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Effectiveness of long-term vortioxetine treatment of patients with major depressive disorder

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Vortioxetine;
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Abstract
To investigate the effectiveness, safety, and tolerability of vortioxetine in patients treated at therapeutic doses (5–20 mg/day) for both acute and maintenance treatment, patient-level data were pooled from 5 long-term (52-week), open-label extension studies of major depressive disorder. The mean (±standard deviation) MADRS total score improved from 17.1±10.2 at the start of maintenance therapy to 7.6±8.2 (observed cases [OC]) or 10.3±9.9 (last observation carried forward [LOCF]) at week 52. The mean HAM-A total scores improved from 11.3±6.9 to 6.0±6.0 (OC) or 7.5±6.7 (LOCF) and the mean CGI-S score improved from 3.11±1.20 to 1.94±1.08 (OC) or 2.27±1.26 (LOCF) at week 52. Response and remission rates increased over time. At week 52, the total response rate was 75.4% (n=916/1215, LOCF) and the total remission rate was 60.7% (n=738/1215, LOCF). There were no differences in effectiveness as assessed by MADRS total scores at week 52 in subgroups based on gender, age (<55 vs ≥55 years), baseline HAM-A total score (<20 vs ≥20), baseline MADRS total score (<30 vs ≥30), previous major depressive episodes (MDEs) (<3 vs ≥3) or current MDE duration (<6 vs ≥6 months) at the start of the lead-in studies, or response status (≥50% decrease in MADRS total score during the lead-in study). The most commonly reported adverse event during the maintenance period was nausea.

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1. Introduction

Major depressive disorder (MDD) affects an estimated 350 million individuals globally (World Health Organization (WHO), 2014) and is associated with substantial societal and economic burden (Druss et al., 2009; IsHak et al., 2014; Kessler et al., 2006; Lépine and Briley, 2011). According to the Global Burden of Disease Study 2013 Collaborators (2015), MDD was second only to low back pain in years lived with disability worldwide. As many as 1 in 4 individuals who recover from a major depressive episode (MDE) will have a recurrence within the first year (Solomon et al., 2000). A greater number of previous episodes, more severe depressive symptoms, and longer duration of MDE are predictive of recurrence (Bauer et al., 2015). Long-term treatment (at least 6–9 months) is recommended for patients with MDD who have responded to acute treatment in order to prevent relapse and recurrence (Bauer et al., 2015). Longer prophylactic treatment is recommended for individuals who are at high risk of recurrence; however, evidence supporting maintenance therapy beyond 9 months is limited (Bauer et al., 2015).

Vortioxetine was approved in 2013 in the US for the treatment of adults with MDD and in the European Union for the treatment of an MDE in adults, and subsequently in other countries. The mechanism of action of vortioxetine is related to its multimodal activity, which combines 2 pharmacological actions: direct modulation of receptor activity and inhibition of the serotonin (5-HT) transporter. In addition to inhibiting the 5-HT transporter, vortioxetine is an antagonist at 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors, a partial agonist at 5-HT_{1B} receptors, and an agonist at 5-HT_{1A} receptors (Bang-Andersen et al., 2011; Mork et al., 2012; Westrich et al., 2012).

Vortioxetine is efficacious in the acute treatment of MDD in the 5–20 mg/day dose range (Thase et al., 2016) and has demonstrated longer-term efficacy and prevention of relapse in an MDD relapse-prevention study (Boulenger et al., 2012). In the relapse prevention study, there was a statistically significant difference in favor of vortioxetine vs placebo in the time to relapse of MDD during the first 24 weeks of the double-blind period, with a significantly lower percentage of vortioxetine-treated patients who relapsed (hazard ratio, 2.01; $P=0.0035$), meaning that the risk of relapse was 2 times higher in the placebo group than in the vortioxetine group (Boulenger et al., 2012). Five open-label, long-term (52-week) extension studies (Alam et al., 2014; Baldwin et al., 2012; Filippov and Christens, 2013; Florea et al., 2012; Jacobsen et al., 2014) support the maintenance of effect established during acute treatment phase. The individual extension studies found that patients receiving vortioxetine 2.5 mg/day to 20 mg/day and who had completed a 6- to 8-week vortioxetine clinical trial continued to show improvement in depressive and anxiety symptoms with long-term vortioxetine treatment regardless of prior therapy. Rates of response and remission also increased substantially during the 52-week extension studies.

A pooled analysis of the safety and tolerability of vortioxetine during short-term treatment found that treatment-emergent adverse events (TEAEs) commonly experienced with most antidepressants (e.g., headache, dry mouth, dizziness, constipation, insomnia, somnolence, fatigue, hyperhidrosis) were observed at placebo-like levels with vortioxetine treatment (Baldwin et al., 2016). The TEAEs occurring in $\geq 5\%$ of patients and at twice the frequency of placebo-treated patients were nausea and vomiting. The incidences of potential clinically significant weight change (increase or decrease) and sexual dysfunction (combination of several preferred terms) occurred in $<2\%$ of any vortioxetine-treated group (Baldwin et al., 2016), underscoring the benign safety profile of vortioxetine treatment. In addition, this analysis found that the number needed to harm with vortioxetine treatment ranged from 24 (with vortioxetine 15 mg/day) to 126 (with vortioxetine 5 mg/day).

To investigate the effectiveness, safety, and tolerability of vortioxetine in patients treated at therapeutic doses (5-20 mg/day) during both acute and maintenance treatment, patient-level data were pooled from the 5 long-term (52 weeks), open-label MDD extension studies (Alam et al., 2014; Baldwin et al., 2012; Filippov and Christens, 2013; Florea et al., 2012; Jacobsen et al., 2014). This post hoc analysis was designed to assess whether improvements in depressive and anxiety symptoms continued after acute (6- to 8-week) vortioxetine treatment and whether the effectiveness of long-term vortioxetine treatment was affected by risk factors such as symptom severity, duration of the index MDE, or number of prior MDEs.

2. Experimental procedures

2.1. Studies

Patient-level data were from 5 long-term, open-label, flexible-dose extension studies (NCT00761306, NCT00694304, NCT00707980, NCT01323478, and NCT01152996) that enrolled patients (aged 18-75 years) with MDD who completed 1 of 8 short-term lead-in studies (Alam et al., 2014; Baldwin et al., 2012; Filippov and Christens, 2013; Florea et al., 2012; Jacobsen et al., 2014). Seven of the lead-in studies were of 8-week duration and 1 study (NCT00761306) was of 6-week duration. These studies were conducted in Asia, Australia, Europe, North America (United States and Canada), and/or South Africa. For 2 of the studies (Filippov and Christens, 2013; Florea et al., 2012), only some countries from the lead-in studies could participate due to late start of the extension studies or delayed approvals. In the extension studies, patients were seen at weeks 1, 2, and 4, then every 4 weeks until week 28, and thereafter every 8 weeks until week 52, with a safety follow-up 4 weeks after completion of the extension study (or after early withdrawal).

In the current analysis, Baseline I is defined as the start of active treatment in the lead-in studies and Baseline II is the start of active treatment in the extension studies.

2.2. Patients

In the current post hoc analysis, only patients who were treated with vortioxetine at an approved therapeutic dose (between 5 and 20 mg/day) and who completed the lead-in studies were included.

2.3. Safety and tolerability

Safety and tolerability were assessed by the incidence, nature, and severity of TEAEs that have an onset that occurred after Baseline II

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and within 30 days after receiving the last dose of study drug. At each study visit, the investigator assessed whether any events had occurred using a non-leading question; however, patients could report events occurring at any other time during the study. Ongoing AEs from the lead-in studies that were present at the time of signing the informed consent for Baseline II were recorded as concurrent medical conditions and would be recorded as a new TEAE if there was a worsening or complication of the condition.

2.4. Effectiveness

The long-term effectiveness of vortioxetine was assessed by mean Montgomery-Åsberg Depression Rating Scale (MADRS) total scores (Montgomery and Asberg, 1979), Hamilton Anxiety Rating Scale (HAM-A) total scores (Hamilton, 1959), and Clinical Global Impressions-Severity of Illness scale (CGI-S) scores (Guy, 1976) calculated at Baseline I, Baseline II, and the end of the extension studies. Remission was defined as a MADRS total score ≤ 10 and response as a $\geq 50\%$ improvement in the MADRS total score from Baseline I at the end of maintenance treatment.

2.5. Subgroups

The following categories were identified for subgroup analysis MADRS total scores in this study: gender (women vs men), age (<55 vs ≥ 55 years), severity of anxiety symptoms (HAM-A total score <20 vs ≥ 20) at Baseline I, severity of depressive symptoms (MADRS total score <30 vs ≥ 30) at Baseline I, responder status after acute treatment ($<50\%$ vs $\geq 50\%$ improvement from Baseline I in MADRS total scores to lead-in study end), duration of the current MDE (<6 vs ≥ 6 months) at Baseline I, and number of previous MDEs (<3 vs ≥ 3) at Baseline I.

2.6. Statistical analysis

All patients who took at least one dose of vortioxetine in an extension study after completion of a lead-in study and with at least one valid post-Baseline II value for MADRS total score were included in the analyses.

Descriptive statistics are presented for the MADRS, HAM-A, and CGI-S scores and for MADRS response and remission, as well as safety and tolerability data. Actual mean values for all continuous variables at the end of 52 weeks of treatment are reported using both observed case (OC) and last observation carried forward (LOCF) methods. In this post hoc analysis, pooled data were analyzed as a total vortioxetine group rather than by dose group as the trials were of a flexible-dose design.

3. Results

3.1. Patient disposition and exposure

In the 5 extension studies, 1231 patients (of potentially 2592 patients) had been previously treated with vortioxetine 5–20 mg/day, after excluding patients previously treated with placebo ($n=700$), duloxetine ($n=326$), venlafaxine ($n=24$), or vortioxetine at sub-therapeutic doses (i.e., 1 and 2.5 mg/day) ($n=311$). This represents 888.8 patient-years of exposure, with a median exposure of 51.7 weeks.

Of the 1231 included patients, 1230 were included in the effectiveness analyses, 706 (57%) completed the 52-week extension studies, and 525 (43%) prematurely withdrew (Table 1).

Table 1 Disposition of patients enrolled in the 52-week, flexible-dose (vortioxetine 5–20 mg/day) extension studies.

	N (%)
Patients included	1231
Patients completed	706 (57%)
Patients withdrawn early	525 (43%)
Primary reasons for early withdrawal	
Withdrawal of consent	145 (11.8%)
Adverse events	97 (7.9%)
Lost to follow-up	88 (7.1%)
Lack of efficacy	68 (5.5%)
Administrative or other	58 (4.7%)
Noncompliance with study product	43 (3.5%)
Protocol violation	26 (2.1%)

3.2. Safety and tolerability

As shown in Table 2, of the 1230 patients included in the current analysis, 96 withdrew due to TEAEs during the 52-week extension studies. TEAEs that most frequently resulted in discontinuation were nausea ($n=18$, 1.5%) and vomiting ($n=9$, 0.7%). Discontinuations due to TEAEs appeared dose-dependent, with 0.9% of the vortioxetine 5–10 mg/day group and 2.0% of the vortioxetine 15–20 mg/day group discontinuing treatment due to nausea; in addition, 0.3% and 1.1% of the lower-dose and higher-dose groups, respectively, withdrew due to vomiting.

A total of 204 (16.6%) patients reported nausea during the extension studies; the incidence was 13.3% in the 5–10 mg/day group and 24.2% in the 15–20 mg/day group. The majority (96%) of nausea events were mild or moderate in severity. Of the 204 patients who had nausea in the extension study, 96 had also reported nausea during the lead-in studies; for most of these patients (79%), the severity of the nausea events was the same or lower than the severity reported in the lead-in studies. TEAEs reported by $\geq 5\%$ of patients in either the lower-dose or higher-dose group are shown in Table 2.

3.3. Effectiveness across endpoints

Maintenance therapy with vortioxetine was associated with continued improvement in depressive symptoms as assessed by MADRS total score (Figure 1, Table 3), with the greatest rate of improvement occurring during the first 4 weeks of the extension studies. The anxiety symptoms assessed by HAM-A total score and the global severity impression assessed by CGI-S score also improved with long-term maintenance therapy (Table 3).

3.3.1. Response and remission

The percentage of MADRS responders increased from 47.8% (588/1230) at Baseline II to 85.8% (606/706) at week 52 (OC). A total of 310 patients who responded withdrew prematurely from the extension study; therefore, the response rate was 75.4% ($n=916/1215$, LOCF). The proportion of patients in remission increased from 29.6% (364/1230) at Baseline II to 71.7% (506/706) at week 52 (OC). As 232 patients who had

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Table 2 Treatment-emergent adverse events (TEAEs) reported during the extension studies.

	N (%)
Patients with ≥1 TEAE	895 (72.8%)
TEAEs leading to withdrawal	96 (7.8%)
Serious TEAEs	34 (2.8%)
Deaths	0
TEAEs with incidence ≥5%	
Nausea	204 (16.6%)
Headache	159 (12.9%)
Nasopharyngitis	116 (9.4%)
Diarrhea	79 (6.4%)
Weight increase	65 (5.3%)
Constipation	56 (4.6%)
Viral URTI	56 (4.6%)
Vomiting	48 (3.9%)

URTI, upper respiratory tract infection.

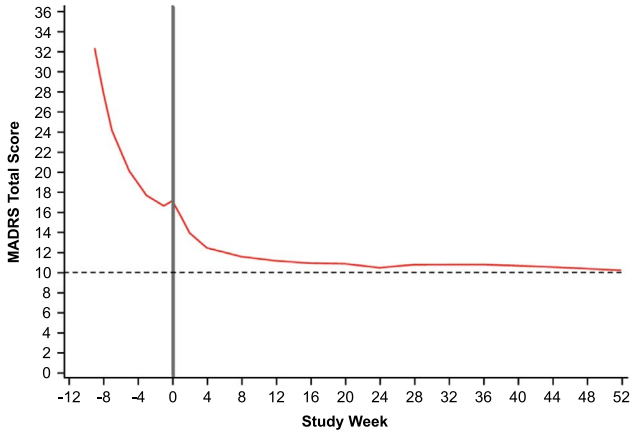

Figure 1 Mean MADRS total scores for patients previously treated with vortioxetine 5–20 mg/day in 6- to 8-week randomized controlled trials who continued treatment in an open-label extension study (N=1230) (LOCF). The vertical line represents Baseline II (start of treatment in the extension study). The horizontal dashed black line indicates the cut point for remission (defined as MADRS total score ≤10).

remitted withdrew prematurely from the study, the remission rate was 60.7% (n=738/1215, LOCF). Of the 364 patients in remission at Baseline II, 66 (18.1%) lost remission (MADRS total score >15), and 29 (8.0%) relapsed (MADRS total score ≥22) during long-term treatment.

3.4. Subgroup analysis

All defined subgroups in this study showed continued improvement in depressive symptoms as assessed by the MADRS total scores (both OC and LOCF) during maintenance treatment with vortioxetine 5–20 mg/day (Table 4). Neither gender nor age appeared to affect clinical outcomes; there were no differences in mean MADRS total scores between men (n=384) and women (n=846) at any point during long-term vortioxetine treatment (LOCF, Figure 2) or between patients aged <55 years (n=948) and those aged ≥55 years (n=282) (LOCF, Figure 3).

Mean MADRS total scores at week 52 were similar for patients with a mean HAM-A total score <20 (n=613) vs mean HAM-A total score ≥20 (n=617) at Baseline I. In patients with mean HAM-A <20 at Baseline I, the mean MADRS total score improved by 6.8 points over the 52-week extension study (LOCF, Figure 4). Patients with a HAM-A total score ≥20 at Baseline I showed an improvement in MADRS total score of 7.0 points during long-term vortioxetine treatment.

For patients moderately depressed (mean MADRS total score <30, n=353) at Baseline I, mean MADRS total score improved by 5.4 points during long-term vortioxetine treatment. For patients severely depressed (mean MADRS total score ≥30, n=877) at Baseline I, mean MADRS total score improved by 7.4 points during long-term vortioxetine treatment (LOCF, Figure 5).

Long-term vortioxetine treatment maintained short-term efficacy for responders to acute treatment (n=643), with mean MADRS total score improving by 3.3 points. Improvement was greater in patients who did not respond to short-term vortioxetine treatment (n=606). In this subgroup, mean MADRS total score improved by 10.5 points (LOCF).

Vortioxetine improved depressive symptoms during long-term treatment regardless of the duration of the index MDE at Baseline I or the number of previous MDEs at Baseline I. After 52 weeks, the mean MADRS total scores in patients whose index MDE was <6 months duration (n=660) improved by 6.3 points and in patients whose index MDE was ≥6 months long (n=568) by 7.6 points (LOCF). There was no difference between patients with <3 previous MDEs (n=722), whose mean MADRS total score improved by 7.1 points, and patients with ≥3 previous MDEs (n=508), for whom the mean MADRS total score improved by 6.5 points during long-term vortioxetine treatment (LOCF).

4. Discussion

Tolerability is important to ensure compliance and adherence to long-term antidepressant therapy (Bauer et al., 2015). The tolerability of vortioxetine in this post hoc analysis of long-term treatment is consistent with what has been previously reported (Baldwin et al., 2016). The previous analysis used a broader patient population, including individuals who were switched to vortioxetine for participation in the extension studies after receiving placebo, duloxetine, or venlafaxine in the acute studies. It is interesting to note that the incidence of some of the TEAEs reported by ≥5% of patients in the short-term studies (e.g., dry mouth, dizziness, and insomnia) did not reach the 5% incidence cutoff in the 52-week studies; although incidences of these TEAEs during the lead-in studies were comparable to the placebo levels (Baldwin et al., 2016). In the current analysis, the incidence of nausea was dose-dependent, but resulted in low rates of premature withdrawal during maintenance therapy. In the Baldwin et al. paper, authors additionally analyzed the long-term safety data without data from the first 8 weeks of the open-label studies. Results of that analysis found that no new types of TEAEs emerged with long-term vs acute vortioxetine

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Table 3 Mean scores for efficacy endpoints in the total population treated with vortioxetine 5-20 mg/day during both the short-term, fixed-dose lead-in studies and the 52-week, flexible-dose extension studies.

	Baseline I	Baseline II	Week 52 (OC)	Week 52 (LOCF)
MADRS total score	32.2±4.2	17.1±10.2	7.6±8.2	10.3±9.9
HAM-A total score	20.1±6.2	11.3±6.9	6.0±6.0	7.5±6.7
CGI-S score	4.67±0.67	3.11±1.20	1.94±1.08	2.27±1.26

Baseline I, start of treatment in the lead-in study; Baseline II, start of treatment in the extension study; CGI-S, Clinical Global Impressions-Severity of Illness; HAM-A, Hamilton Anxiety Rating Scale; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; OC, observed cases.

Tablee 4 Mean MADRS total scores for subgroups of patients treated with vortioxetine 5-20 mg/day during both the short-term, fixed-dose lead-in studies and the 52-week, flexible-dose extension studies.

Subgroup[a]	*n*[b]	Baseline I	Baseline II	Week 52 (OC)	Week 52 (LOCF)
MADRS ≥30	877	34.1±3.4	18.2±10.7	8.0±8.7	10.7±10.2
MADRS <30	353	27.6±1.4	14.6±8.3	6.5±6.7	9.1±8.9
Non-responders[c]	606	32.3±4.1	24.9±6.7	11.2±8.7	14.4±10.2
Responders[d]	624	32.2±4.3	9.6±6.7	4.6±6.4	6.3±7.6
HAM-A ≥20	617	33.3±4.3	17.4±10.3	7.7±8.7	10.4±10.2
HAM-A <20	613	31.2±3.7	16.9±10.0	7.5±7.6	10.1±9.5
Women	846	32.5±4.3	17.2±10.3	7.7±8.4	10.4±9.9
Men	384	31.7±3.9	17.1±9.9	7.4±7.8	10.1±9.7
Aged <55 years	948	32.3±4.2	16.9±10.2	7.6±8.2	10.3±9.9
Aged ≥55 years	282	32.0±4.1	17.9±9.9	7.6±8.2	10.2±9.7
<3 previous MDEs	722	31.9±4.2	16.3±9.9	6.7±7.4	9.2±9.4
≥3 previous MDEs	508	32.8±4.1	18.3±10.4	9.0±9.1	11.8±10.3
Current MDE <6 months	660	32.0±4.1	15.5±9.8	6.6±7.3	9.2±9.2
Current MDE ≥6 months	568	32.5±4.2	19.1±10.3	8.9±9.1	11.5±10.4

Baseline I, start of treatment in the lead-in study; Baseline II, start of treatment in the extension study; HAM-A, Hamilton Anxiety Rating Scale; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; OC, observed cases.

[a] Status at Baseline I, unless otherwise indicated.

[b] Number of patients at Baseline II.

[c] <50% improvement in MADRS total score from Baseline I to end of lead-in study.

[d] ≥50% improvement in MADRS total score from Baseline I to end of lead-in study.

treatment, that TEAEs occurred in <10% of patients after omission of data from the first 8 weeks, and that most TEAEs were transient during acute treatment (Baldwin et al., 2016).

The rate of withdrawal during the long-term extension due to any TEAE was low (7.8%), with no reports of sexual dysfunction, a side effect of antidepressant therapy associated with poor adherence. The overall discontinuation rate of 43% is not unexpected for a 1-year, open-label, extension study. Discontinuation rates were 26% with escitalopram (Wade et al., 2006), 59% with vilazodone (Robinson et al., 2011), and 59% with duloxetine (Dunner et al., 2008) in studies of similar duration. Overall, the safety and tolerability findings from this study suggest that vortioxetine is well tolerated over the long term.

This post hoc analysis, designed to assess the effectiveness, safety, and tolerability of long-term treatment with therapeutic doses (5-20 mg/day) of vortioxetine, found that continuation therapy with vortioxetine maintained effectiveness or further improved depressive and anxiety symptoms initiated or established during acute treatment of patients receiving a therapeutic dose of vortioxetine. Mean MADRS total scores, HAM-A total scores, and CGI-S scores improved over the 52 weeks of treatment with vortioxetine 5-20 mg/day in the total population, with no observed effect of gender or age on clinical outcomes. Moreover, individuals at high risk of recurrence (i.e., MADRS total score >30, HAM-A ≥20, current MDE ≥6 months, and/or ≥3 previous MDEs at Baseline I) showed a similar response to vortioxetine maintenance therapy compared with those at a lower risk. Improvements in these outcome measures were seen in both responders and non-responders (as assessed by the MADRS total score) to short-term treatment. The proportion of patients achieving remission or response also increased with long-term vortioxetine therapy.

Among the subset of patients who achieved remission during the acute phase, 8% relapsed during the maintenance phase. In a 24-week relapse-prevention study of acute-phase remitters (n=396), 13% of patients who were

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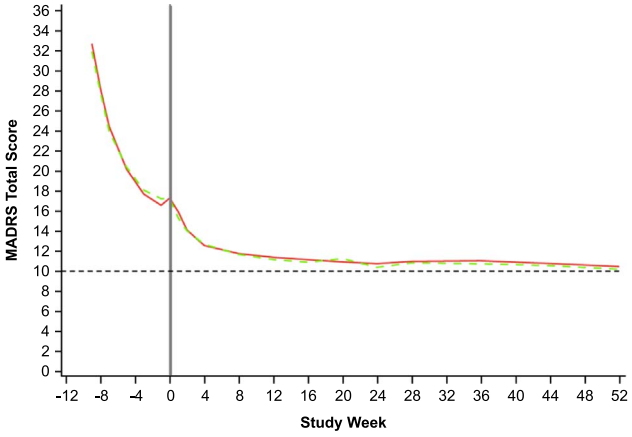

Figure 2 Mean MADRS total scores during short-term and long-term treatment with vortioxetine 5–20 mg/day in women (red, $n=846$) and men (green dashed, $n=384$) with MDD (LOCF). The vertical line represents Baseline II (start of treatment in the extension study). The horizontal dashed black line indicates the cut point for remission (defined as MADRS total score ≤ 10). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

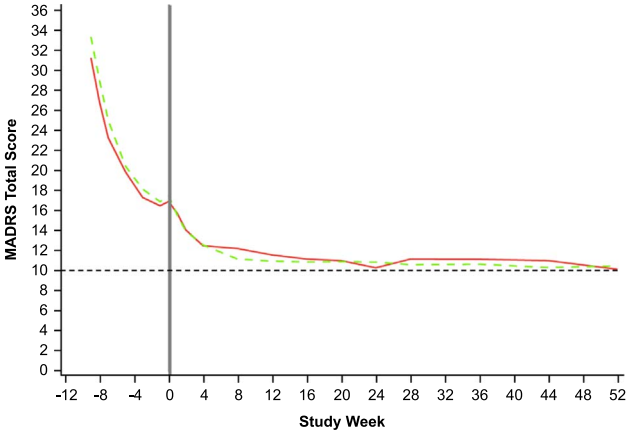

Figure 4 Mean MADRS total scores during short-term and long-term treatment with vortioxetine 5–20 mg/day in MDD patients with HAM-A total score <20 (red, $n=613$) or ≥ 20 (green dashed, $n=617$) at Baseline I (start of treatment in the lead-in study) (LOCF). The vertical line represents Baseline II (start of treatment in the extension study). The horizontal dashed black line indicates the cut point for remission (defined as MADRS total score ≤ 10). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

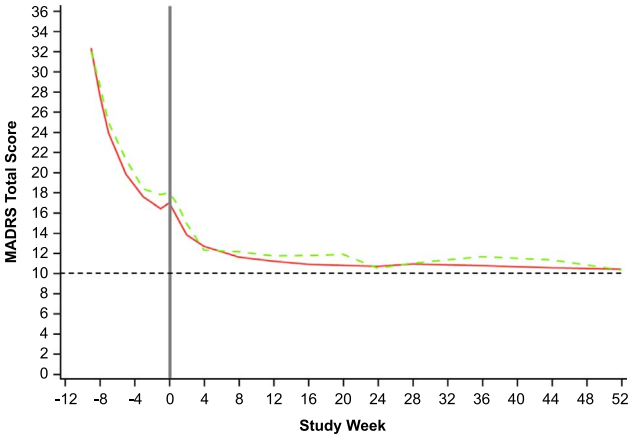

Figure 3 Mean MADRS total scores during short-term and long-term treatment with vortioxetine 5–20 mg/day in MDD patients aged <55 years (red, $n=948$) or ≥ 55 years (green dashed, $n=282$) at Baseline I (start of treatment in the lead-in study) (LOCF). The vertical line represents Baseline II (start of treatment in the extension study). The horizontal dashed black line indicates the cut point for remission (defined as MADRS total score ≤ 10). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

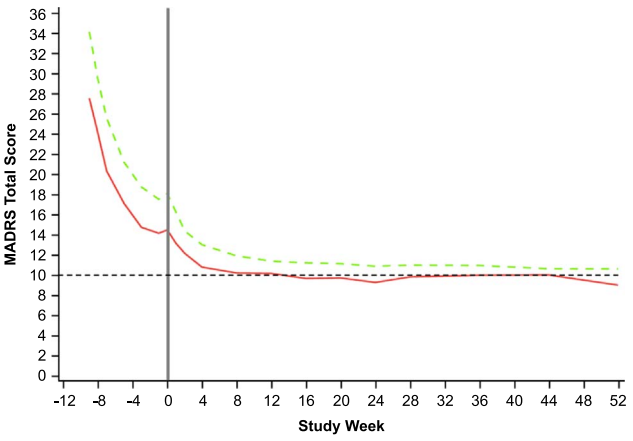

Figure 5 Mean MADRS total scores during short-treatment and long-term treatment with vortioxetine 5–20 mg/day in MDD patients with MADRS total score <30 (red, $n=353$) or ≥ 30 (green dashed, $n=877$) at Baseline I (start of treatment in the lead-in study) (LOCF). The vertical line represents Baseline II (start of treatment in the extension study). The horizontal dashed black line indicates the cut point for remission (defined as MADRS total score ≤ 10). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

randomized to continue vortioxetine (5 or 10 mg/day) treatment and 26% of those randomized to placebo relapsed (Boulenger et al., 2012). An important difference between the current analysis and the relapse-prevention trial is that in the current analysis, patients could receive vortioxetine doses up to 20 mg/day, whereas the maximum dose allowed in the relapse-prevention study was 10 mg/day. This suggests that dose adjustments may be needed during post-remission maintenance. Overall, the effectiveness analysis from this study demonstrates that long-term treatment of MDD with vortioxetine can be beneficial for patients having been treated acutely with this drug.

4.1. Strengths and limitations of the study

The strength of this post hoc analysis is that it provides a profile of the response to therapeutic doses of vortioxetine

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in patients with MDD treated continuously for up to 60 weeks. However, because this is a post hoc analysis, the power to assign statistical significance to differences in outcome measures is limited. Moreover, the analysis is based on data from open-label studies that did not include a control group.

4.2. Conclusions

Long-term treatment with vortioxetine at doses up to 20 mg/day maintained and further improved the effectiveness established during acute treatment with vortioxetine. This was consistent across patient subgroups regardless of gender, age, initial level of depressive or anxiety symptoms, number of previous MDEs, or duration of the current MDE. Moreover, long-term therapy with vortioxetine was well tolerated.

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Contributors

All authors were responsible for the interpretation of the analysis, contributed to critically revising the content, and approved the final manuscript for submission to *European Neuropsychopharmacology*.

Conflict of interest

The authors of this manuscript have the following competing interests: E Vieta is a consultant to H. Lundbeck A/S and the Takeda Pharmaceutical Company Ltd. He has also received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, Allergan, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute. H Loft and I Florea are employees of H. Lundbeck A/S.

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