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Original article

Comparison of vortioxetine versus venlafaxine XR in adults in Asia with major depressive disorder: a randomized, double-blind study

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Abstract

Objective:
This randomized, double-blind 8 week study compared the efficacy and tolerability of fixed-dose treatment with vortioxetine (10 mg/day) and venlafaxine extended release (XR) (150 mg/day) in major depressive disorder (MDD) patients.

Research design and methods:
Patients aged 18–65 years with a primary diagnosis of recurrent MDD, a Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≥26 and a Clinical Global Impression–Severity (CGI-S) score ≥4 were randomized (1:1) to treatment with either vortioxetine or venlafaxine XR. The primary endpoint was change from baseline to Week 8 in MADRS total score (analysis of covariance [ANCOVA], full-analysis set [FAS], last observation carried forward [LOCF]), using a non-inferiority margin of +2.5 points. Pre-specified secondary endpoints included MADRS response and remission rates, anxiety symptoms (HAM-A), CGI, overall functioning (SDS), and health-related quality of life (Q-LES-Q).

Clinical trial registration:
This study (SOLUTION) has the www.ClinicalTrials.gov identifier: NCT01571453.

Results:
On the primary efficacy endpoint at Week 8, non-inferiority was established with a difference of −1.2 MADRS points in favor of vortioxetine (95% CI: −3.0 to 0.6). The MADRS total score decreased (improved) from 32.3 ± 4.6 at baseline to 13.6 ± 9.6 (vortioxetine: $n = 209$) and from 32.3 ± 4.5 to 14.8 ± 10.4 (venlafaxine XR: $n = 215$) (FAS, LOCF). At Week 8, the HAM-A and SDS total scores, CGI and Q-LES-Q scores, and response and remission rates demonstrated similar improvement for vortioxetine and venlafaxine XR, with remission rates (MADRS ≤10) of 43.1% (vortioxetine) versus 41.4% (venlafaxine XR) (LOCF). Fewer vortioxetine than venlafaxine XR patients withdrew for any reason (18.0% versus 27.4%) or for adverse events (6.6% versus 13.7%). The most frequent adverse events (≥5%) for both treatments were nausea, dizziness, headache, and dry mouth. In addition, accidental overdose, decreased appetite, constipation and insomnia were reported by (≥5%) of patients treated with venlafaxine XR.

Limitations:
The inclusion and exclusion criteria may limit the generalizability of the study. Since patients with a history of lack of response to venlafaxine XR were excluded from this study, there is a selection bias in favor of venlafaxine XR.

Conclusion:
Vortioxetine was at least as efficacious as venlafaxine XR and was safe and better tolerated than venlafaxine XR.

Introduction

One of the most pressing issues in the treatment of depression in clinical practice is to know which antidepressants to use first and how to proceed in cases of non-response. The studies required by regulators in order to bring a new antidepressant to the market are focused on finding efficacy in an untreated population with depression and have brought us a range of first-line antidepressant choices. However, they provide very little evidence of relative efficacy or whether one antidepressant is better than another. These studies are mostly carried out in widely different populations derived from different healthcare systems in different countries, in different continents and from different racial and cultural groups. These populations carry their own biases in terms of ethics, acceptable tolerability, and efficacy, so a reliable judgment of relative efficacy based on comparing differences from placebo would be difficult.

A better approach to obtain data to help guide the choice of antidepressant is to undertake direct comparator studies. The use of a an approved reference antidepressant in placebo-controlled studies as a validator of the sensitivity of the population to treatment is of some help, but these studies have an inherent bias in favor of the reference antidepressant due to factors such as the prior knowledge of the optimum dose of the particular comparator antidepressant both for efficacy and safety, which is not yet known for the experimental antidepressant.

These studies have drawbacks since the presence of a placebo arm increases the understandable concerns of both investigator and patient, and consequently the withdrawal rate and post-hoc comparisons of the relative efficacy may be less informative. Very few individual placebo-controlled studies are sufficiently powered to make a meaningful comparison between the two antidepressants included in the study, for which much larger numbers are needed[1]. Meta-analysis of studies combining quite different populations is often undertaken to address this problem, but these are often unbalanced and therefore less valid than the results from a single study with a direct comparison of antidepressants in a randomized population under double-blind conditions, without the potential prejudice of a placebo treatment group.

In the absence of any apparent differences in efficacy, common sense suggests that the best choice of first-line treatment should be based on safety and tolerability and that the less safe and less well tolerated antidepressant be relegated to second-line treatment. However, relative efficacy is important and a careful clinician would prefer to use the most effective of the well tolerated antidepressants. A consensus group review of the comparative efficacy of antidepressants in 2007 has ranked escitalopram, venlafaxine and clomipramine as the most effective antidepressants, based on at least two randomized controlled studies showing, under conditions of fair comparison, superiority over another licensed antidepressant[2].

Most current treatment guidelines suggest that selective serotonin reuptake inhibitors (SSRIs), despite their limitations, should be the first choice and, in the case of non-response, an antidepressant from a different pharmacological class should be used. There are relatively few data to inform the choice of which antidepressant from which class should be used in non-responders. A meta-analysis of the limited studies available focused on the data indicating venlafaxine might be useful, and some have suggested that serotonin-noradrenaline reuptake inhibitors (SNRIs) should be the second step choice[3–6]. The first direct test of second step treatment between members of different classes of antidepressants following non-response to SSRIs or SNRIs found that vortioxetine was significantly better than agomelatine in terms of efficacy and function at a clinically relevant dosage[1].

The question then arises whether a direct evaluation of vortioxetine and venlafaxine XR under conditions of fair comparison would show an advantage for one or the other antidepressant in first-line treatment. Alvarez *et al.* compared vortioxetine 5 mg and 10 mg and the active reference venlafaxine XR titrated to 225 mg against placebo. In this study, both antidepressants were efficacious[7].

Vortioxetine was licensed in late 2013 in the US, the EU and other countries for the treatment of adults with MDD with approved dosages of 5 mg, 10 mg, 15 mg and 20 mg. It is a $5HT_3$, $5HT_7$ and $5HT_{1D}$ receptor antagonist, a $5HT_{1B}$ partial agonist, a $5HT_{1A}$ agonist and an inhibitor of the serotonin (5-HT) transporter. Venlafaxine XR is a well-known SNRI which is licensed at 37.5 mg, 75 mg, 150 mg and 225 mg. Both antidepressants may be titrated depending on response and tolerability.

The present study was designed to make a fair comparison between the more commonly used median doses of 10 mg of vortioxetine and 150 mg of venlafaxine XR in an adequately powered study that took withdrawals into account using an LOCF analysis.

Patients and methods

Study design

This randomized, double-blind, multinational, fixed dose of vortioxetine versus an active comparator (venlafaxine XR) study included 443 randomized patients recruited from 31 psychiatric in- and outpatient specialist settings in four countries (China, South Korea, Taiwan and Thailand) from April 2012 to October 2013. The study was conducted in accordance with the principles of Good Clinical Practice[8] and the Declaration of Helsinki[9]. Local research ethics committees approved the study, and eligible patients provided written informed consent before

participating. Advertisements were used to recruit patients in all four countries.

Following a screening period of up to 7 days, eligible patients were randomized (1:1) to vortioxetine (10 mg/day) or venlafaxine XR (150 mg/day) for 8 weeks of double-blind treatment. Patients in the venlafaxine XR group received 75 mg/day for the first 4 days of treatment in accordance with the recommendations provided in the Summary of Product Characteristics for venlafaxine XR[10]. Patients were seen at baseline and Weeks 1, 2, 4, 6 and 8. Patients who withdrew were seen as soon as possible after withdrawal. Patients who completed the 8 week treatment period entered a 1 week double-blind down-taper period, during which patients in the vortioxetine group received placebo and patients in the venlafaxine XR group received 75 mg/day. A safety follow-up contact was scheduled for 4 weeks after completion of the treatment period or after withdrawal from the study. Study medication was given as venlafaxine XR capsules or encapsulated vortioxetine tablets of identical appearance. Patients were instructed to take one capsule per day, orally, preferably in the morning.

Main entry criteria

Eligible patients of either sex were aged >18 and ≤65 years, with a primary diagnosis of recurrent MDD according to DSM IV-TR criteria[11], and a current major depressive episode (MDE) of ≥3 months' duration. The diagnosis was confirmed using the Mini International Neuropsychiatric Interview (MINI)[12]. Patients were required to have a Montgomery–Åsberg Depression Rating Scale (MADRS)[13] total score ≥26 and a Clinical Global Impression–Severity (CGI-S)[14] score ≥4 at screening and baseline visits. Non-responders to treatment with venlafaxine in the present MDE were excluded and in addition any patient with a history of non-response to venlafaxine, or who were considered by the investigator to have been resistant to two adequate antidepressant treatments of at least 6 weeks' duration each at the recommended dose, were excluded from the study. Patients were also excluded if they had any other current Axis I disorder, as defined in DSM-IV-TR and assessed using the MINI, or if they had a history of a manic or hypomanic episode, schizophrenia or any other psychotic disorder (including major depression with psychotic features), mental retardation, organic mental disorders or mental disorders due to a general medical condition, any substance abuse disorder within the previous 2 years, or any disorder that might interfere with study treatment or impair treatment compliance. Based on the warnings in the venlafaxine XR package leaflet[10], patients with an identified high risk of a serious cardiac ventricular arrhythmia or uncontrolled hypertension or at risk of acute narrow-angle glaucoma were also excluded.

Patients at serious risk of suicide, based on the investigator's clinical judgment, and those who had a score ≥5 on item 10 of the MADRS scale ('suicidal thoughts') were excluded, as were those receiving formal cognitive or behavioral therapy or systematic psychotherapy and pregnant or breast-feeding women. Patients were also excluded if they were taking disallowed concomitant medication, as previously described[7]. Episodic use of zolpidem, zopiclone or zaleplon for insomnia was allowed for a maximum of two nights per week, but not the night before a study visit.

The following clinical laboratory tests were made: B-hemoglobin, B-erythrocyte count, B-hematocrit, B-total leucocyte count, B-neutrophils, B-basophils, B-lymphocytes, B-monocytes, B-thrombocyte count, S-total bilirubin, S-conjugated bilirubin, S-alkaline phosphatase (AP), S-alanine aminotransferase (ALT), S-aspartate aminotransferase (AST), S-γ-glutamyl transferase (γGT), S-cholesterol (total), S-triglycerides, S-low density lipoprotein (LDL), S-high density lipoprotein (HDL), S-creatinine, B-urea nitrogen (BUN), S-urea acid, S-albumin, S-glucose, S-sodium, S-potassium, S-calcium (total), U-protein, U-glucose, U-blood, U-ketones, S-TSH, S-hCG, C-reactive protein (where B = blood, S = serum, U = urine; blood pressure and pulse rate were also measured). Patients were excluded if they had one or more clinical laboratory test values outside the reference range of potential risk to the patient's safety, or a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 times the upper limit of the reference range (ULN), a serum creatinine value >1.5 times ULN, or a serum total bilirubin value >1.5 times ULN.

Withdrawals from the study for safety reasons used the criteria previously described[15]. In addition, patients with a QTcF interval >500 ms confirmed by ECG at a subsequent follow-up visit within 2 weeks or ALT/AST values >3 times ULN were to be withdrawn. If adverse events (AEs) contributed to withdrawal, they were regarded as the primary reason for withdrawal.

Efficacy rating

The effect of vortioxetine versus venlafaxine XR after 8 weeks of treatment was assessed using the MADRS total score. All raters were psychiatrists involved in clinical practice and underwent formal training in the MADRS and the scoring conventions for the Clinical Global Impression (CGI), and the Hamilton Anxiety Rating Scale (HAM-A)[16] in order to maximize inter-rater reliability. Only raters who passed the qualification test were allowed to rate patients. Overall functioning and health-related quality of life were assessed using patient reports and the Sheehan Disability Scale (SDS)[17] and the Q-LES-Q (SF)[18] at baseline and completion/Week 8.

Allocation to treatment

At each site, sequentially enrolled patients were assigned the lowest randomization number available in blocks of four using an interactive voice/web response system (IVRS). The IVRS randomly allocated each patient to a treatment group during the call and assigned the patient a randomization number according to a randomization list that was computer generated by H. Lundbeck A/S, the manufacturer of vortioxetine. All investigators, trial personnel and patients were blinded to treatment assignment for the duration of the study. The randomization code was not broken for any patient.

Analysis sets

Safety analyses were based on the all-patients-treated set (APTS), comprising all randomized patients who took at least one dose of study medication. Efficacy analyses were based on a modified intent-to-treat set – the full-analysis set (FAS), comprising all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the primary efficacy variable (MADRS total score).

Power and sample size calculations

Power calculations showed that with a power of $\geq$80% and an expected withdrawal rate of 20% a total of 410 patients should be randomized to demonstrate non-inferiority of vortioxetine to venlafaxine XR, using a 5% level of significance and a standard *t*-test from an ANCOVA. This was based on a non-inferiority comparison of the treatment groups in MADRS total score using a two-sided 95% confidence interval against a margin of +2.5 points[7], a standard deviation of 9.0 and an expected true mean difference of 0 points between treatments.

Analysis of the primary efficacy endpoint

The primary analysis tested for non-inferiority of vortioxetine and venlafaxine XR using the change from baseline in MADRS total score at Week 8 based on the FAS. Comparison between treatments was performed using an analysis of covariance, with treatment and centre as fixed factors and the baseline MADRS total score as a covariate, using the last observation carried forward (LOCF). Vortioxetine was declared to be non-inferior to venlafaxine XR if the upper limit of the two-sided 95% confidence interval was <2.5 MADRS points. Robustness of the results was confirmed by pre-specified sensitivity analyses using ANCOVA [FAS, observed cases (OC)] and mixed model for repeated measures [FAS, MMRM]. As significantly more venlafaxine XR patients were excluded from the FAS, a post-hoc sensitivity analysis using ANCOVA (APTS, LOCF) was also made.

Analysis of secondary efficacy endpoints

The following secondary analyses were prospectively defined: the change from baseline in MADRS total score at other visits; the change from baseline to each visit in CGI-S score; CGI-I score at each visit; change from baseline in HAM-A total score at each visit; MADRS response ($\geq$50% decrease from baseline) and remission (MADRS total score $\leq$10) at each visit; CGI-S remission (CGI-S score $\leq$2) at each visit; and CGI-I response (CGI-I score $\leq$2) at each visit. Secondary analyses were performed for MADRS total score, CGI-S score, CGI-I score and HAM-A total score at each visit using both OC and LOCF methods. Change from baseline in MADRS total score, CGI-S score and HAM-A total score were analyzed using ANCOVA with treatment and center as fixed factors and baseline score as a covariate, using both OC and LOCF methods. Change from baseline to Week 8 in SDS total score and subscales, Q-LES-Q (SF) scores and global items of satisfaction were analyzed using an ANCOVA model (FAS, LOCF), similar to that for the other secondary efficacy endpoints. Dichotomous outcomes, such as MADRS response and remission, were analyzed using logistic regression and Wald's test with treatment as a factor and the MADRS total baseline score as a covariate. For all analyses involving CGI-I, the CGI-S score served as baseline value. The effect of treatment on withdrawal rates was analyzed using a chi-square test.

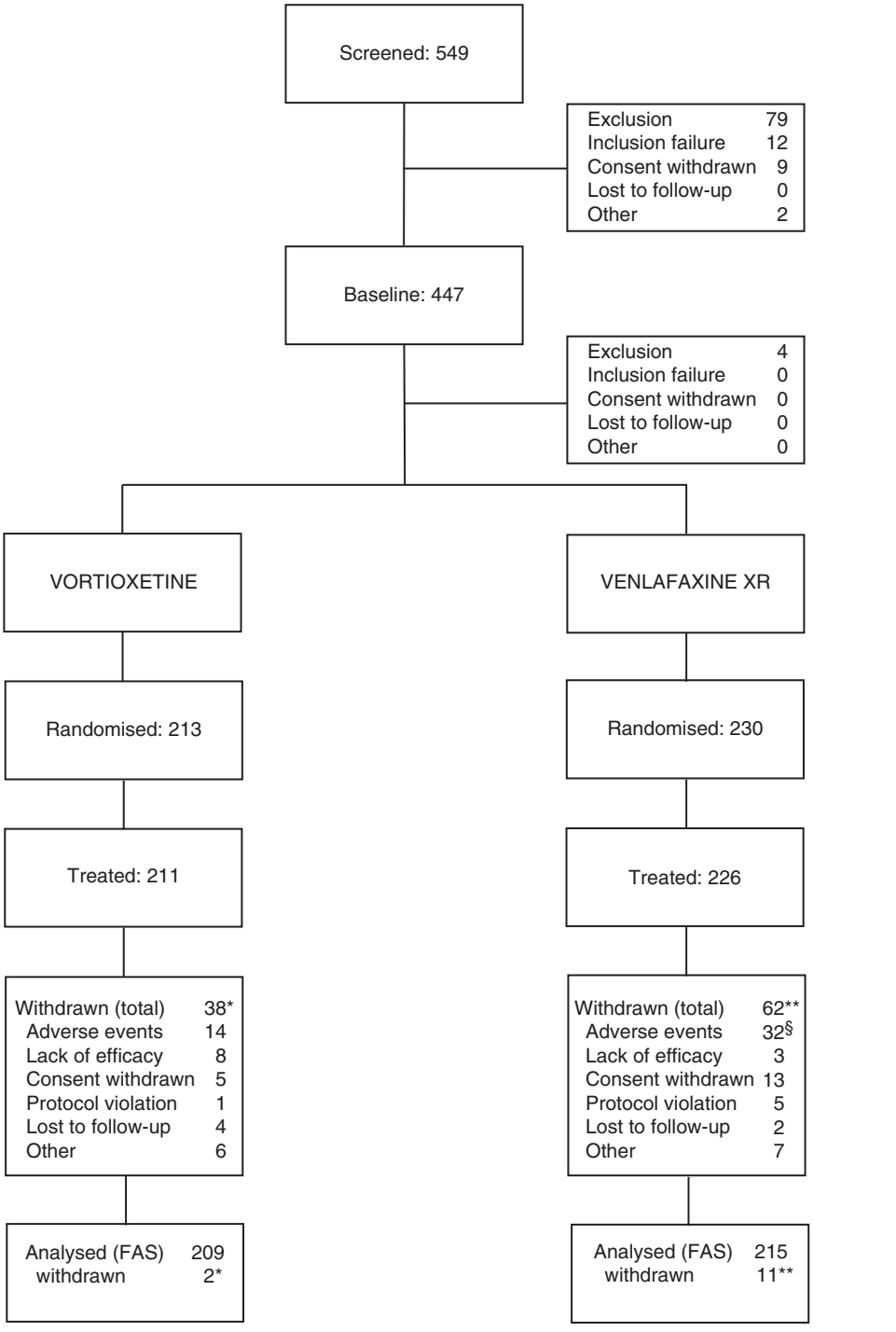
Tolerability assessment

At each visit, starting at baseline, patients were asked a non-leading question (such as 'how do you feel?'). All treatment-emergent adverse events (TEAEs) either observed by the investigator or reported spontaneously by the patient were recorded. Qualified personnel coded TEAEs using the lowest level term according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0. The incidence of individual TEAEs was compared between treatment groups using Fisher's exact test. The chi-square test was used for comparison of treatment groups with respect to withdrawal rates. Clinical safety laboratory tests, vital signs, weight, BMI, ECGs, and physical examination findings were also evaluated.

Results

Patient baseline characteristics

The all-patients-treated set (APTS) consisted of 437 patients ($n = 211$ vortioxetine and $n = 226$ for venlafaxine XR) after the exclusion of six patients who did not take any study medication (Figure 1). Patients had a mean age of



*including 2 and **11 patients withdrawn from the FAS due to no valid post-baseline MADRS assessment
§including 1 patient withdrawn after the last dose of venlafaxine XR

Figure 1. Flow chart of patient disposition. MADRS: Montgomery–Åsberg Depression Rating Scale, BL: baseline, APTS: all-patients-treated set, FAS: full-analysis set.

about 40 years, approximately 60% were women, and all were Asian: China ($n = 253$), Korea ($n = 128$), Taiwan ($n = 28$) and Thailand ($n = 28$). There were no apparent clinically relevant differences at baseline between treatment groups in demographic or baseline clinical characteristics (Table 1). The full-analysis set (FAS) comprised 424 patients after the exclusion of two patients from the vortioxetine group and 11 patients from the

Table 1. Baseline patient characteristics.

APTS	Vortioxetine 10 mg ($n = 211$)	Venlafaxine XR 150 mg ($n = 226$)
Women *n* (%)	123 (58.3)	139 (61.5)
Mean age ± SD	40 ± 12	41 ± 12
Range, years	19–65	19–64
Mean BMI ± SD, kg/m^2	23.1 ± 3.5	23.1 ± 3.6
Asian	100%	100%
Mean duration of current MDE, weeks	29 ± 25	31 ± 35
Number of previous MDEs ± SD	1.7 ± 1.2	1.6 ± 0.9
Mean rating scale scores ± SD (FAS)	($n = 209$)	($n = 215$)
MADRS total score	32.3 ± 4.6	32.3 ± 4.5
HAM-A total score	20.6 ± 7.3	21.1 ± 7.0
CGI-S	4.8 ± 0.7	4.9 ± 0.7
SDS total	18.9 ± 6.4 ($n = 196$)	19.2 ± 6.2 ($n = 195$)
SDS social	6.3 ± 2.4 ($n = 209$)	6.6 ± 2.3 ($n = 215$)
SDS family	6.2 ± 2.4 ($n = 208$)	6.2 ± 2.4 ($n = 215$)
SDS work	6.4 ± 2.4 ($n = 197$)	6.5 ± 2.2 ($n = 195$)
Q-LES-Q total score	34.4 ± 6.7	34.4 ± 7.0
Q-LES-Q item 15[a]	2.57 ± 0.87	2.88 ± 0.88
Q-LES-Q item 16[b]	2.06 ± 0.71	2.15 ± 0.74

[a]Satisfaction with medication item.
[b]Overall life satisfaction and contentment item.
APTS: all-patients-treated set, BMI: body mass index, CGI-S: Clinical Global Impression–Severity, FAS: full-analysis set, HAM-A: Hamilton Rating Scale for Anxiety, MADRS: Montgomery–Åsberg Depression Rating Scale, MDE: major depressive episode, SD: standard deviation, SDS: Sheehan Disability scale.

venlafaxine XR group with no valid post-baseline MADRS assessment. In the vortioxetine group, patients withdrew due to adverse events (one patient) and withdrawal of consent (one patient). In the venlafaxine XR group, withdrawals were due to adverse events (five patients), withdrawal of consent (four patients), protocol violation (one patient) and other (one patient).

The mean baseline MADRS total score was 32.3 ± 4.6, indicating moderate to severe depression, as also reflected in the mean CGI-S score of 4.9 ± 0.7. The current MDE had started an average of about 30 weeks (median duration 21 weeks, range 12–374 weeks) before enrolment. Most patients had had 1–2 previous depressive episodes (range: 1–9). There was a substantial level of anxiety symptoms, indicated by a mean baseline HAM-A total score of 20.9 ± 7.1.

Withdrawals from the study

There were 100 (22.9%) patients who withdrew during the entire study (38 [18.0%] in the vortioxetine group and 62 [27.4%] in the venlafaxine XR group, $p = 0.0191$ [chi-square test]) (Figure 1). The most frequent primary reason for withdrawal was adverse events (10.5%) (14/211 [6.6%] [vortioxetine] and 32/226 [14.2%] [venlafaxine XR]) followed by lack of efficacy (2.5%) (8/211 [3.8%] [vortioxetine] and 3/226 [1.3%] [venlafaxine XR]). The total exposure to the study drugs in the study was 29 (vortioxetine) and 28 (venlafaxine XR) patient years.

Efficacy

Primary endpoint

In the primary efficacy analysis, the mean change from baseline in MADRS total score at Week 8 (ANCOVA, FAS, LOCF) was −19.4 (vortioxetine) and −18.2 points (venlafaxine XR). The mean difference from venlafaxine XR for vortioxetine was −1.2 (95% CI: −3.0 to 0.6) in favor of vortioxetine. Non-inferiority was established, as the upper bound of the 95% CI was 0.6 MADRS points, clearly below the non-inferiority margin of +2.5 MADRS points. To analyze the robustness of the results of the primary efficacy analysis, a pre-specified sensitivity analysis was performed: at Week 8, the difference to venlafaxine XR was 0.6 (95% CI: −0.9 to 2.2) points using ANCOVA (FAS, OC) which also showed non-inferiority to venlafaxine XR with a numerical advantage for venlafaxine XR. As significantly ($p = 0.0160$, chi-square) more patients treated with venlafaxine XR (11 patients) than vortioxetine (two patients) withdrew from the study and did not have a valid post-baseline MADRS assessment and were excluded from the FAS, a post-hoc efficacy analysis was made on the APTS, imputing a zero change from baseline for these non-FAS patients. The mean change from baseline in MADRS total score at Week 8 was −19.2 and −17.3 points in the vortioxetine and venlafaxine XR groups, respectively, giving a mean difference of −1.90 (95% CI: −3.76 to −0.04; $p = 0.0452$) points in favor of vortioxetine (ANCOVA, APTS, LOCF), which is the full intention to treat analysis.

Secondary efficacy analysis

Clinician rated assessments

Vortioxetine showed a numerical advantage over venlafaxine XR in pre-defined secondary efficacy analyses (MADRS total score, HAM-A total score, CGI-S score, CGI-I score; FAS, LOCF) (Table 2), including response and remission based on the MADRS, the CGI-S and the CGI-I.

At Week 8, the mean MADRS total score decreased (improved) from 32.3 ± 4.6 at baseline to 13.6 ± 9.6 (vortioxetine) and from 32.3 ± 4.5 to 14.8 ± 10.4 (venlafaxine XR) (FAS, LOCF) (Figure 2). Time to response was not analyzed, but a reduction of approximately 50% from baseline in the mean MADRS total score was seen at 4–6 weeks. By Week 6, 54.5% of vortioxetine patients and 53.0% of venlafaxine XR patients had responded (≥50% decrease from baseline) (FAS, LOCF). At Week 8, 66.5% of the patients in the vortioxetine group were MADRS responders compared to 61.4% of the patients in the venlafaxine XR group and 43.1% of the patients in the vortioxetine group were MADRS remitters compared to 41.4% of the patients in the venlafaxine XR group (FAS, LOCF) (Table 2). The mean HAM-A total score decreased from 20.6 ± 7.3 at baseline to 9.7 ± 7.3 at Week 8 (vortioxetine) and from 21.1 ± 7.0 at baseline to 10.8 ± 7.7 at Week 8 (venlafaxine XR) (FAS, LOCF).

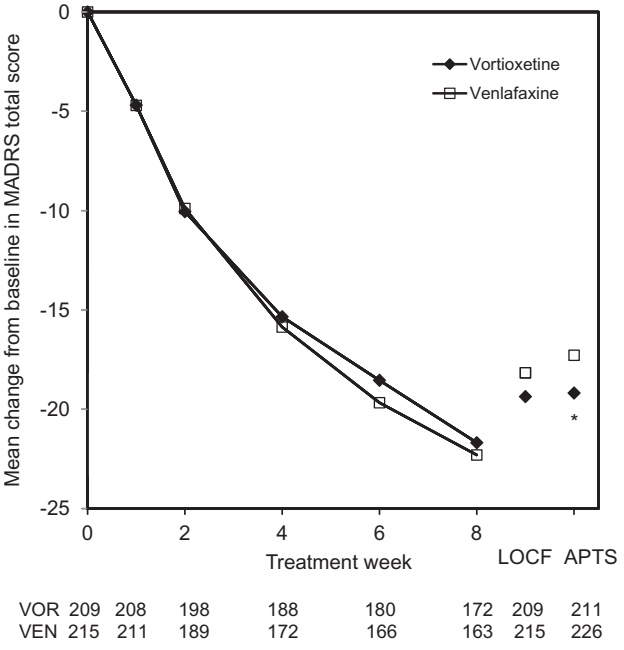


Figure 2. Estimated change in Montgomery–Åsberg Depression Rating Scale (MADRS) total scores from baseline to Week 8 (FAS, OC by visit) and FAS, LOCF (ANCOVA) at Week 8. FAS: full-analysis set, LOCF: last observation carried forward, OC: observed cases. Patient numbers at each visit are shown below the *x*-axis for each treatment group. The primary endpoint is at Week 8 (FAS, ANCOVA, LOCF), whereas the analysis based on the APTS is post hoc. $*p<0.05$.

Table 2. Change from baseline and mean difference (±SE) between vortioxetine and venlafaxine XR at Week 8 (ANCOVA, FAS, LOCF).

Efficacy Variable	Change from baseline: Vortioxetine (*n* = 209)	Change from baseline: Venlafaxine XR (*n* = 215)	Difference	95% CI
Primary				
MADRS total score	−19.4 ± 0.7	−18.2 ± 0.7	−1.2 ± 0.9	(−3.03 to 0.63)
Secondary				
Clinician-rated assessments				
HAM-A total score	−11.4 ± 0.5	−10.6 ± 0.5	−0.8 ± 0.7	(−2.09 to 0.45)
CGI-S score	−2.26 ± 0.09	−2.12 ± 0.09	−0.15 ± 0.12	(−0.39 to 0.09)
CGI-I score[a]	1.99 ± 0.08	2.14 ± 0.08	−0.14 ± 0.11	(−0.35 to 0.06)
MADRS response (%)[a]	66.5	61.4	—	1.25 (0.84 to 1.86)
CGI-I ≤2 (response) (%)[a]	74.2	67.4	—	1.39 (0.91 to 2.11)
MADRS remission (%)[a]	43.1	41.4	—	1.07 (0.73 to 1.58)
CGI-S ≤2 (remission) (%)[a]	49.8	47.0	—	1.11 (0.76 to 1.63)
Patient reported outcomes				
SDS total score	−7.59 ± 0.61	−6.56 ± 0.60	−1.03 ± 0.79	(−2.58 to 0.53)
SDS family life subscale	−2.61 ± 0.21	−2.28 ± 0.21	−0.33 ± 0.27	(−0.87 to 0.21)
SDS work subscale	−2.48 ± 0.22	−2.20 ± 0.22	−0.28 ± 0.28	(−0.83 to 0.28)
SDS social life subscale	−2.74 ± 0.21	−2.52 ± 0.20	−0.22 ± 0.27	(−0.75 to 0.31)
Q-LES-Q total score	8.5 ± 0.6	8.6 ± 0.6	−0.1 ± 0.8	(−1.67 to 1.47)
Q-LES-Q item 15[b]	0.56 ± 0.18	0.77 ± 0.23	−0.21 ± 0.27	(−0.77 to 0.34)
Q-LES-Q item 16[c]	1.10 ± 0.07	1.02 ± 0.07	0.08 ± 0.09	(−0.09 to 0.26)
Post-hoc analysis	*n* = 211	*n* = 226		
MADRS total score[d]	−19.2 ± 0.7	−17.3 ± 0.7	−1.9 ± 0.9	(−3.76 to −0.04)

[a]Absolute value, 95% CI given with the odds ratio.
[b]Satisfaction with medication item.
[c]Overall life satisfaction and contentment item.
[d]Post-hoc ANCOVA, APTS, LOCF analysis.
APTS: all-patients-treated set, 95% CI: 95% confidence interval, CGI-I: Clinical Global Impression–Improvement, CGI-S: Clinical Global Impression–Severity, FAS: full-analysis set, HAM-A: Hamilton Rating Scale for Anxiety, LOCF: last observation carried forward, MADRS: Montgomery–Åsberg Depression Rating Scale, Q-LES-Q: Quality of Life, Enjoyment and Satisfaction Questionnaire, SDS: Sheehan Disability Scale.

Mean CGI-I and CGI-S scores improved throughout the 8 week treatment period in both treatment groups. The mean CGI-S score decreased from 4.84 ± 0.71 at baseline to 2.66 ± 1.25 at Week 8 (vortioxetine) and from 4.87 ± 0.69 at baseline to 2.80 ± 1.35 at Week 8 (venlafaxine XR) (FAS, LOCF). The CGI-I score decreased from 3.38 ± 0.77 at Week 1 to 2.05 ± 1.10 at Week 8 (vortioxetine) and from 3.41 ± 0.83 at Week 1 to 2.20 ± 1.16 at Week 8 (venlafaxine XR) (FAS, LOCF). At Week 8, 74.2% of the patients in the vortioxetine group were CGI-I responders compared to 67.4% of the patients in the venlafaxine XR group and 49.8% of the patients in the vortioxetine group were CGI-S remitters compared to 47.0% of the patients in the venlafaxine XR group (FAS, LOCF).

Patient reported outcomes

For patient-reported outcomes relating to overall functioning, including the SDS total score and all three subscales (family, work and social life), there was a numerical advantage for vortioxetine. The mean SDS total score decreased (improved) from approximately 19 at baseline to approximately 11 (vortioxetine), and approximately 12 (venlafaxine XR) at Week 8 (FAS, LOCF) (Table 2). Comparable reductions were observed in the vortioxetine and venlafaxine XR groups in mean SDS total and subscale scores (family, work and social) at Week 8 (FAS, LOCF). The number of underproductive or lost days per week decreased in both treatment groups from 5.3 (vortioxetine) and 5.2 days (venlafaxine XR) at baseline to 2.7 (vortioxetine) and 3.0 days (venlafaxine XR) at Week 8.

At Week 8, the mean Q-LES-Q total score increased (improved) in both treatment groups from approximately 34 at baseline (both groups) to 42.3 (vortioxetine) and 42.6 (venlafaxine XR), whereas the mean Q-LES-Q item 15 score (satisfaction with medication) increased from 2.6 (vortioxetine) and 2.9 points (venlafaxine XR) at baseline to 3.1 (vortioxetine) and 3.4 points (venlafaxine XR) at Week 8, and the mean Q-LES-Q item 16 score (overall life satisfaction and contentment) increased from 2.1 (both groups) at baseline to approximately 3.1 points at Week 8 in both groups.

Safety and tolerability

During the 8 week treatment period, approximately three-fifths of the patients in each treatment group had one or more treatment-emergent adverse events (TEAEs). During this period, 45 patients withdrew due to TEAEs, 14 (6.6%) in the vortioxetine group and 31 (13.7%) in the venlafaxine XR group ($p = 0.0149$, chi-square test). The only TEAEs leading to withdrawal of ≥3 patients in either treatment group were nausea (3.3%) in the vortioxetine group and nausea (4.9%), dizziness (2.7%), palpitations (1.8%), dry mouth (1.3%) and asthenia (1.3%) in the venlafaxine XR group. The most common TEAEs reported by at least 5% of patients for vortioxetine were nausea, dizziness, headache, and dry mouth (Table 3). TEAEs led to withdrawal of 6.6% of vortioxetine patients and 13.7% of venlafaxine XR patients, mostly in the first 2 weeks of treatment. The most common TEAEs leading to withdrawal were nausea (vortioxetine 3.3%, venlafaxine XR 4.9%), dizziness (vortioxetine 0%, venlafaxine XR 2.7%) and erectile dysfunction (vortioxetine 0%, venlafaxine XR 2.3%). In the entire study period (including the 4 week safety follow-up period), the incidence of suicide-related TEAEs (intentional overdose, suicide attempt, suicidal ideation) was low and comparable between treatment groups (1.4% for vortioxetine and 1.8% for venlafaxine XR).

Table 3. Treatment-emergent adverse events (TEAEs) with an incidence of ≥5% in either treatment group in the 8 week treatment period (APTS).

Preferred Term	Vortioxetine 10 mg *n* (%) (*n* = 211)	Venlafaxine XR 150 mg *n* (%) (*n* = 226)
Patients with TEAEs	125 (59.2)	153 (67.7)
Nausea	51 (24.2)	53 (23.5)
Dizziness	17 (8.1)	29 (12.8)
Headache	17 (8.1)	15 (6.6)
Dry mouth	12 (5.7)	24 (10.6)
Accidental overdose†	10 (4.7)	12 (5.3)
Decreased appetite	10 (4.7)	23 (10.2)*
Constipation	9 (4.3)	18 (8.0)
Insomnia	5 (2.4)	16 (7.1)*

APTS: all-patients-treated set.
†Defined as a dose of study medication that exceeds the dose prescribed.
*$p < 0.05$ (Fisher's exact test).

In the entire study period, serious AEs (SAEs) were reported by 10 patients, two patients in the vortioxetine group and eight patients in the venlafaxine XR group. The only SAE reported by more than one patient was suicide attempt, with one patient in the vortioxetine group and two patients in the venlafaxine XR group. An improvement from baseline in the scores for MADRS item 10 (suicidal thoughts) was seen in both treatment groups. No deaths occurred during this study.

No clinically relevant changes over time or differences between treatment groups were seen in clinical laboratory test results, vital signs, weight, or ECG parameters. At last assessment, patients in the vortioxetine group had a mean weight gain of 0.2 kg and patients in the venlafaxine XR group had a mean weight loss of 0.5 kg compared to baseline.

Discussion

The results of the study show that vortioxetine 10 mg is at least as effective as venlafaxine XR 150 mg in a non-inferiority comparison with a numerical advantage in favor of

vortioxetine of 1.2 points on the pivotal MADRS. The comparison on the secondary measures of response, remission, SDS and CGI scores were all numerically in favor of vortioxetine. A sensitivity analysis using MMRM shows a similar pattern, with a smaller numerical advantage for vortioxetine.

There were 13 patients who did not have a valid post-baseline MADRS assessment and were therefore excluded from the FAS population. There were 11 patients on venlafaxine XR compared to two patients on vortioxetine, showing a significant imbalance in the FAS population that is biased against vortioxetine. The post-hoc analysis of the APTS population addresses this bias and includes all randomized patients who received at least one dose of study medication. It has been suggested, based on the mean difference from placebo of about 2 points for a range of antidepressants in regulatory studies[19,20], that it would be fairer to accept a mean difference of 1 point between active antidepressants as indicating clinical relevance[21]. In the present study, the post-hoc APTS analysis shows statistical and clinically significant advantage for vortioxetine compared to venlafaxine XR of 1.9 points on the MADRS ($p < 0.05$).

The response to antidepressants may be influenced by genetic make-up and can vary between different ethnic populations[22]. This study was carried out in Asia, where patients are reported to be more sensitive to TEAEs than in Europe. Asian populations also have a higher incidence of poor metabolizers, resulting in higher drug plasma levels. The cytochrome P450 isozymes responsible for the metabolism of vortioxetine include CYP2D6, CYP3A4/5, CYP2C9, CYP2C19, CYP2A6, CYP2C8, and CYP2B6[23], the most important being CYP2D6, and the frequency of different alleles varies between different groups[24]. The most common TEAEs reported in this study by patients treated with vortioxetine are nausea, dizziness, headache, and dry mouth, and with venlafaxine XR they are nausea, dizziness, dry mouth, decreased appetite, constipation and insomnia. This distribution of TEAEs is similar to those reported in a study in MDD patients from Australia, Austria, Canada, the Czech Republic, Finland, France, Italy, Malaysia, Slovakia, Spain and Sweden treated with vortioxetine 10 mg or venlafaxine XR 225 mg[7], although the proportions of patients reporting these TEAEs are lower in the present study. Vortioxetine was well tolerated in this study compared to venlafaxine XR, as measured by discontinuation due to TEAEs (6.6% vs 13.7%) and fewer patients who withdrew for any reason on vortioxetine (18.0%) than on venlafaxine XR (27.4%). These results are consistent with the literature[7,25,26], and vortioxetine appears to have fewer TEAEs and better tolerability than a therapeutically equivalent dose of venlafaxine XR, supporting the view that vortioxetine is safe and well tolerated.

This study has some limitations. The inclusion and exclusion criteria may limit the generalizability of the study, as may the inclusion only of Asian patients from China, South Korea, Taiwan and Thailand. This study used fixed-dose treatment. Since patients with a history of lack of response to venlafaxine XR were excluded from this study, there is a selection bias in favor of venlafaxine XR. The use of the FAS population is also seen to have favored venlafaxine XR, in that more venlafaxine XR patients withdrew in the first week, and were excluded in the modified ITT (FAS) population. A more appropriate analysis would have been the LOCF analysis in the APTS population.

While the present results suggest similar levels of TEAEs to those reported in other studies carried out in the US and Europe, some caution is needed in generalizing the TEAEs reported here to other populations. This study was carried out in a population that was roughly equally divided between moderate and severe depression and therefore caution is needed in generalizing to those suffering from mild depression.

Conclusion

In conclusion, vortioxetine in a dose of 10 mg/day was at least as effective as venlafaxine XR 150 mg/day in treating MDD over 8 weeks, with a numerical advantage on the MADRS of 1.2 points. This advantage was statistically significant in the post-hoc analysis of the APTS population, and vortioxetine was better tolerated. The results of this study further support the established efficacy of vortioxetine and also confirm the safety and good tolerability of vortioxetine seen in the pivotal clinical studies.

Transparency

Declaration of funding

H. Lundbeck A/S sponsored the study as part of a joint clinical development program with the Takeda Pharmaceutical Company, Ltd. Lundbeck was involved in the study design, collection, analysis and interpretation of data, writing of the report, and the decision to submit the paper for publication.

Declaration of financial/other relationships

G.W. has disclosed that he has received grant funding as well as honoraria and consultancy fees from Lundbeck, Pfizer, MSD, Janssen, Eli Lilly and AstraZeneca. M.G. and G.F. have disclosed that they are employees of Lundbeck. S.M. has disclosed that he has received honoraria and/or has participated in advisory boards on behalf of: Alkermes, AstraZeneca, Grunenthal, Johnson & Johnson, Lundbeck, Merck, Merz, M's Science Corporation, Otsuka Pharmaceuticals, Pierre Fabre Pharmaceuticals, Pfizer, PharmaNeuroBoost, Richter, Roche, Servier, Synosis, Takeda, Theracos, Targacept, Transcept and Xytis.

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