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Results of a real-world study on vortioxetine in patients with major depressive disorder in South East Asia (REVIDA)

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Abstract

Objective: The REVIDA study aimed to assess the evolution of major depression symptoms in South East Asian (SEA) patients treated with vortioxetine for major depression in real-world clinical practice.
Methods: This non-interventional study was conducted from Aug 2016 to Apr 2017. A total of 138 patients (aged 18–65 years) with an active episode of major depression were recruited from Malaysia, Philippines, Singapore, and Thailand. Vortioxetine was initiated on the first visit and patients were followed for 3 months. Depression severity was assessed using the PHQ-9 questionnaire (patient-assessed) and CGI-S scale (physician-assessed); cognitive function was assessed with the PDQ-D questionnaire; work productivity and activity impairment (WPAI) was assessed with the WPAI questionnaire.
Results: At baseline, 89.9% of patients were moderately to severely depressed (PHQ-9 score ≥ 10). During the 3-month treatment period, mean±SD PHQ-9 score decreased from 18.7±5.7 to 5.0±5.3, mean±SD CGI-S score decreased from 4.4±0.7 to 2.2±1.1, and mean±SD PDQ-D score decreased from 42.1±18.8 to 13.4±13.0. By month 3, response and remission rates reached 80.8% and 59.0%, respectively. Work productivity loss decreased from 73.6% to 30.5%, while activity impairment decreased from 71.5% to 24.6%. Positive correlations were observed between PHQ-9, PDQ-D, and WPAI work productivity loss and activity impairment. By month 3, 82.0% of patients were either not depressed or only mildly depressed (PHQ-9 score ≤ 9).
Conclusion: In real-world clinical settings, vortioxetine was effective in reducing depression severity and improving cognitive function and work productivity in SEA patients with major depression.

Keywords: antidepressant, major depressive disorder, vortioxetine, real-world study

Introduction

Major depressive disorder (MDD) is characterized by depressed mood, loss of interest or pleasure, weight changes, sleep disorders, low energy, feelings of worthlessness, indecisiveness, and suicidal thoughts [1]. MDD is also often associated with impairments in cognition (such as diminished ability to think or concentrate, or indecisiveness [1]) and work function (such as increased absenteeism and reduced work productivity [2, 3]). Despite clinical and therapeutic advances over the years, real-world data show that a proportion of patients treated with antidepressants continue to face challenges in responding to treatment [4], making a complete recovery [5], or achieving remission [6, 7]. Furthermore, residual symptoms (e.g. cognitive dysfunction) and side effects common with current antidepressant therapies (e.g. weight gain, sleep disturbance, and sexual dysfunction) present major barriers to achieving treatment goals [8, 9].

Efforts to overcome the limitations of current antidepressants have led to the development of vortioxetine, a novel antidepressant with a distinct pharmacodynamic profile [10]. Vortioxetine displays multiple molecular mechanisms of action [11]; its antidepressant effects are thought to be exerted through direct modulation of 5-HT receptor activity and inhibition of the 5-HT transporter. *In vitro* studies indicate antagonistic effects on 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors, agonistic effects on 5-HT_{1A} receptors, partial agonistic effects on 5-HT_{1B} receptors, and inhibitory effects on the 5-HT transporter [10, 12]. Data from *in vivo* studies further suggest modulation of the serotonergic, noradrenergic, dopaminergic, glutamatergic, histaminergic, and cholinergic systems by vortioxetine [10, 13, 14]. These diverse actions were postulated to contribute to vortioxetine's beneficial effects on mood and cognition.

Vortioxetine's efficacy and safety in mitigating depressive symptom severity in patients with MDD have been established in a number of randomized, double-blind, placebo-controlled trials [15-19]. The findings of these pivotal studies have led to vortioxetine's approval in the United States and Europe for the treatment of MDD [20]. Since then, a growing body of evidence also suggests potential clinical benefits of vortioxetine on cognitive functioning in adults with MDD [21-25]; further studies focused on clarifying the magnitude of vortioxetine's effects on cognitive functioning will thus be important.

To complement efficacy and safety data from short-term randomized controlled trials that used restrictive inclusion and exclusion criteria, further investigation is needed in real-world settings where the patient population is more diverse and clinical management practice may be more variable. Following vortioxetine's recent approval in Singapore, Malaysia, Thailand, and the Philippines for treatment of adults with MDD, the REVIDA (REal-world study on Vortioxetine In patients with major Depression in South East Asia) study was planned to assess vortioxetine's effectiveness in routine clinical practice in these countries. Specifically, the REVIDA study aimed to assess the evolution of major depressive symptoms, cognitive function, and work productivity in patients treated with vortioxetine over a 3-month treatment period.

Materials and methods

Study design

This multi-country, multi-site, prospective non-interventional study was conducted between August 2016 and April 2017 at 18 sites across 4 countries in Asia (Malaysia, Philippines, Singapore, and Thailand). The participating sites were primarily private psychiatric clinics or psychiatric clinics affiliated to private hospitals in the respective countries.

Patient eligibility for the study was assessed after the physician's decision to prescribe vortioxetine for a major depressive episode. The patients were followed for 3 months. Data were collected when patients initiated treatment (Baseline), and when they returned to the clinic for routine visits at approximately 1 week (±3 days), 1 month (±7 days), and 3 months (±14 days) after treatment initiation. All treatments were prescribed according to the recommendations provided in the local summary of product characteristics. No compensation was provided to patients for participation in the study.

The study protocol was reviewed and approved by the local Institutional Review Board/Ethics Committee for each site before study initiation. The sites in Malaysia received approval from the Medical Research and Ethics Committee, Ministry of Health Malaysia. Trial registration was not required for this non-interventional real-world study. All patients provided written informed consent before study enrolment.

Patients

Patients were assessed for study eligibility at the baseline visit based on the following inclusion and exclusion criteria. Inclusion criteria included patients between the ages of 18 and 65 years (inclusive), clinically diagnosed with a major depressive episode in the current visit, initiated treatment with vortioxetine on the day of the visit, and signed written informed consent. Exclusion criteria included concurrent diagnosis or past history of schizophrenia or any psychotic disorders, bipolar disorder, dementia or any other neurodegenerative disease, alcohol or substance dependence, any other psychiatric disorders due to substances or a general medical condition, a member of the study personnel or of their immediate families, or was a subordinate (or immediate family member of a subordinate) to any of the study personnel, previous enrollment in this study, participation in another clinical trial, unlikely to comply with the protocol based on the investigator's opinion, and met any other contraindication listed in the respective summary of product characteristics of vortioxetine. Age range of recruited patients follows that of previous studies of vortioxetine [15-19].

Study assessments

Treatment compliance

Patient compliance with vortioxetine treatment was assessed by the physician via patient interview. Compliance was estimated based on the proportion of prescribed dose taken since the last visit and recorded as a percentage between 0% and 100%; 0% represents no dose taken and 100% represents all doses taken as prescribed.

Depression severity

The self-administered Patient Health Questionnaire-9 (PHQ-9) [26] consists of a 9-item scale to assess how much patients were bothered by the symptoms over the past two weeks. Each item has 4 possible answers: "not at all" (0 points), "several days" (1 point), "more than half of the days" (2 points), and "nearly every day" (3 points). The PHQ-9 score (ranges from 0 to 27) is the sum of the 9-item scale scores, with higher scores indicating greater depression severity: none (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27) depression.

Depression severity was also assessed by the physician, using the Clinical Global Impression – Severity (CGI-S) scale. Based on the physician's clinical experience, he or she rated the severity of the patient's illness on a 7-point scale ranging from 1 (normal – not at all ill) to 7 (among the most

extremely ill patients). Higher CGI-S scores indicate greater severity of illness: normal to mildly ill (1–3), moderately ill (4), and markedly ill to among the most extremely ill (5–7).

Improvement in illness

The physician also assessed overall improvement or worsening of the patient's illness using the Clinical Global Impression – Improvement (CGI-I) scale. The physician assessed the patient's condition relative to baseline and rated the change on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Lower CGI-I scores indicate greater improvement of illness: very much improved to minimally improved (1–3), no change (4), and minimally worse to very much worse (5–7).

Cognitive function

The self-administered Perceived Deficit Questionnaire – Depression (PDQ-D) [27] was used to assess perceived cognitive deficits. It comprises four subscales (attention/concentration, prospective memory, planning/organization, and retrospective memory) which contain 20 items scored between 0 (never in the past 7 days) to 4 (very often, more than once a day). The PDQ-D score (ranges from 0 to 80) is the sum of the 20-item scale scores, with higher scores reflecting worse cognitive function.

Work Productivity and Activity Impairment (WPAI)

The self-administered WPAI questionnaire [28] was used to measure work productivity and activity impairment due to depression. It assesses activities over the preceding 7 days and consists of 6 questions (Q1 = currently employed; Q2 = hours missed due to health problems; Q3 = hours missed other reasons; Q4 = hours actually worked; Q5 = degree health affected productivity while working; Q6 = degree health affected productivity in regular unpaid activities) to assess how much the patient's condition affected their productivity at work and their ability to complete normal daily activities.

Four outcome scores planned a priori were derived based on the answers to the WPAI questionnaire:

- Percent absenteeism = [Q2/(Q2+Q4)] × 100
- Percent presenteeism = (Q5/10) × 100
- Percent work productivity loss = {Q2/(Q2+Q4) + [(1-(Q2/(Q2+Q4)) × (Q5/10)]} × 100
- Percent activity impairment = (Q6/10) × 100

Percent absenteeism, presenteeism (health-related impairment in productivity while at work), and work productivity loss were calculated for those who were currently employed, whereas percent activity impairment was calculated for all patients. All four WPAI outcome scores range from 0% to 100%, with greater values indicating greater absenteeism, presenteeism, work productivity loss, and activity impairment, respectively.

Safety

Adverse drug reactions (ADRs) were any adverse effects that were reported by the physician to be possibly related to vortioxetine treatment. All ADRs spontaneously reported by the patient or observed by the investigator were collected using an ADR report form. Data on ADRs were collected as part of Lundbeck's pharmacovigilance activities.

Statistical analyses

The Safety population consisted of all patients who received the patient information, provided informed consent, met the selection criteria, and took at least one dose of vortioxetine; the Eligible population included patients in the Safety population who completed at least one post-baseline evaluation by the physician as captured in the case report form and at least one post-baseline patient-reported outcome questionnaire. Sociodemographic variables, baseline data, and safety data were analyzed in the Safety population; PHQ-9, CGI-S, CGI-I, WPAI outcome scores were analyzed in the Eligible population.

All assessment data were summarized using descriptive statistics. Partially answered questionnaires were treated as missing and were not replaced. Summary statistics (mean, standard deviation (SD), median, minimum and maximum values) are presented for continuous variables. Counts and

percentages are presented for categorical and binary variables. All statistical analyses were performed using SAS™ statistical analysis software (SAS Institute, Cary, NC, USA, version 9.3).

Results

Sociodemographic and baseline characteristics

A total of 138 patients were enrolled in the study. All patients took at least 1 dose of vortioxetine and were included in the Safety population. Among them, 7 patients did not complete at least one post-baseline patient-reported outcome questionnaire and were excluded from the efficacy analyses, leaving 131 patients in the Eligible population. Overall, 34 patients discontinued the study before the last visit (20 due to lost to follow-up, 9 due to ADR, 3 due to poor compliance, and 2 due to other unspecified reasons).

Sociodemographic variables and baseline characteristics are presented in Table 1. Mean age of the patients was 39.7 years (SD 12.49 years, range 18 to 64 years); 65.9% were female. The majority were married or living as a couple (51.4%). A total of 58 patients (42.3%) had at least one concomitant clinical diagnosis with the current MDD episode, the most common of which were generalized anxiety disorder (35 patients; 27.6%), followed by panic disorder (26 patients; 21.1%), agoraphobia (11 patients; 9.1%), obsessive-compulsive disorder (7 patients; 5.8%), social phobia (4 patients; 3.3%), specific phobia (1 patient; 0.8%), and post-traumatic stress disorder (1 patient 0.8%). Mean PHQ-9 score of the eligible population at baseline was 18.7 (SD 5.7; Figure 1A), and mean CGI-S score was 4.4 (SD 0.7; Figure 2A), indicating that overall, patients had moderate-to-severe depressive symptoms and were moderately to markedly ill. The majority of patients (57.7%) had not received treatment for the current MDD episode prior to the baseline visit. For those who were treated prior to baseline (58 patients; 42.3%), most were treated with selective serotonin reuptake inhibitors (41/58 patients; 70.7%) or tricyclic antidepressants (6/58 patients; 10.3%).

The median daily dose of vortioxetine prescribed was 10.0 mg (range 2.5–20.0 mg) throughout the treatment period. The mean patient compliance was more than 87% at all study time points (Week 1: 90.5%, Month 1: 88.8%, Month 3: 87.1%). The proportion of patients using anxiolytics decreased over the 3 month study period, from 70.3% at baseline to 30.4% at Month 3.

Depression severity

Patient-assessed depressive symptom severity

Mean PHQ-9 score decreased steadily from 18.7 (SD 5.7) at baseline to 5.0 (SD 5.3) at Month 3 (Figure 1A). The proportion of patients who had moderately severe to severe depressive symptoms based on their PHQ-9 scores reduced from 76.7% (moderately severe: 24.0%; severe: 52.7%) at baseline to 6.0% (moderately severe: 5.0%; severe: 1.0%) at Month 3 (Figure 1B). At Month 3, the majority of patients had mild or no depressive symptoms (23% and 59%, respectively; Figure 1B).

Physician-assessed depressive symptom severity

Mean CGI-S score decreased over the treatment period, from 4.4 (SD 0.7) at baseline to 2.2 (SD 1.1) at Month 3 (Figure 2A). The proportion of patients who were moderately to markedly ill based on their CGI-S scores decreased from 96.3% (moderately ill: 53.3%; markedly ill to among the most extremely ill: 43.0%) at baseline to 12.4% (moderately ill: 10.2%; markedly ill to among the most extremely ill: 2.2%) at the end of Month 3 (Figure 2B). By Month 3, the majority of patients (87.7%) were assessed to be normal to mildly ill (Figure 2B) based on their CGI-S scores.

Improvement, response, and remission

Mean CGI-I score was 3.2 (SD 1.0) at Week 1, and decreased to 2.3 (SD 1.0) at Month 1 and 1.6 (SD 0.9) at Month 3 (Figure 3A). Overall, 65.0% of patients showed improvement (CGI-I score 1–3) at Week 1; this further increased to 91.1% at Month 1 and 97.8% at Month 3 (Figure 3B).

Patient-assessed treatment response (PHQ-9 response: ≥50% reduction in PHQ-9 score) was achieved in 18.9% of patients at Week 1, 57.5% at Month 1, and 80.8% at Month 3 (Figure 3C).

Patient-assessed remission (PHQ-9 remission: PHQ-9 score ≤4) was achieved in 12.4%, 25.9%, and 59.0% of patients at Week 1, Month 1, and Month 3, respectively (Figure 3D). Similar trends in physician-assessed response (CGI-S response: ≥50% reduction in CGI-S score) and remission (CGI-S remission: CGI-S score ≤3) were observed over the 3-month treatment period (Figures 3C and 3D).

Patient-reported cognitive deficit

Mean PDQ-D score decreased steadily from 42.1 (SD 18.8) at baseline to 13.4 (SD 13.0) at Month 3 (Figure 4A). Compared with responders, non-responders had smaller reductions from baseline in PDQ-D total score at all time-points (Week 1, Month 1, and Month 3); the trend was similar for patient-assessed response (PHQ-9 responders/non-responders; Figure 4B) and physician-assessed response (CGI-S responders/non-responders; Figure 4C).

Work productivity and activity impairment

Approximately half of the patients were employed during the study period (Baseline: 65/131, 49.6%; Month 3: 52/100, 52.0%). Mean work productivity and activity impairment (WPAI) outcome scores at baseline and Month 3 are presented in Figure 5. Over the 3-month treatment period, mean percent absenteeism per patient improved from 56.5% to 19.5%, presenteeism reduced from 67.5% to 23.9%, work productivity loss decreased from 73.6% to 30.5%, and activity impairment decreased from 71.5% to 24.6%.

Correlations between depressive symptom severity, cognitive deficit, and work productivity and activity impairment

At baseline, positive correlations were observed for PHQ-9 scores versus PDQ-D scores and WPAI activity impairment scores; and PDQ-D scores versus WPAI activity impairment scores (correlation coefficients ranged between 0.5 and 0.6; all 95% CI ranges >0; Supplementary Table 1). At Month 3, positive correlations were observed for PHQ-9 scores versus PDQ-D scores, WPAI work productivity loss scores and WPAI activity impairment scores; and PDQ-D scores versus WPAI work productivity loss scores and WPAI activity impairment scores (correlation coefficients ranged between 0.7 and 0.9; all 95% CI ranges >0; Supplementary Table 1).

Safety

Overall, 13 (9.4%) patients experienced 20 events of adverse drug reactions (ADRs) during the study period (Table 2). The most common ADRs were abdominal discomfort (4 events) and nausea (3 events). Nine patients (6.5%) discontinued the study due to ADRs.

Discussion

The REVIDA study is the first real-world study of vortioxetine treatment in Asia. Consistent with previously reported randomized controlled trials, we observed a notable reduction in depression severity in patients treated with vortioxetine. By the end of the 3-month treatment period, most patients reported depressive symptom severity scores within the "not depressed" or "mildly depressed" range (82.0%; PHQ-9 score ≤9). Consistent with this observation, most patients were also clinically assessed as normal to mildly ill by their physicians (87.8%; CGI-S score ≤3) at Month 3. Almost all patients (97.8%; CGI-I score ≤3) showed improvement relative to baseline, with over 80% responding to treatment and 59% achieving remission by the end of the 3-month treatment period. The reduction in depression severity observed was accompanied by notable improvements in cognitive function and work function. Safety results indicate that treatment with vortioxetine was generally well tolerated, with a discontinuation rate of around 6% due to ADRs. The most common ADRs were abdominal discomfort and nausea.

These data support previous studies that showed the efficacy of vortioxetine in the acute treatment of MDD [15-19]. Improvements in symptoms, both patient-assessed and physician-assessed, were apparent within 4 weeks, and almost 60% of patients achieved remission by the end of the study. Remission rates observed in this study were on the higher end of those reported in randomized trials, which ranged from 20% to 60% [15-19]. As remission rates are closely related to the length of the treatment period, the high remission rate observed may be associated with the longer vortioxetine treatment period in the present study (3 months) compared with the shorter randomized controlled trials (6 to 8 weeks) [15-19]. Indeed, the proportion of patients achieving remission increased steadily over the study period, from 12.4% at Week 1 to 25.9% at Month 1 and 59.0% at Month 3. Other longer-term extension studies have reported even higher remission rates, up to 83%, after 52 weeks of open-label vortioxetine treatment [29, 30]. These results are particularly encouraging given that remission rates in real-world patients with MDD were only 28% upon completion of the first-step treatment and reached 50-55% only after two sequential treatment interventions [31]. Other factors that should be taken into consideration when interpreting remission rates include the open-label uncontrolled nature of the study and patient drop out over time.

Our findings also demonstrate the effectiveness of vortioxetine for the treatment of MDD in an Asian population, similar to randomized controlled trials conducted in majority- Caucasian populations. While a recent systematic review and meta-analysis of vortioxetine suggested some variation in efficacy depending on racial composition of the patient population [32], the potential reasons for these variations require further research.

This study used the PHQ-9 to assess depression severity from the patient's perspective. Response to treatment was defined as a more than 50% reduction of the PHQ-9 score from baseline, and remission was defined as a PHQ-9 score of 4 or lower [26]. The PHQ-9 was chosen for its validity and reliability in assessing depression in Asian primary care settings [33-35]. In addition, its brevity makes it relatively quick for patients to complete and for physicians to review, thus making the PHQ-9 suitable for the assessment of MDD in the busy setting of real-world clinical practice. Importantly, the PHQ-9 shows good correlation with the MADRS scale [36], which was used in a number of vortioxetine randomized controlled trials [15-19].

Vortioxetine has been observed to display some clinical efficacy in the treatment of cognitive deficits associated with MDD [21-25]. Although the mechanism that mediate the effects of vortioxetine on cognitive function has not been elucidated, some evidence suggests that in vortioxetine-treated patients, improvements in cognition were independent of improvements in depressive symptoms [23, 37]. In this study, cognitive function was evaluated using the PDQ-D – a self-report questionnaire developed to evaluate cognition specifically in patients with MDD [38]. The validity of the PDQ-D has been demonstrated in several studies [27, 39], and patients have found the PDQ-D easy to understand and relevant to their experiences with MDD [27]. Our results with the PDQ-D

indicated an improvement in cognitive function in patients treated with vortioxetine for MDD. Although we noted greater cognitive improvement in responders compared with non-responders, further analyses are needed to understand the clinical significance of these differences. Notably, a recent post-hoc analysis reported a more pronounced effect on cognitive function amongst working patients treated with vortioxetine for MDD, and noted greater improvements in individuals with professional types of positions compared to the overall working population [22]. Our study was too small to analyze for such subgroup differences, but future studies could consider exploring the relative improvements across domains of cognitive function amongst working patients, or across the patient population as a whole.

Work function is another important factor in the journey to recovery for patients with MDD. Improvements in work function and productivity have been noted following antidepressant treatment [40]. In the present study, we observed a reduction in percent absenteeism and work productivity loss amongst working patients over the study period; both of which are indicative of effective antidepressant treatment. Notably, there was a significant correlation between work productivity (WPAI outcome scores), depression severity (PHQ-9 scores), and cognitive function (PDQ-D scores). Further studies may thus be warranted on whether the observed improvement in work function is linked to vortioxetine's positive effects on depression symptoms and cognition. Other possible contributory factors may include less anhedonia, remission of majority of depressive symptoms, and changes to work function over the study period.

As vortioxetine was prescribed according to the local summary of product characteristics of the participating countries, the prescribed dose ranged from 2.5 to 20.0 mg/day. Dosing flexibility allowed tailoring of the dose to the individual patient for optimal efficacy and tolerability. Treatment compliance among those who remained on vortioxetine treatment was assessed as 87%; however total compliance which includes patients who discontinued the study prematurely would be closer to 50%, consistent with patient adherence rates with antidepressant therapy reported in the literature [41]. The reasons for early study discontinuation were mostly due to lost to follow-up; only a small proportion of patients discontinued the study early due to medication side effects or poor treatment adherence.

Consistent with previously published studies, nausea was one of the most commonly reported ADRs in this study [15-19]. Abdominal discomfort, a less reported side effect in previous trials, emerged as the most common ADR in this study. Notably, no adverse events of vomiting, sexual dysfunction, and dry mouth were reported. In addition, very few patients left the study due to ADRs. Thus, vortioxetine treatment up to 20 mg/day appeared to be safe and well-tolerated in the population of Asian patients studied here. With a relatively good tolerability and safety profile in Asian patients, vortioxetine may thus be an alternative treatment option for patients in South East Asia who fail to achieve sufficient response or remission with other antidepressant treatments.

Limitations of this study include its open-label design and the lack of an active or placebo comparator arm. The findings may not be fully generalizable to the entire range of patients and clinical settings in Southeast Asia, since the participating study sites were mostly private psychiatric clinics or psychiatric clinics affiliated to private hospitals. In our experience, patients utilizing private unsubsidized healthcare are typically more willing to be treated and motivated to recover compared with patients utilizing public subsidized healthcare. Additionally, given that almost a quarter of patients had depressive episodes of 4 weeks or shorter and more than half were in their first depressive episode, further studies are needed to explore the effectiveness of vortioxetine for treating patients with chronic or treatment-resistant depression. It should also be noted that some patients were pre-treated with other antidepressants and anxiolytics before study recruitment, which may make the interpretation of vortioxetine's effects on cognition challenging as tricyclic antidepressatns and anxiolytics are known to alter the cognitive state. Although such drug-drug interactions were not studied in this real world study, further studies could focus on exploring these so as to clarify vortioxetine's effects on cognitive capacity and recovery in patients with MDD. Finally, ADR rates may be underestimated in this study as safety data were based on patient self-

reports and observations by investigators rather than via specific queries of potential ADRs by trained health care professionals. Nonetheless, the prospective non-interventional study design provides a useful indicator of treatment outcomes of vortioxetine in Asian primary care settings.

Conclusion

In this real-world study, vortioxetine was effective in reducing depressive symptom severity and improving cognitive function and work productivity in Asian patients with major depression.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed.: Arlington: American Psychiatric Association; 2013.
2. Woo JM, Kim W, Hwang TY, et al. Impact of depression on work productivity and its improvement after outpatient treatment with antidepressants. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(4):475-82.
3. Harvey SB, Glozier N, Henderson M, et al. Depression and work performance: an ecological study using web-based screening. Occupational medicine (Oxford, England). 2011;61(3):209-11.
4. Rizvi SJ, Grima E, Tan M, et al. Treatment-resistant depression in primary care across Canada. Can J Psychiatry. 2014;59(7):349-57.
5. Seemuller F, Meier S, Obermeier M, et al. Three-Year long-term outcome of 458 naturalistically treated inpatients with major depressive episode: severe relapse rates and risk factors. Eur Arch Psychiatry Clin Neurosci. 2014;264(7):567-75.
6. Novick D, Hong J, Montgomery W, et al. Predictors of remission in the treatment of major depressive disorder: real-world evidence from a 6-month prospective observational study. Neuropsychiatr Dis Treat. 2015;11:197-205.
7. Saragoussi D, Touya M, Haro JM, et al. Factors associated with failure to achieve remission and with relapse after remission in patients with major depressive disorder in the PERFORM study. Neuropsychiatr Dis Treat. 2017;13:2151-2165.
8. Ashton AK, Jamerson BD, W LW, et al. Antidepressant-related adverse effects impacting treatment compliance: Results of a patient survey. Current therapeutic research, clinical and experimental. 2005;66(2):96-106.
9. Morehouse R, Macqueen G, Kennedy SH. Barriers to achieving treatment goals: a focus on sleep disturbance and sexual dysfunction. Journal of affective disorders. 2011;132 Suppl 1:S14-20.
10. Bang-Andersen B, Ruhland T, Jorgensen M, et al. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. Journal of medicinal chemistry. 2011;54(9):3206-21.
11. Richelson E. Multi-modality: a new approach for the treatment of major depressive disorder. The International Journal of Neuropsychopharmacology. 2013;16(6):1433-1442.
12. Westrich LP, A., Zhong H, Nielsen SM, et al. In vitro and in vivo effects of the multimodal antidepressant vortioxetine (Lu AA21004) at human and rat targets. Int J Psychiatry Clin Pract. 2012;16(Suppl. 1):47.
13. Pehrson AL, Leiser SC, Gulinello M, et al. Treatment of cognitive dysfunction in major depressive disorder--a review of the preclinical evidence for efficacy of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and the multimodal-acting antidepressant vortioxetine. European journal of pharmacology. 2015;753:19-31.
14. Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. Pharmacology & therapeutics. 2015;145:43-57.
15. Alvarez E, Perez V, Dragheim M, et al. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. Int J Neuropsychopharmacol. 2012;15(5):589-600.
16. Boulenger JP, Loft H, Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. International clinical psychopharmacology. 2014;29(3):138-49.

17. Henigsberg N, Mahableshwarkar AR, Jacobsen P, et al. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. J Clin Psychiatry. 2012;73(7):953-9.
18. Jacobsen PL, Mahableshwarkar AR, Serenko M, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. J Clin Psychiatry. 2015;76(5):575-82.
19. Mahableshwarkar AR, Jacobsen PL, Chen Y, et al. A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. Psychopharmacology. 2015;232(12):2061-2070.
20. Gibb A, Deeks ED. Vortioxetine: first global approval. Drugs. 2014;74(1):135-45.
21. Mahableshwarkar AR, Zajecka J, Jacobson W, et al. A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder. Neuropsychopharmacology. 2015;40(8):2025-37.
22. McIntyre RS, Florea I, Tonnoir B, et al. Efficacy of Vortioxetine on Cognitive Functioning in Working Patients With Major Depressive Disorder. J Clin Psychiatry. 2017;78(1):115-121.
23. McIntyre RS, Harrison J, Loft H, et al. The Effects of Vortioxetine on Cognitive Function in Patients with Major Depressive Disorder: A Meta-Analysis of Three Randomized Controlled Trials. Int J Neuropsychopharmacol. 2016.
24. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. Int J Neuropsychopharmacol. 2014;17(10):1557-67.
25. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. International clinical psychopharmacology. 2012;27(4):215-23.
26. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a Brief Depression Severity Measure. Journal of General Internal Medicine. 2001;16(9):606-613.
27. Fehnel SE, Forsyth BH, DiBenedetti DB, et al. Patient-centered assessment of cognitive symptoms of depression. CNS spectrums. 2016;21(1):43-52.
28. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics. 1993;4(5):353-65.
29. Baldwin DS, Hansen T, Florea I. Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. Current medical research and opinion. 2012;28(10):1717-24.
30. Alam MY, Jacobsen PL, Chen Y, et al. Safety, tolerability, and efficacy of vortioxetine (Lu AA21004) in major depressive disorder: results of an open-label, flexible-dose, 52-week extension study. International clinical psychopharmacology. 2014;29(1):36-44.
31. Huynh NN, McIntyre RS. What Are the Implications of the STAR*D Trial for Primary Care? A Review and Synthesis. Primary Care Companion to The Journal of Clinical Psychiatry. 2008;10(2):91-96.
32. Meeker AS, Herink MC, Haxby DG, et al. The safety and efficacy of vortioxetine for acute treatment of major depressive disorder: a systematic review and meta-analysis. Systematic reviews. 2015;4:21.
33. Sung SC, Low CC, Fung DS, et al. Screening for major and minor depression in a multiethnic sample of Asian primary care patients: a comparison of the nine-item Patient Health Questionnaire (PHQ-9) and the 16-item Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR16). Asia-Pacific psychiatry : official journal of the Pacific Rim College of Psychiatrists. 2013;5(4):249-58.
34. Lotrakul M, Sumrithe S, Saipanish R. Reliability and validity of the Thai version of the PHQ-9. BMC Psychiatry. 2008;8:46-46.

35. Sherina MS, Arroll B, Goodyear-Smith F. Criterion validity of the PHQ-9 (Malay version) in a primary care clinic in Malaysia. The Medical journal of Malaysia. 2012;67(3):309-15.
36. Hawley CJ, Gale TM, Smith PS, et al. Equations for converting scores between depression scales (MADRS, SRS, PHQ-9 and BDI-II): good statistical, but weak idiographic, validity. Human psychopharmacology. 2013;28(6):544-51.
37. Al-Sukhni M, Maruschak NA, McIntyre RS. Vortioxetine: a review of efficacy, safety and tolerability with a focus on cognitive symptoms in major depressive disorder. Expert Opinion on Drug Safety. 2015;14(8):1291-1304.
38. Cognitive Impairment in Major Depressive Disorder: Clinical Relevance, Biological Substrates, and Treatment Opportunities. McIntyre RS, editor. Cambridge: Cambridge University Press; 2016.
39. Lam R, Saragoussi, D., Danchenko, N., Rive, B., Lamy, F., Brevig, T. Psychometric validation of perceived deficits questionnaire - depression (PDQ-D) in patients with major depressive disorder (MDD) [Abstract]. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2013;16(7).
40. Beck A, Crain LA, Solberg LI, et al. The effect of depression treatment on work productivity. The American journal of managed care. 2014;20(8):e294-301.
41. Sansone RA, Sansone LA. Antidepressant Adherence: Are Patients Taking Their Medications? Innovations in Clinical Neuroscience. 2012;9(5-6):41-46.

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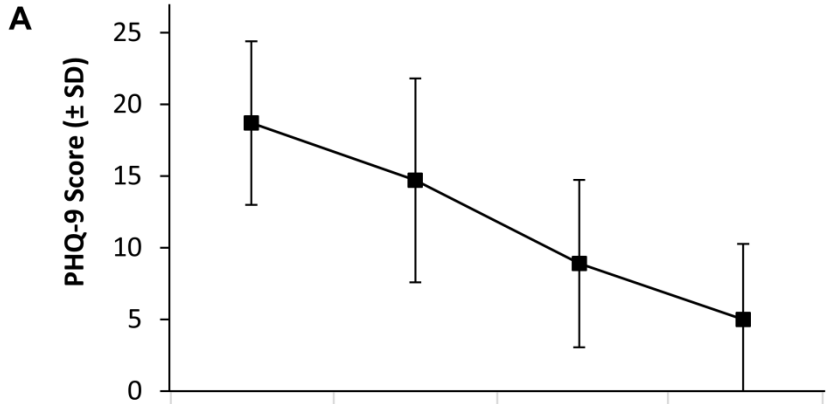
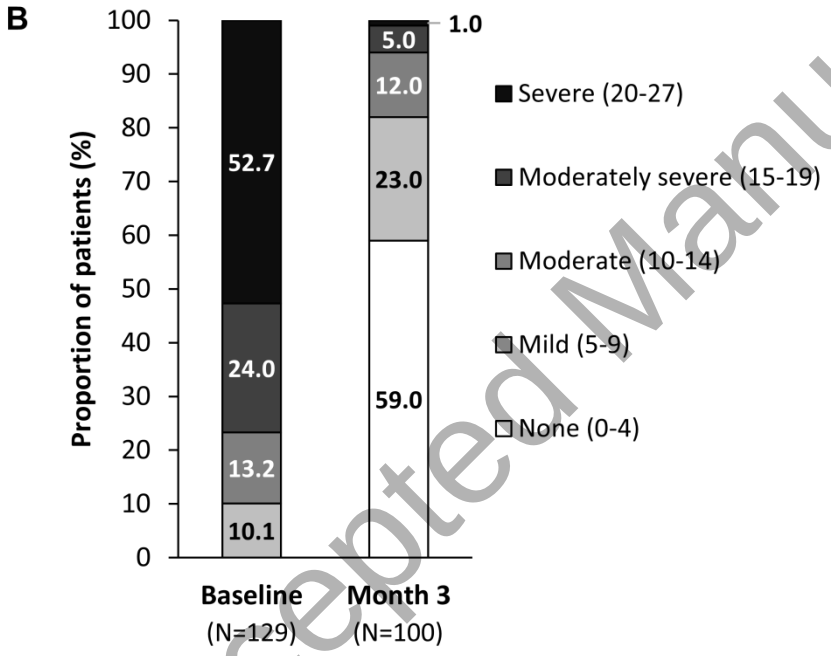
Table 2. Adverse drug reactions (Safety population).
Supplementary Table 1. Pearson correlations between PHQ-9, PDQ-D, and work productivity and activity impairment outcome scores at baseline and Month 3.

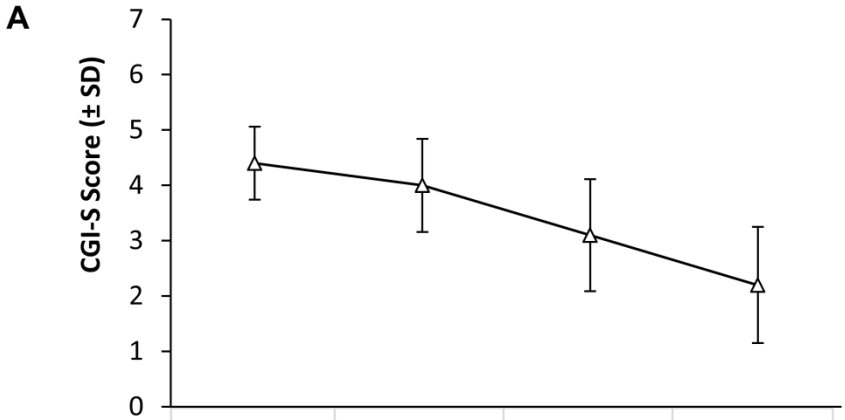
Figure legends

Figure 1. Patient-assessed depression severity as measured with the PHQ-9 (Eligible population). (A) PHQ-9 scores over the 3-month treatment period. (B) Levels of depression based on PHQ-9 scores at Baseline and Month 3.
Figure 2. Physician-assessed depression severity as measured with the CGI-S (Eligible population). (A) CGI-S scores over the 3-month treatment period. (B) Severity of illness based on CGI-S scores at Baseline and Month 3.
Figure 3. Improvement, response, and remission over the 3-month treatment period (Eligible population). (A) CGI-I scores and (B) improvement in illness based on CGI-I scores. (C) Patient-assessed response (PHQ-9 response: ≥50% reduction in PHQ-9 score) and physician-assessed response (CGI-S response: ≥50% reduction in CGI-S score). (D) Patient-assessed remission (PHQ-9 remission: PHQ-9 score ≤4) and physician-assessed remission (CGI-S remission: CGI-S score ≤3).
Figure 4. Cognitive function measured with the PDQ-D (Eligible population). (A) PDQ-D scores over the 3-month treatment period. Change from baseline in PDQ-D score by (B) patient-assessed responder status (PHQ-9 responder: ≥50% reduction in PHQ-9 score) and (C) physician-assessed responder status (CGI-S responder: ≥50% reduction in CGI-S score).
Figure 5. Mean WPAI outcome scores at Baseline and Month 3 (Eligible population).

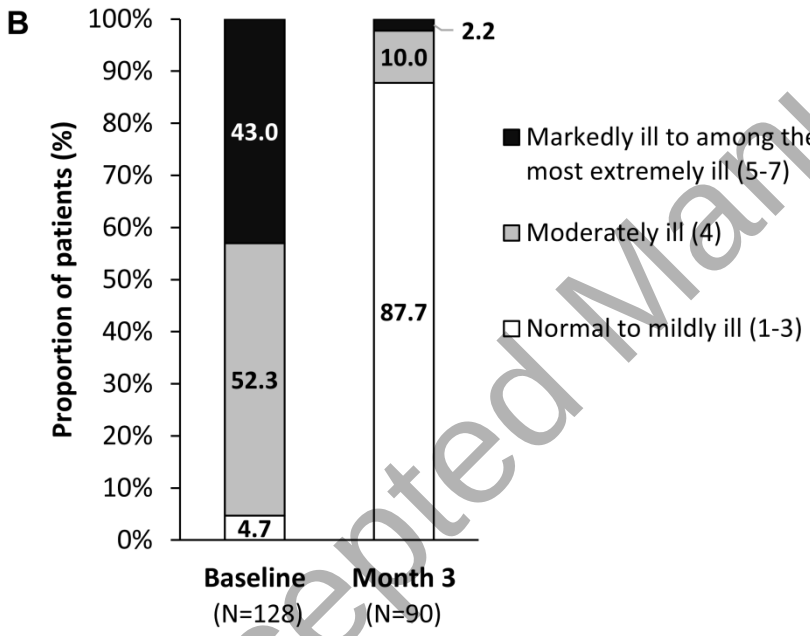


	Baseline	Week 1	Month 1	Month 3
PHQ-9 score, mean (SD)	18.7 (5.7)	14.7 (7.1)	8.9 (5.8)	5.0 (5.3)
No. of patients	129	129	108	100





	Baseline	Week 1	Month 1	Month 3
CGI-S score, mean (SD)	4.4 (0.7)	4.0 (0.8)	3.1 (1.0)	2.2 (1.1)
No. of patients	128	120	101	90



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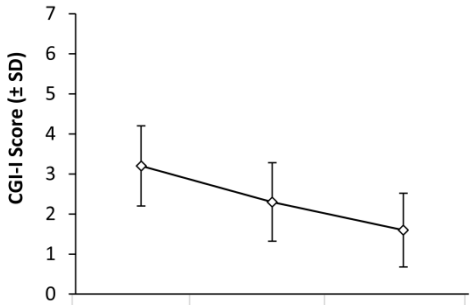
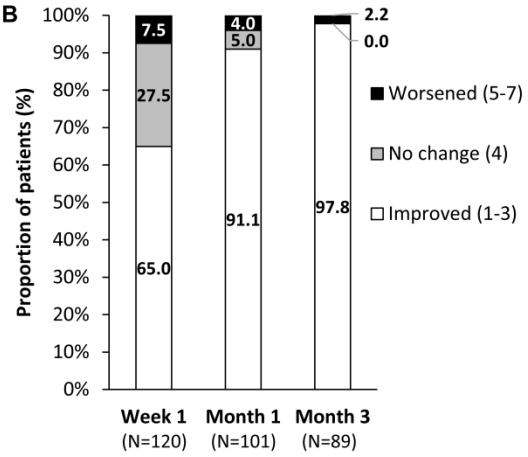


	Week 1	Month 1	Month 3
CGI-I score, mean (SD)	3.2 (1.0)	2.3 (1.0)	1.6 (0.9)
No. of patients	120	101	89

B



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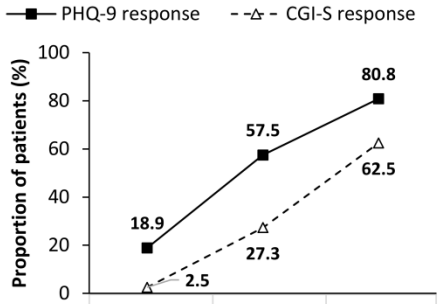
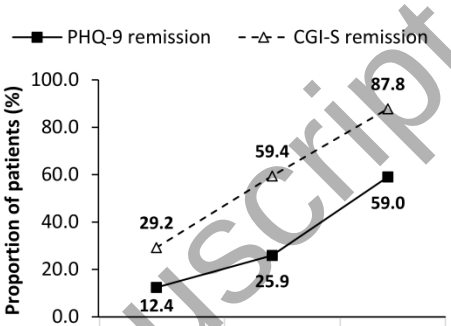


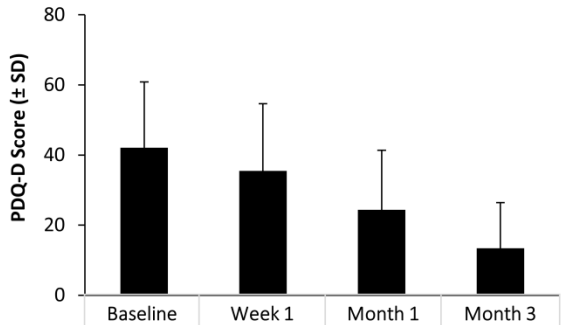
		Week 1	Month 1	Month 3
No. of patients	PHQ-9	127	106	99
	CGI-S	118	99	88

D



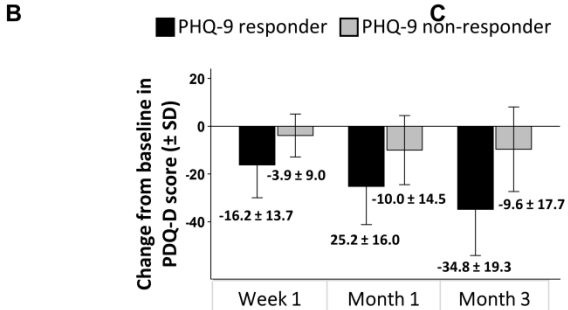
		Week 1	Month 1	Month 3
No. of patients	PHQ-9	129	108	100
	CGI-S	120	101	90

A



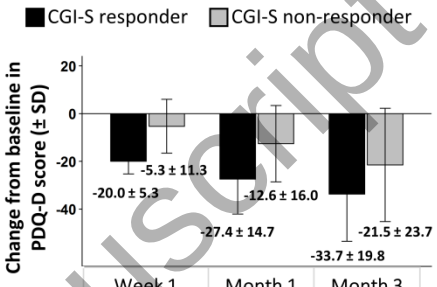
	Baseline	Week 1	Month 1	Month 3
PDQ-D score, mean (SD)	42.1 (18.8)	35.5 (19.2)	24.4 (17.0)	13.4 (13.0)
No. of patients	126	127	109	100

B

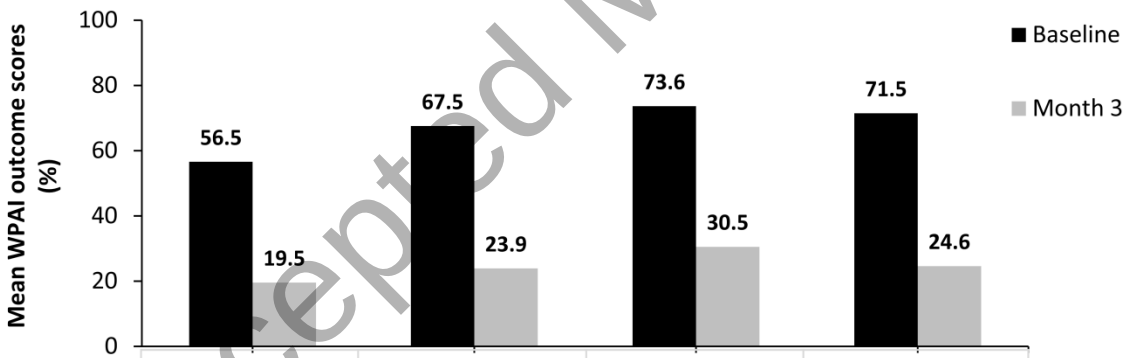


		Week 1	Month 1	Month 3
No. of patients	Responder	22	59	78
	Non-responder	98	43	19

C



		Week 1	Month 1	Month 3
No. of patients	Responder	3	25	52
	Non-responder	106	68	33



	Absenteeism		Presenteeism		Work Productivity Loss		Activity Impairment	
	Baseline	Month 3	Baseline	Month 3	Baseline	Month 3	Baseline	Month 3
No. of patients	39	27	24	26	24	24	131	100

Table 1. Sociodemographic and baseline characteristics (Safety population).

	Data	**n**
Age (years), mean (SD, range)	39.7 (12.5, 18–64)	137
Gender, n (%)		138
Male	47 (34.1)	
Female	91 (65.9)	
Marital status, n (%)		138
Single	57 (41.3)	
Married or living as a couple	71 (51.4)	
Divorced/separated	10 (7.2)	
Living area, n (%)		133
City	103 (77.4)	
Small town	27 (20.3)	
Rural	3 (2.3)	
Educational years (years), median (Min, Max)	15 (4, 22)	129
Main work status, n (%)		137
Paid work	65 (47.4)	
Self-employed	28 (20.4)	
Non-paid work	1 (0.7)	
Student	13 (9.5)	
Homemaker	15 (10.9)	
Retired	5 (3.6)	
Unemployed (health reasons)	4 (2.9)	
Unemployed (other reasons)	5 (3.6)	
Other	1 (0.7)	
Duration of inability to work due to current major depressive episode (weeks), median (Min, Max)	3 (0.0, 52.0)	81
Length of current episode, n (%)		137
<1 week	1 (0.7)	
1 to 2 weeks	7 (5.1)	
2 to 4 weeks	24 (17.5)	
4 to 8 weeks	18 (13.1)	
>8 weeks	87 (63.5)	
Had a significant life event within the past 3 months, n (%)	76 (55.5)	137
Had suicidal ideation, n (%)	39 (28.3)	138
First depressive episode, n (%)	87 (63.0)	138
At least one concomitant clinical diagnosis with current MDD episode	58 (42.3)	137
Received treatment for current MDD episode prior to baseline visit, n (%)	58 (42.3)	137

Percentages are based on the number of patients with non-missing values in each specified category. MDD: major depressive disorder; n: number of patients with non-missing values in the specified category; SD: standard deviation.

Table 2. Adverse drug reactions (Safety population).

	Vortioxetine (N=138)
All ADRs, n (%)	13 (9.4)
No. of ADRs	20
Abdominal discomfort	4
Nausea	3
Somnolence	2
Urticaria	2
Hypersensitivity	2
Rash	1
Dizziness	1
Headache	1
Drug ineffective	1
Not specified	3
ADRs leading to study discontinuation, n (%)	9 (6.5)

ADRs, adverse drug reactions.