Regular Article

Randomized, double-blind, placebo-controlled 8-week trial of the efficacy, safety, and tolerability of 5, 10, and 20 mg/day vortioxetine in adults with major depressive disorder

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Aim: This study assessed the efficacy and safety of vortioxetine in adults with major depressive disorder.

Methods: In this double-blind, placebo-controlled study, 600 patients with major depressive disorder were randomly assigned (1:1:1:1) to receive vortioxetine 5, 10, or 20 mg, or placebo once daily for 8 weeks. The primary end-point was change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at week 8, evaluated by the last-observation-carried-forward method. Secondary end-points included response (≥50% decrease in the MADRS total score from baseline) and remission (MADRS total score ≤10), Clinical Global Impression Scale-Improvement, and change from baseline in Sheehan Disability Scale. Adverse events were summarized.

Results: Vortioxetine failed to show significant differences from placebo in the primary end-point. Nominally significant improvements over placebo were observed for vortioxetine doses of 10 and 20 mg when the primary end-point was evaluated using the mixed model for repeated measures as the secondary analysis, and 10 mg in secondary measures of response and patient functioning. Vortioxetine was well tolerated. Nausea, constipation, dry mouth, dizziness, and insomnia each occurred at a >twofold higher rate than placebo. Discontinuation symptom scores were comparable between all groups after 1 and 2 weeks following withdrawal of the study drug.

Conclusion: While vortioxetine failed to meet significance versus placebo in the primary efficacy analysis, there was evidence of efficacy for the 10- and 20-mg doses in secondary analyses. Vortioxetine was safe and well tolerated. Additional studies appear warranted.

Key words: 5-HT, antidepressant, major depressive disorder, multimodal treatment, vortioxetine.

**M**AJOR DEPRESSIVE DISORDER (MDD) is a common psychiatric disorder, affecting around 350 million people globally.1 MDD is heterogeneous, with multiple physical, cognitive, and emotional symptoms that contribute to an overall challenging condition to treat.2 Currently, several classes of first-line treatment options are available, including selective serotonin hydroxytryptamine (5-HT) reuptake inhibitors, 5-HT and norepinephrine reuptake inhibitors, and mirtazapine,3 all of which show efficacy over placebo in a range of clinical trials.4 However, only around 30% of patients achieve full remission (defined as a Montgomery-Åsberg Depression Rating Scale [MADRS] total score ≤10) with a first-line therapy after an adequate duration.5 Further, these classes of antidepressants are frequently associated with increased incidence of adverse effects, such as nausea, headache, or dizziness, which may contribute to tolerability issues and affect patient adherence.6–8
Vortioxetine (Lu AA21004) is an antidepressant thought to work through two main modes of action. By both directly modulating 5-HT receptors and inhibiting the serotonin transporter, vortioxetine has a distinct pharmacological profile from current treatment options. Pre-clinical studies have suggested that vortioxetine is a 5-HT₃, 5-HT₇, and 5-HT₁D receptor antagonist, a 5-HT₁B receptor partial agonist, and a 5-HT₁A receptor agonist. These pre-clinical studies indicate that vortioxetine may elevate serotonin, norepinephrine, dopamine, and acetylcholine levels in the brain. Positron emission tomography imaging studies conducted in healthy adults have revealed that mean occupancy of the serotonin transporter in the raphe nuclei is approximately 50% at 5 mg/day, 65% at 10 mg/day, and greater than 80% at 20 mg/day. This mode of action may account for the antidepressant properties of vortioxetine, as demonstrated in 11 short-term phase 3 studies. These studies assessed over 5000 patients and demonstrated significantly improved MADRS scores in those who were administered vortioxetine (10, 15, 20 mg/day) compared with placebo. Phase 3 trials have also shown vortioxetine to have a favorable safety and tolerability profile.

Vortioxetine is approved for the treatment of MDD in 64 countries worldwide, including the USA since September 2013 and Europe since December 2013. Because of genetic polymorphisms, different races and ethnicities have exhibited variations in the pharmacokinetics and pharmacodynamics of antidepressants. In Asia, vortioxetine is approved in South Korea, Hong Kong, and Singapore. Over 5 million people diagnosed with MDD are currently living in Japan, accounting for 4.7% of the population. While vortioxetine is not yet approved in Japan, phase 3 studies in the Japanese population have suggested that vortioxetine treatment improves depressive symptoms at concentrations approved for treatment in non-Japanese MDD patients [Inoue et al., 2017; manuscript submitted]. Here, we report findings from the preceding phase 2 study, which was the first to include a subset of Japanese patients.

METHODS

This was a multinational, randomized, double-blind, placebo-controlled, dose-ranging study, designed to assess the efficacy and safety of three fixed doses (5, 10, and 20 mg/day) of vortioxetine in the treatment of MDD. Patients were enrolled in 90 sites in 14 countries comprising: 44 in Europe, 31 in Japan, and an additional 15 sites in Asia/Oceania. This study was conducted according to the institutional review boards and independent ethics committees of each of the 90 participating regions. Both the institutional review boards and the independent ethics committees continued to review the study according to the ethical requirements of the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice and local regulations.

Study participants

The study aimed to enroll a total of 600 to 615 patients, including at least 20% of Japanese participants (Fig. 1). This sample size would allocate 150 patients to each treatment arm, allowing at least 85% power to detect a 3.0-point difference between each vortioxetine dose and placebo with an SD of 8.2 by a two-sample t-test and a two-sided significance level of 0.05 adjusted with the Dunnett–Hsu procedure.

Patients were screened 1 week before the start of the study. Patients had a primary diagnosis of MDD according to the DSM-IV-TR criteria (classification code 296.2x and 296.3x), an MADRS total score ≥ 26, a Clinical Global Impression Scale – Severity (CGI-S) score ≥ 4, and had the current major depressive episode for ≥ 3 months at baseline. Additional eligibility criteria included age ≥ 20 and ≤ 64 years; capacity to understand and comply with protocol requirements; signed informed consent form; and agreement from female patients to routinely use adequate contraception throughout the duration of the study.

Patients were ineligible for enrollment if they had any current psychiatric or neurological disorder other than MDD as defined in the DSM-IV-TR; had a significant health-related issue, or an abnormal test result, or taken any disallowed medication; had current depressive symptoms resistant to two adequate antidepressant treatments of at least 6 weeks’ duration each; and had significant risk of suicide, a score ≥ 5 on Item 10 (suicidal thoughts) of the MADRS, or had attempted suicide within 6 months; and had received vortioxetine or a disallowed treatment. The patient was also excluded if he or she were, in the investigator’s opinion, unsuitable for any reason.
**Study design**

The study consisted of a 1-week screening period, an 8-week double-blind treatment period, a 2-week single-blind discontinuation period, and a 2-week follow-up period (Fig. 1). Patients were randomized (1:1:1:1) at baseline to receive either placebo once daily (q.d.), vortioxetine 5 mg q.d., vortioxetine 10 mg q.d., or vortioxetine 20 mg q.d. during the 8-week double-blind treatment period. Patients who were assigned vortioxetine 20 mg q.d. received 10 mg q.d. for the first week and were then titrated up to 20 mg q.d. for the remaining 7 weeks of the treatment period. After treatment initiation, patients were seen weekly during the first 2 weeks and then every 2 weeks up to the end of the 8-week treatment period. On completion of the 8-week study, patients entered a 2-week discontinuation period to assess any potential symptoms arising from withdrawal of treatment. During the discontinuation period, all patients received placebo q.d. in a single-blind manner. Patients who prematurely discontinued the study during the 8-week double-blind treatment period were requested to visit the study site for a withdrawal visit as soon as possible. All patients were contacted for a safety follow-up assessment, either by personal visit or phone call, 4 weeks after the last dose of study medication.

**Efficacy evaluation**

The primary end-point was change from baseline in the MADRS total score at week 8, and was analyzed with the last-observation-carried-forward (LOCF) method to account for any data that may have been missing from the final analysis. An analysis of covariance (ANCOVA) model with treatment as a fixed effect and the baseline MADRS total score as a covariate was used for treatment comparisons between each of the vortioxetine treatment arms and placebo in all patients who were randomized and received ≥ 1 dose of study drug (the full analysis set [FAS]). To adjust for multiplicity, the Dunnett–Hsu procedure was used. The change from baseline in the MADRS total score was also analyzed on the per protocol set (PPS), a subset of patients in the FAS who had no major protocol violations, satisfied the minimum protocol specifications, and were eligible for evaluation of the primary end-point to examine the robustness of the result. In addition to the primary analysis that used the ANCOVA model with LOCF approach, secondary analyses were performed using a mixed effect model for repeated measures (MMRM) with treatment, visit, treatment-by-visit interaction, and baseline MADRS total score-by-visit interaction as fixed effects. An unstructured variance–covariance matrix was used to model the within-patient errors and Satterthwaite’s method was used to approximate the degree of freedom. Various secondary end-points were also assessed at week 8 using the LOCF method, including MADRS response, defined as a ≥ 50% decrease in the MADRS total score from baseline; MADRS remission, defined as a MADRS total score ≤ 10; Clinical Global Impression Scale – Improvement (CGI-I).

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**Figure 1.** Study design. Study patients were randomized at week 0 and received double-blind study drug for 8 weeks. Patients randomized to the vortioxetine 20-mg group were started on 10 mg for the first week and titrated up to 20 mg for the remainder of the 8-week study. All patients were switched to placebo at week 8 for 2 weeks. q.d., once daily; V, visit; W, week.
score; and change from baseline in Sheehan Disability Scale (SDS) total score. All secondary end-points were analyzed in the FAS.

Safety evaluation

Treatment-emergent adverse events (TEAE) were collected from the first dose (Visit 2) through the end of discontinuation period (Visit 9) or early termination, but TEAE spontaneously reported after Visit 9 were also included. TEAE were summarized using the safety analysis set, which included all patients who received at least one dose of study drug. The TEAE were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 15.0, https://www.meddra.org) and were summarized by system organ class and preferred term. The intensity of the TEAE was characterized as mild if the event was transient and easily tolerated by the patient, moderate if the event caused the patient discomfort and interrupted the patient’s usual activities, or severe if the event caused considerable interference with the patient’s usual activities.

Serious adverse events (SAE) were recorded from Visit 2 through Visit 10 or early termination, but SAE spontaneously reported after Visit 10 until database-lock were also included. SAE were defined as any medical occurrence that resulted in death; was life threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; led to a congenital anomaly/birth defect; or was otherwise an important medical event. Suicide-related events were assessed at every study visit using the Columbia-Suicide Severity Rating Scale. Discontinuation symptoms were assessed during the 2-week single-blind discontinuation period using the Discontinuation-Emergent Signs and Symptoms (DESS) scale. All safety results were summarized descriptively, and no statistical testing or inferential statistics were generated.

RESULTS

Study participants

Of the 720 patients screened, 600 were randomized into one of the four treatment arms (vortioxetine 5, 10, or 20 mg, or placebo) including 21.5% of whom were Japanese (Table 1 and Fig. S1). The number of patients making up the FAS and the PPS datasets were 593 and 548 patients, respectively (Fig. S1). A total of 73 (12.2%) patients prematurely discontinued the study, with the most common reason being a pre-treatment event or adverse event in 26 (35.6%) patients. Overall, there were no meaningful differences at baseline between the treatment groups in patient demographics or disease characteristics, although the proportion of male patients was smaller in the vortioxetine 5-mg group (32% vs > 37%; Table 1).

| Table 1. Baseline characteristics |
|-----------------------------------|
| Characteristic                    | Placebo (n = 152) | Vortioxetine 5 mg (n = 144) | 10 mg (n = 150) | 20 mg (n = 154) | Total (N = 600) |
| Age (years), mean ± SD            | 43.6 ± 11.57     | 44.2 ± 11.89                 | 45.7 ± 10.9     | 44 ± 11.79       | 44.4 ± 11.54     |
| Sex (male), n (%)                 | 61 (40.1)        | 46 (31.9)                    | 57 (38)         | 61 (39.6)        | 225 (37.5)       |
| Race                              |                  |                              |                |                |                   |
| Caucasian, n (%)                  | 104 (68.4)       | 101 (70.1)                   | 104 (69.3)      | 105 (68.2)       | 414 (69)         |
| Asian, n (%)                      | 48 (31.6)        | 43 (29.9)                    | 46 (30.7)       | 49 (31.8)        | 186 (31)         |
| Japanese only, n (%)              | 33 (21.7)        | 32 (22.2)                    | 31 (20.7)       | 33 (21.4)        | 129 (21.5)       |
| BMI (kg/m²), mean ± SD           | 24.82 ± 5.13     | 25.06 ± 5.43                 | 25.93 ± 5.46    | 24.82 ± 5.21     | 25.15 ± 5.31     |
| Recurrent MDE, n (%)              | 101 (66.4)       | 89 (61.8)                    | 101 (67.3)      | 105 (68.2)       | 396 (66)         |
| Pharmacotherapy for current MDE, n (%) | 73 (48)        | 60 (41.7)                    | 69 (46)         | 75 (48.7)        | 277 (46.2)       |
| MADRS total score, mean ± SD     | 31.6 ± 3.56      | 31.6 ± 3.67                  | 31.8 ± 4.02     | 31.7 ± 3.73      | 31.7 ± 3.74      |
| CGI-S, mean ± SD                 | 4.7 ± 0.66       | 4.7 ± 0.65                   | 4.7 ± 0.66      | 4.7 ± 0.65       | 4.7 ± 0.65       |

BMI, body mass index; CGI-S, Clinical Global Impression Scale – Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode.
Efficacy

Change in MADRS total score

In the primary efficacy analysis, no statistically significant differences in the least square (LS) mean change from baseline in the MADRS total scores were observed at week 8 between placebo and any vortioxetine group in the overall population (Table 2) or in the Japanese-only population (Table S1). However, despite the lack of statistical significance, numerical differences from placebo appeared to increase with increased vortioxetine doses (Table 2). Similar results were observed when the analysis was repeated in the PPS. In contrast, in the secondary analysis using MMRM, nominally significant differences from placebo were observed for the vortioxetine 10-mg group (LS mean: −2.15, \( P = 0.0447 \)) and 20-mg group (LS mean: −2.39, \( P = 0.0249 \); Table 3).

MADRS response and remission

Patients treated with vortioxetine 10 and 20 mg had nominally higher MADRS response rates at week 8 (LOCF) than those in the placebo group (Table 4), resulting in odds ratios (OR) of 1.837 (95% confidence interval [CI]: 1.158–2.914; \( P = 0.0098 \)) for the 10-mg group and 1.604 (95%CI: 1.013–2.538; \( P = 0.0437 \)) for the 20-mg group. Response rates were not significantly different in patients treated with vortioxetine 5 mg and those receiving placebo (Table 4). Remission rates were not significantly different between placebo and any vortioxetine group (Table 4).

Additional outcomes

Overall improvement and patient functioning, when assessed with the CGI-I and SDS, respectively, showed numerical improvement with vortioxetine 10 mg q.d. At week 8, mean CGI-I scores and mean changes from baseline in the SDS total scores were nominally significantly greater for those treated with vortioxetine 10 mg than those receiving placebo. These findings were not repeated in the vortioxetine 5-mg and 20-mg groups (Table 3).

Safety

The incidence of any TEAE in the total population was 66% (Table 5). The most common TEAE were gastrointestinal disorders, such as nausea, constipation, and abdominal pain. Among those treated with vortioxetine, nausea was the most common. Nausea, constipation, dry mouth, dizziness, and insomnia each had an incidence of ≥5% in at least one of the vortioxetine groups that was also more than twofold higher than in the placebo group. The most common adverse event in the placebo group was headache. Twenty-three patients (3.9%) experienced severe TEAE, including four (2.6%) in the placebo group, six (4.2%) in the vortioxetine 5-mg group, six (4.1%) in the vortioxetine 10-mg group, and seven (4.7%) in the vortioxetine 20-mg group (Table 5). These included ear and labyrinth disorders (placebo: 1), gastrointestinal disorders (placebo: 1; vortioxetine 10 mg: 4; vortioxetine 20 mg: 4), general disorders and administration site conditions (vortioxetine 10 mg: 1), musculoskeletal and connective tissue disorders (placebo: 1; vortioxetine 5 mg: 2; vortioxetine 10 mg: 1), nervous system disorders (two in each vortioxetine group), psychiatric disorders (placebo: 1; vortioxetine 5 mg: 1), renal and urinary disorders (vortioxetine 5 mg: 1; vortioxetine 20 mg: 1), and skin and subcutaneous tissue disorders (vortioxetine 10 mg: 1). One patient experienced a serious pre-treatment event of acute sinusitis. The most common SAE were psychiatric disorders, including suicide attempts (one patient

| Table 2. Efficacy outcomes for primary end-point at week 8 |
|---------------------------------|----------------|----------------|-------------------|-----------------|
| Scale                          | Treatment group | LS mean       | LS mean diff from PBO (95%CI) | \( P \)-value<sup>1</sup> |
| MADRS (FAS, LOCF, ANCOVA)      | PBO            | −13.99        |                                 |                 |
|                                | VOR 5 mg       | −14.61        | −0.61 (−3.258–2.035)            | 0.9070          |
|                                | VOR 10 mg      | −15.68        | −1.69 (−4.310–0.938)           | 0.3006          |
|                                | VOR 20 mg      | −15.82        | −1.82 (−4.436–0.794)           | 0.2399          |

<sup>1</sup>Adjusted by Dunnett–Hsu procedure.

ANCOVA, analysis of covariance; CI, confidence interval; diff, difference; FAS, full analysis set; LOCF, last observation carried forward; LS, least square; MADRS, Montgomery–Åsberg Depression Rating Scale; PBO, placebo; VOR, vortioxetine.
Table 3. Secondary efficacy outcomes at week 8

| Scale                  | Treatment group | LS mean | LS mean diff from PBO (95%CI) | P-value |
|------------------------|-----------------|---------|------------------------------|---------|
| MADRS (FAS, MMRM)      | PBO             | −14.73  |                              |         |
|                        | VOR 5 mg        | −15.40  | −0.67 (−2.78–1.44)            | 0.5325  |
|                        | VOR 10 mg       | −16.87  | −2.15 (−4.24–0.05)            | 0.0447  |
|                        | VOR 20 mg       | −17.12  | −2.39 (−4.48–0.30)            | 0.0249  |
| CGI-I (FAS, LOCF, ANCOVA) | PBO           | 2.54    |                              |         |
|                        | VOR 5 mg        | 2.37    | −0.17 (−0.418–0.071)          | 0.1633  |
|                        | VOR 10 mg       | 2.27    | −0.27 (−0.510–0.026)          | 0.0303  |
|                        | VOR 20 mg       | 2.36    | −0.18 (−0.419–0.063)          | 0.1477  |
| SDS (FAS, LOCF, ANCOVA) | PBO             | −6.20   |                              |         |
|                        | VOR 5 mg        | −6.38   | −0.19 (−1.925–1.549)          | 0.8316  |
|                        | VOR 10 mg       | −7.97   | −1.78 (−3.494–0.063)          | 0.0421  |
|                        | VOR 20 mg       | −7.26   | −1.06 (−2.762–0.638)          | 0.2202  |

ANCOVA, analysis of covariance; CI, confidence interval; CGI-I, Clinical Global Impression Scale – Improvement; diff, difference; FAS, full analysis set; LS, least square; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; MMRM, mixed model repeated measures; PBO, placebo; SDS, Sheehan Disability Scale; VOR, vortioxetine.

Each in the vortioxetine 20-mg group and placebo group), depression (vortioxetine 10 mg: 1), and suicidal ideation (vortioxetine 20 mg: 1).

Overall, 24 patients experienced TEAE leading to study discontinuation. Six patients discontinued after treatment with placebo, and 18 patients who were treated with vortioxetine (2, 8, and 8 in the 5-, 10-, and 20-mg groups, respectively). Gastroenterology disorders accounted for the most treatment discontinuations, with nausea the most common of these (n = 6), followed by constipation (n = 3). First-degree atrioventricular block, vertigo, abdominal pain, abdominal pain upper, flatulence, vomiting, asthenia, malaise, mucosal dryness, alcoholic liver disease, and abnormal hepatic function all accounted for one patient’s discontinuation each. One patient discontinued the study because of pregnancy and later experienced a missed abortion.

Symptoms emerging after discontinuation of treatment were evaluated using the DESS at 1 and 2 weeks after treatment discontinuation (weeks 9 and 10). Mean scores were similar between the treatment groups at week 9 (Table S2). Mean DESS total scores decreased in those receiving placebo, from a mean of 1.0 at week 9 to 0.5 at week 10. In the vortioxetine groups, mean DESS scores decreased from week 9 to week 10 in those treated with 5 mg (1.2 to 0.8) and 20 mg (1.4 to 0.7). Mean DESS scores were comparable in the 10-mg treatment group at both week 9 (1.0) and week 10 (1.1).

DISCUSSION

The primary objective of this study was to assess the efficacy of fixed doses of vortioxetine for the treatment of MDD as measured by the MADRS. The

Table 4. Patients with MADRS response and remission at week 8

| Treatment group | Patients, n | MADRS response | MADRS remission |
|-----------------|------------|----------------|-----------------|
|                 |             | Responder, n (%) | P-value vs PBO  | Remitter, n (%) | P-value vs PBO |
| PBO             | 150        | 59 (39.3) [31.5–47.6] | 0.0866 | 40 (26.7) [19.8–34.5] | 0.6908 |
| VOR 5 mg        | 142        | 70 (49.3) [40.8–57.8] | 0.0098 | 43 (29.3) [22.1–37.3] | 0.6084 |
| VOR 10 mg       | 147        | 80 (54.4) [46.0–62.7] | 0.0437 | 46 (30.9) [23.6–39.0] | 0.1470 |
| VOR 20 mg       | 149        | 76 (51.0) [42.7–59.2] |           |                 |            |

CI, confidence interval; MADRS, Montgomery–Åsberg Depression Rating Scale; PBO, placebo; VOR, vortioxetine.
study failed to reach significance when vortioxetine was compared with placebo. However, nominally significant improvements over placebo were observed for vortioxetine doses of 10 and 20 mg when the primary end-point was evaluated using MMRM as the secondary analysis. This finding is supported by previous studies that have shown improved MADRS scores in patients with MDD to a greater extent after treatment with similar doses of vortioxetine (5–20 mg/day) than those administered placebo.9,11,15–18,20,30–32 Together, these observations are consistent with the established antidepressant effects of vortioxetine. The observed overall improvements, as assessed by the CGI-I and SDS scores at week 8 and MMRM analysis of the MADRS total score, further lend support to the efficacy of vortioxetine in our study. In addition, vortioxetine 5, 10, and 20 mg was found to be generally safe and well tolerated in those with MDD. Similar to other studies of vortioxetine, nausea was the most common adverse event reported.21,33

That ethnic differences can impact antidepressant drug metabolism and call for dosing adjustments is well documented in the literature.25,26 In addition to polymorphisms in key drug metabolizing enzymes, differences in diet as well as other genetic and lifestyle factors can contribute to the variability observed in an antidepressant’s pharmacokinetic and pharmacodynamic profile, especially between Asian and Caucasian populations.26,27,34 It is unsurprising then that regulatory agencies consider these ethnic factors – both intrinsic and extrinsic – when evaluating foreign clinical data in their approval process.34

Our study is the first to evaluate the efficacy of vortioxetine in a subpopulation of Japanese patients. Although our primary analysis did not reveal any statistically significant differences between placebo and vortioxetine at any dose, there was evidence of the efficacious effects of vortioxetine (10 and 20 mg). Improved functioning and response rates in those treated with vortioxetine further support its efficacy. Within the limitations of this study, we have shown that vortioxetine was safe and well tolerated.

### Table 5. Summary of safety outcomes

| Event                         | Placebo (n = 151) | Vortioxetine 5 mg (n = 144) | Vortioxetine 10 mg (n = 148) | Vortioxetine 20 mg (n = 150) | Total (N = 593) |
|-------------------------------|-------------------|-----------------------------|-----------------------------|-----------------------------|-----------------|
|                              | Events, n (%)     | Events, n (%)               | Events, n (%)               | Events, n (%)               | Events, n (%)   |
| Any AE                        | 193 (64.2)        | 240 (66.7)                  | 240 (62.8)                  | 282 (70.7)                  | 955 (66.1)      |
| Mild                          | 57 (37.7)         | 151 (43.1)                  | 151 (41.1)                  | 197 (49.3)                  | 559 (34.3)      |
| Moderate                      | 36 (23.8)         | 78 (21.7)                   | 78 (21.7)                   | 73 (18.5)                   | 264 (16.5)      |
| Severe                        | 2 (1.3)           | 11 (3.1)                    | 11 (3.1)                    | 12 (3.1)                    | 46 (1.6)        |
| Treatment-related AE          | 125 (40.4)        | 143 (48.6)                  | 143 (48.6)                  | 197 (50.0)                  | 552 (26.7)      |
| AE leading to discontinuation | 6 (4.0)           | 14 (4.8)                    | 14 (4.8)                    | 17 (4.4)                    | 41 (2.4)        |
| Any SAE                       | 1 (0.7)           | 3 (1.4)                     | 3 (1.4)                     | 5 (1.3)                     | 11 (2.0)        |
| Nausea                        | 11 (7.3)          | 26 (18.2)                   | 27 (18.2)                   | 37 (24.7)                   | 101 (17.0)      |
| Nasopharyngitis               | 18 (11.9)         | 24 (16.7)                   | 24 (16.7)                   | 21 (14.0)                   | 81 (13.7)       |
| Headache                      | 21 (13.9)         | 16 (11.1)                   | 19 (12.8)                   | 23 (15.3)                   | 79 (13.3)       |
| Diarrhea                      | 14 (9.3)          | 7 (4.9)                     | 6 (4.1)                     | 5 (3.3)                     | 32 (4.0)        |
| Dizziness                     | 5 (3.3)           | 7 (4.9)                     | 8 (5.4)                     | 10 (6.7)                    | 30 (4.0)        |
| Constipation                  | 3 (2.0)           | 6 (4.2)                     | 5 (3.4)                     | 5 (3.4)                     | 22 (3.7)        |
| Dry mouth                     | 3 (2.0)           | 2 (1.4)                     | 6 (4.1)                     | 9 (6.0)                     | 21 (3.5)        |
| Insomnia                      | 2 (1.3)           | 4 (2.8)                     | 4 (2.7)                     | 9 (6.0)                     | 19 (3.2)        |

AE, adverse events; MedDRA, Medical Dictionary for Regulatory Activities (version 15.0, https://www.meddra.org); pts., patients; SAE, serious adverse events.
tolerated in patients with MDD. Direct comparisons between the Japanese and non-Japanese patients were beyond the scope of this study. However, when dosed at 10 and 20 mg, vortioxetine showed not significant but numerical improvement in symptoms of depression in the Japanese and non-Japanese subpopulations. The findings of this cross-population study suggest that the doses of vortioxetine currently approved in Europe and the USA would be safe and well tolerated in the Japanese population. Two subsequent phase 3 studies in Japan provide further evidence of the safety and efficacy of vortioxetine in this population [Inoue et al., 2017; manuscript submitted]. A third phase 3 study (ClinicalTrials.gov ID: NCT02389816) is currently underway in Japan to corroborate these findings. Together these studies will expand the evidence base supporting vortioxetine use in the Japanese population.

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AUTHOR CONTRIBUTIONS
All authors were involved in the design of the clinical study, acquisition of data, and analysis and interpretation of data. All authors were involved in the drafting and revising of the manuscript and have approved the final version.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Table S1. Change from baseline MADRS total score at week 8 (FAS, LOCF, ANCOVA) in the Japanese and non-Japanese populations

Table S2. Summary of DESS total score by visit

Figure S1. Patient disposition