The study participant had no identifiable risk factors (i.e. hypertension, hyperlipidemia, previous transient ischemic attack, or cardiovascular concerns); however, she did have a previous history of falls that required hospitalization, including a fall during the double-blind phase and a fall after initiation on vortioxetine. The study participant received vortioxetine for a total of 17 days at a daily dose of 5 mg for the initial 7 days and 2.5 mg for 10 days before hospitalization for left hemispheric ischemic stroke. The patient was discharged with right-side weakness and speech deficits. No deaths were reported during the study.

An AE subanalysis during the first 14 days of open-label treatment showed that study participants treated previously with duloxetine (this treatment arm only in the short-term US study), when abruptly switched to vortioxetine as part of this long-term study, experienced a significantly higher rate of dizziness (19.4%) compared with those who had previously received placebo (0.9%) or vortioxetine 2.5 and 5 mg (3.5 and 5.6%, respectively).

The incidence of treatment-emergent sexual dysfunction was low, with 18 events among the 834 study participants. Decreased libido was the most commonly reported sexual complaint (n = 8; 1%), followed by erectile dysfunction (n = 4; 0.5%) and delayed ejaculation (n = 2; 0.2%). None of the study participants discontinued the study because of sexual dysfunction-related AEs. With respect to weight, no clinically meaningful differences were observed among the groups administered vortioxetine 2.5, 5, or 10 mg/day. Overall, there was a mean increase in weight of 0.67 kg at the final visit relative to the open-label baseline. Weight changed (increase or decrease) by at least 7% in 155 (18.6%) of 834 study participants (n = 105 with an increase $\geq$ 7% and n = 50 with a decrease $\geq$ 7%). There were 36 study participants (4.3%) with TEAEs of weight increased and 10 study participants (1.2%) with TEAEs of weight decreased. Insomnia was reported in 17 study participants (2.0%).

Serum chemistry test results showed no clinically meaningful differences among the treatment groups. Alanine aminotransferase and aspartate aminotransferase values of at least three times the upper limit of normal occurred in three (0.4%) and six (0.7%) study participants, respectively; however, these elevations did not lead to discontinuation from the study. No identifiable trend was observed in changes in levels of serum cholesterol or triglycerides. Mean changes from baseline in urinalysis were minimal and not considered clinically meaningful. There were also no clinically meaningful treatment-related trends for vital signs, physical findings, or ECG readings. There were two ECG-related events that were considered serious: one instance of atrial fibrillation (considered unrelated to vortioxetine) and one case of supraventricular tachycardia (possibly related to vortioxetine). One participant had a prolonged Bazett-corrected QT interval; however, this participant had been newly diagnosed with Wolff–Parkinson–White syndrome, and the QT prolongation was not considered by the investigator to be related to vortioxetine. This participant was discontinued from the study.

Of the 834 study participants included in the analysis, 204 (24.5%) and 74 (8.9%) reported a previous history of suicidal ideation and behavior, respectively (Table 4). During the study, 83 (10%) and three (0.4%) study participants reported suicidal ideation and behavior, respectively. One suicide attempt and two cases of suicidal ideation were reported as serious. None of the three events were considered related to vortioxetine; all study participants recovered.

Symptoms of depression and anxiety

The changes in severity of depressive and anxiety symptoms as measured by HAM-D24, HAM-A, and CGI-S during the double-blind phase and the open-label

Table 4 Suicide-related events on the basis of C-SSRS

C-SSRS score	Number in extension study [*n* (%)]	
	Using all previous history[a] (*n*=834)	During the entire study (*n*=830)
No suicidal ideation or behavior (0)	556 (66.7)	747 (90.0)
Any suicidal ideation or behavior (1–10)	278 (33.3)	83 (10.0)
Suicidal ideation (1–5)	204 (24.5)	80 (9.6)
1. Wish to be dead	134 (16.1)	58 (7.0)
2. Nonspecific active suicidal thoughts	36 (4.3)	9 (1.1)
3. Active suicidal ideation with any methods (not plan) without intent to act	29 (3.5)	1 (0.1)
4. Active suicidal ideation with some intent to act, without specific plan	3 (0.4)	2 (0.2)
5. Active suicidal ideation with specific plan and intent	2 (0.2)	0 (0.0)
Suicidal behavior (6–10)	74 (8.9)	3 (0.4)
6. Preparatory acts or behavior	6 (0.7)	1 (0.1)
7. Aborted attempt	8 (1.0)	1 (0.1)
8. Interrupted attempt	1 (0.1)	0 (0.0)
9. Nonfatal suicide attempt	59 (7.1)	1 (0.1)
10. Completed suicide	0 (0.0)	0 (0.0)
Nonsuicidal self-injurious behavior	26 (3.1)	1 (0.1)

C-SSRS, Columbia-Suicide Severity Rating Scale.
[a]All previous history includes events that occurred before administration of the study drug in the initial double-blind study, including screening and baseline visits.

Table 5 Efficacy measures

Parameters	*N*	Open-label study participants (*n* =834)
HAM-D24 total score [mean (SD)]		
Double-blind baseline	829	31.2 (5.46)
Open-label baseline	829	17.6 (9.41)
Week 24	613	9.5 (7.26)
Week 52	522	8.2 (7.12)
Final visit[a]	829	9.7 (8.24)
HAM-D24 response rate [*n* (%)]		
Week 24	613	301 (49.1)
Week 52	522	314 (60.2)
Final visit[a]	829	423 (51.0)
HAM-D17 remission rate [*n* (%)]		
Week 24	613	342 (55.8)
Week 52	522	322 (61.7)
Final visit[a]	829	461 (55.6)
HAM-A total score [mean (SD)]		
Double-blind baseline	818	19.3 (6.40)
Open-label baseline	818	12.1 (7.18)
Week 24	642	7.1 (5.78)
Week 52	527[a]	5.9 (5.35)
Final visit[a]	818	6.9 (5.92)
CGI-S score [mean (SD)]		
Double-blind baseline	818	4.71 (0.74)
Open-label baseline	818	3.24 (1.26)
Week 24	642	2.28 (1.04)
Week 52	527[a]	1.97 (0.97)
Final visit[a]	818	2.24 (1.14)

'HAM-D24 response' indicates a decrease of $\geq$ 50% from the open-label baseline value. 'HAM-D17 remission' denotes a total score of $\leq$ 7.
CGI-S, Clinical Global Impressions Scale – Severity of Illness Scale; HAM-A, Hamilton Anxiety Scale; HAM-D17, 17-item Hamilton Rating Scale for Depression; HAM-D24, 24-item Hamilton Depression Scale.
[a]Study participants' last available visit during the open-label study period.

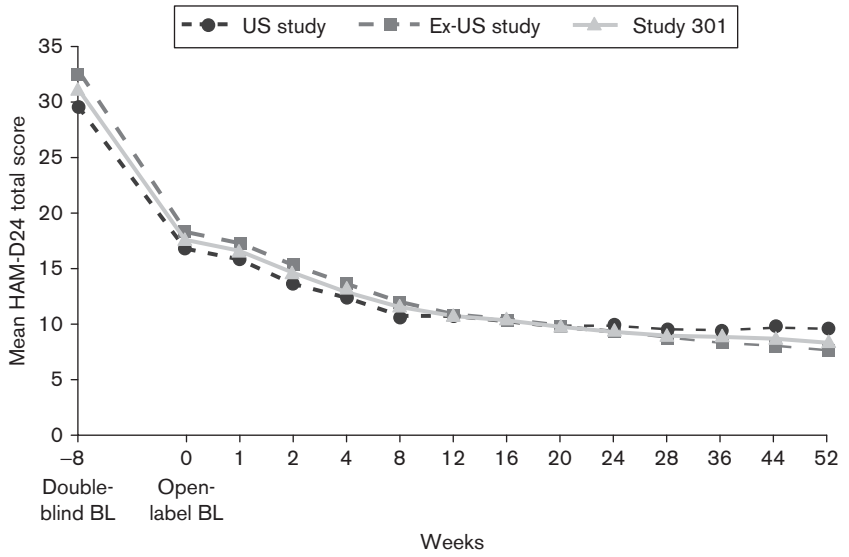
extension phase are summarized in Table 5 and Figs 3–5. These results indicate that the improvements achieved during the double-blind phase were maintained when study participants were continued on or switched to vortioxetine, with scores decreasing further from the open-label baseline values irrespective of the original double-blind assigned treatment. For example, the mean (±SD) HAM-D24 scores decreased from 31.2 (±5.5) at the double-blind lead-in baseline to 17.6 (±9.4) at the open-label baseline, with a further improvement to 9.7 (±8.2) at the final visit (OC analysis). These results reflect a total mean change from double-blind baseline to the end point of the open-label study of –21.5 (±9.4) (Fig. 3). Response (defined as a $\geq$ 50% decrease in the HAM-D24 score from the open-label baseline to the final visit) was achieved in 423/829 (51.0%) study participants (OC analysis). Improvements in HAM-D24 scores were evident irrespective of the dosage assignment in the lead-in trial (i.e. there was no difference in response rates on the basis of treatment in the lead-in study). Decreases in HAM-D24 scores ranged from 16.2 to 25.0 across all vortioxetine dose groups relative to the double-blind baseline, with a further improvement of 4.0–10.2 points at the final visit relative to the open-label baseline. Remission, defined as a HAM-D17 total score of up to 7, was achieved in 461/829 (55.6%) study participants at the final visit. These overall improvements in HAM-D24 scores were similar to those observed in the subgroup of study participants who received duloxetine during the double-blind trial (US study). Here, that subgroup showed a decrease of 18.2 points at the final visit relative to the double-blind baseline and a decrease of 3.4 points relative to the open-label baseline.

Similar changes in symptom severity were noted for the MADRS total score, MADRS response (defined as a $\geq$ 50% decrease in the total score from baseline), and MADRS remission (defined as a total score $\leq$ 10). Mean changes in HAM-A and CGI-S scores from double-blind baseline to the final visit were –12.4 (±7.4) and –2.5 (±1.3) points, respectively, among those treated with vortioxetine, with decreases continuing after the initiation of the open-label phase (Table 5 and Figs 4 and 5). For the double-blind duloxetine group, the improvement in HAM-A and CGI-S scores was –9.5 (±6.88) and –2.18 (±1.255) points, respectively. For patient-reported outcomes, study participants receiving vortioxetine experienced improvements in all SF-36 subscale scores from open-label baseline for all previous treatment groups. Similarly, study participants experienced improvements from double-blind baseline and open-label baseline in the mean SDS scores and in individual items, indicating continued improvement.

Discussion

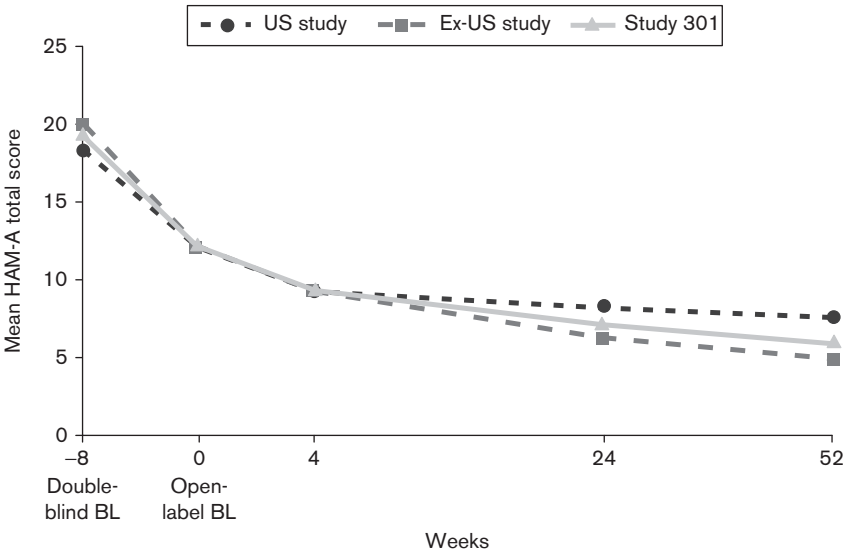
The safety results indicate that treatment with vortioxetine was generally well tolerated, with most AEs mild or moderate in intensity. The AE profile was consistent with AEs (occurring in $\geq$ 5% of study participants) comprising nausea, headache, nasopharyngitis, diarrhea, dizziness, and upper respiratory tract infection. Overall, 62.9% of the 836 enrolled study participants completed the 52-week extension study. The withdrawal rate

Fig. 3



Mean HAM-D24 total scores by study visit. BL, baseline; HAM-D24, 24-item Hamilton Depression Scale.

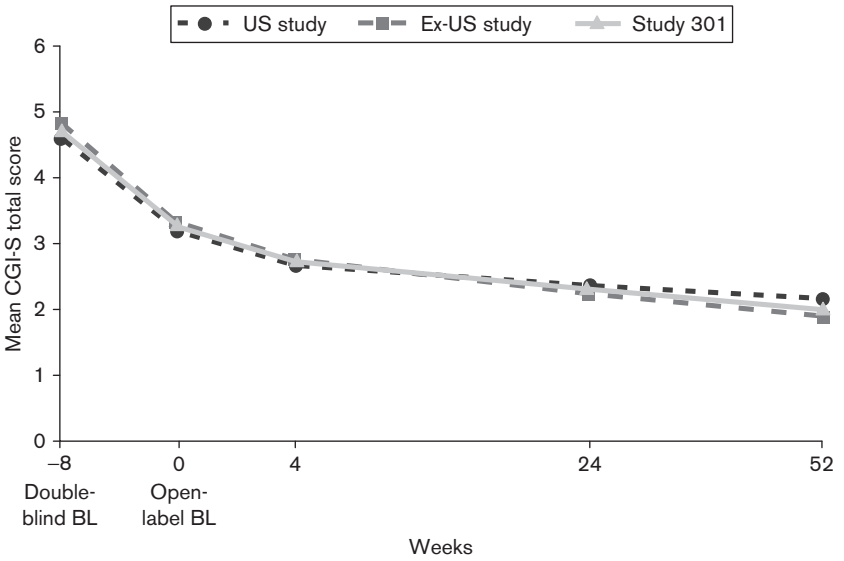
Fig. 4



Mean HAM-A total scores by study visit. BL, baseline; HAM-A, Hamilton Anxiety Scale.

because of AEs in this study was 6.0%, which is similar to that reported in another recent long-term vortioxetine extension study (7.9%) (Baldwin *et al.*, 2012a), even though the current study population included a broader geographic distribution (i.e. both US and non-US). Further, this AE withdrawal rate was lower compared with similar long-term studies with escitalopram (8.8%) (Wade *et al.*, 2006) and duloxetine (11.9%) (Dunner *et al.*, 2008). There were no clinically meaningful differences between treatment groups with respect to serum chemistry, urinalysis, vital signs, physical findings, or ECGs. A higher rate of dizziness (19.4%) was observed during the first 2 weeks of the open-label treatment in study participants treated previously with duloxetine in the original acute double-blind trial, which may be related to an abrupt switch from duloxetine to vortioxetine. Study participants who were enrolled in the USA reported more AEs (79.3%) compared with those enrolled in Asia, Australia, and

Fig. 5



Mean CGI-S total scores by study visit. BL, baseline; CGI-S, Clinical Global Impressions Scale – Severity of Illness Scale.

Europe (63.2%), although the AE rate in another non-US long-term vortioxetine extension study reported an AE rate of 72.7% (Baldwin *et al.*, 2012a).

Suicidality has been linked to antidepressant use, particularly in younger patients (Mori, 2002; Stone *et al.*, 2009; Reeves and Ladner, 2010). In the current study, suicide-related AEs were monitored prospectively using the C-SSRS; the incidence of such events was low, and no clinically meaningful trends were observed. The rate of self-reported sexual dysfunction was low; none of the study participants discontinued the study because of sexual dysfunction-related AEs. The low insomnia rate in the current study (2.0%) was notable, given the high rate of insomnia (10.2%) reported as a concurrent condition in the feeder studies.

There was a small increase in mean weight over the duration of the study, but the absolute weight effect was low, with a mean increase of 0.67 kg at the final visit relative to the open-label baseline. The increase in mean weight in study participants treated with vortioxetine during this study was comparable with that observed in the placebo group (0.8 kg) of a meta-analysis of long-term (> 8 months) placebo-controlled clinical studies that involved 12 antidepressants (Serretti and Mandelli, 2010).

The results of the current study indicate that over 52 weeks of treatment, study participants taking vortioxetine experienced improvement in depressive symptoms, as reflected in continued decreases in HAM-D24 total scores, MADRS total scores, and CGI-S scores, and in anxiety symptoms as measured by HAM-A. These improvements were sustained from the double-blind baseline through week 52 of the open-label phase (60 weeks total), with further improvements in scores after the initiation of the open-label study phase. For example, the mean change in the HAM-D24 score during the double-blind phase was –13.6 points, with a further decrease of 7.4 points during the open-label extension phase. These scores achieved during the study participants' previous trial (US or non-US study) further improved during this extension study. In addition, improvements were evident when the results were compared by dosage in the previous acute double-blind trial. Thus, efficacy gains were evident irrespective of the treatment assigned at the end of the double-blind phase (i.e. not influenced by patients treated previously with placebo or lower vortioxetine doses).

There were differences in patient characteristics between feeder studies primarily related to geographical regions. Overall, study participants in the non-US study were slightly older (mean age, 47 vs. 43.8 years) and leaner (BMI, 26.5 vs. 30.65 kg/m^2) than those in the US study. There were also no black (0 vs. 22.2%) or Hispanic study participants (0 vs. 13.7%) in the non-US study compared with the US study. Furthermore, study participants in the non-US study also had fewer concurrent medical conditions at baseline including gastrointestinal disorders (26.3 vs. 59.6%), headaches (11.4 vs. 41.5%), insomnia (4.0 vs. 17.4%), seasonal allergy (2.5 vs. 14.1%), asthma (2.5 vs. 7.5%), and arthritis (0.4 vs. 5.7%). Nevertheless, the results of the study were consistent across study participants within both studies.

Study limitations include the open-label design, the lack of a comparator/placebo arm, and the lack of a suitable scale to assess treatment-emergent sexual dysfunction. Thus, a clinical perspective is difficult to ascertain from the reported AEs and the changes in efficacy parameters.

In summary, this 52-week open-label, flexible-dose extension study found that vortioxetine was safe and well tolerated, with no new or unexpected safety signals identified. In addition, the change in the severity of depressive and anxiety symptoms shown with vortioxetine in the double-blind studies was maintained over the course of 52 weeks, with continued and further improvements in depression, anxiety, and global symptoms.

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Conflicts 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. Dr Mohammed Alam has received research grants from Janssen Pharmaceuticals, Sandoz Pharmaceuticals, Abbott Laboratories, New River Pharmaceuticals, Pfizer Inc., Eli Lilly and Company, Hoechst Marion Roussel Inc., Bristol-Myers Squibb, Merck, Sumitomo, Novartis Pharmaceuticals, GlaxoSmithKline, AstraZeneca, Organon, Solvay, Cephalon Inc., Johnson & Johnson, Jazz Pharmaceuticals, sanofi-aventis, Takeda Pharmaceuticals, Wyeth, Otsuka Pharmaceuticals, Neuropharm, Shire, Solace, Lundbeck, Dainippon Sumitomo Pharma, Forest, Sepracor, Adolor, Rexahn, Catalyst Pharmaceuticals, and Hoffman-La Roche.

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