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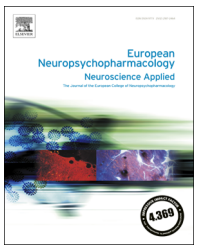

A meta-analysis of randomized, placebo-controlled trials of vortioxetine for the treatment of major depressive disorder in adults

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Vortioxetine;
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Drug dose-response relationship

Abstract
The efficacy and safety of vortioxetine, an antidepressant approved for the treatment of adults with major depressive disorder (MDD), was studied in 11 randomized, double-blind, placebo-controlled trials of 6/8 weeks' treatment duration. An aggregated study-level meta-analysis was conducted to estimate the magnitude and dose-relationship of the clinical effect of approved doses of vortioxetine (5–20 mg/day). The primary outcome measure was change from baseline to endpoint in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Differences from placebo were analyzed using mixed model for repeated measurements (MMRM) analysis, with a sensitivity analysis also conducted using last observation carried forward. Secondary outcomes included MADRS single-item scores, response rate ($\geq$50% reduction in baseline MADRS), remission rate (MADRS $\leq$10), and Clinical Global Impressions scores. Across the 11 studies, 1824 patients were treated with placebo and 3304 with vortioxetine (5 mg/day: n=1001; 10 mg/day: n=1042; 15 mg/day: n=449; 20 mg/day: n=812). The MMRM meta-analysis demonstrated that vortioxetine 5, 10, and 20 mg/day were associated with significant reductions in MADRS total score (Δ-2.27, Δ-3.57, and Δ-4.57, respectively; $p<0.01$) versus placebo. The effects of 15 mg/day (Δ-2.60; p=0.105) were not significantly different from placebo. Vortioxetine 10 and 20 mg/day were associated with significant reductions in 10 of 10 MADRS single-item scores. Vortioxetine treatment was also associated with significantly higher rates of response and remission and with significant improvements in other depression-related scores versus placebo. This meta-analysis of vortioxetine (5–20 mg/day) in adults with MDD

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supports the efficacy demonstrated in the individual studies, with treatment effect increasing with dose.

1. Introduction

Major depressive disorder (MDD) is a challenging clinical condition in which only about 30% to 40% of patients achieve full remission with first-line therapy of adequate duration (Trivedi et al., 2006; Warden et al., 2007) and about one-third of patients do not achieve remission even after therapy with as many as four different antidepressants (Warden et al., 2007). Furthermore, many antidepressants are associated with side effects that limit their tolerability and reduce compliance (Papakostas, 2010). The limitations of existing therapies have led to calls for better treatment options for patients with MDD (Rosenzweig-Lipson et al., 2007), many of whom experience prolonged and recurrent depressive episodes (American Psychiatric Association (APA), 2010).

Vortioxetine is an antidepressant that was approved in 2013 in the United States (US) for the treatment of adults with MDD and in the European Union (EU) for the treatment of major depressive episodes in adults. Vortioxetine differs from other currently available antidepressants owing to its multimodal activity within the central nervous system. In addition to inhibiting the serotonin (5-HT) transporter (Bang-Andersen et al., 2011), 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). As of 1 March 2015, 23 phase 2/3 clinical trials of vortioxetine in MDD have been completed with results reported (US National Institutes of Health (NIH), 2015), including 11 short-term, randomized, double-blind, parallel-group, placebo-controlled studies of up to eight weeks' duration (Alvarez et al., 2012; Baldwin et al., 2012; Boulenger et al., 2014; Henigsberg et al., 2012; Jacobsen et al., 2015b; Jain et al., 2013; Mahableshwarkar et al., 2015a, 2013, 2015b; McIntyre et al., 2014; Takeda, 2013).

To date, four independent meta-analyses of vortioxetine in patients with MDD have been published. Berhan and Barker (2014) conducted a literature-based analysis focusing on study-level data from seven peer-reviewed publications of placebo-controlled studies using doses of 1 to 20 mg/day. Pae et al. (2015) analyzed seven peer-reviewed publications, four congress abstracts, and one clinical study report of studies using the doses of 1 to 20 mg/day. Meeker et al. (2015) analyzed peer-reviewed publications for eight studies data from US Food and Drug Administration (FDA) review documents, and www.ClinicalTrials.gov for another 3 studies with doses of 1 to 20 mg/day. All three meta-analyses included non-therapeutic doses of vortioxe tine (1 and 2.5 mg/day) and the vortioxetine trial in elderly patients (Katona et al., 2012). One used the predefined primary endpoints, based on either the Montgomery–Åsberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale–24 item (HAM-D_{24}) and all doses of vortioxetine were collapsed (Pae et al., 2015). Another used the MADRS, based on either mixed model for repeated measurements (MMRM) or analysis of covariance (ANCOVA), last observation carried forward (LOCF), as input for the meta-analyses (Meeker et al., 2015). Behzadifar et al. (2015) performed a meta-analysis of only studies with vortioxetine 20 mg/day and placebo groups ($n=4$) and results from each trial were statistically combined using the Mantel–Haenszel random effects model.

We have conducted an aggregated data (AD) meta-analysis of vortioxetine clinical trials in MDD, using MMRM results from each study based on MADRS total score as the primary analysis, with a sensitivity analysis conducted using results from ANCOVA, LOCF for missing data. This statistical plan was chosen because it would provide the most consistent input to the overall meta-analysis. The AD meta-analysis was designed to estimate the magnitude and dose-dependent effects of vortioxetine on depressive symptoms in patients with MDD. Depressive symptoms were assessed using the MADRS (Montgomery and Asberg, 1979) total score, MADRS single-item scores, MADRS response, MADRS remission, and the Clinical Global Impressions (CGI) (Guy, 1976) scores. The AD meta-analysis was restricted to patients who where treated with the approved therapeutic vortioxetine dosages of 5 to 20 mg/day, in line with the doses approved in the US and the EU (H. Lundbeck A/S, 2015; Takeda Pharmaceuticals America Inc., 2014). The 15-mg/day dose, although only used in three studies (two of which were conducted in the US), was included for completeness.

2. Experimental procedures

2.1. Short-term placebo-controlled vortioxetine clinical trials in patients with MDD

The clinical development program for vortioxetine in MDD was international in nature, with the studies conducted at multiple sites within countries. The studies were designed, conducted, and reported in accordance with the principles of the World Medical Association Declaration of Helsinki and in compliance with the principles of the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice. The study sponsors (Takeda Development Center Americas, Inc. and H. Lundbeck A/S) assumed overall responsibility for the studies, including those in which monitoring was delegated to a contract research organization.

This meta-analysis was limited to short-term (6 or 8 weeks), double-blind, placebo-controlled, fixed-dose studies evaluating vortioxetine 5-20 mg in adults (aged 18–75 years) with MDD that have been previously published in a public forum and have reported results on the ClinicalTrials.gov database prior to 1 March 2015 (Alvarez et al., 2012; Baldwin et al., 2012; Boulenger et al., 2014; Henigsberg et al., 2012; Jacobsen et al., 2015b; Jain et al., 2013; Mahableshwarkar et al., 2015a, 2013, 2015b; McIntyre et al., 2014; Takeda, 2013). Table 1 provides a summary of treatment dosages, number of participants in each dosage arm, treatment duration, and key MDD

inclusion criteria for the 11 trials included in this meta-analysis. For each trial, participants had to meet the criteria for a major depressive episode, as described in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), lasting at least three months and be 18 to 75 years of age, inclusive. Additional inclusion criteria included MADRS total scores of at least 22 (NCT00672620) (Mahableshwarkar et al., 2013), 30 (NCT00839423 (Alvarez et al., 2012) and NCT00672958 (Jain et al., 2013)), or 26 (all other studies). An additional eligibility requirement for a Clinical Global Impressions – Severity of Illness (CGI-S) (Guy, 1976) score of at least 4 was required for the NCT01140906 (Boulenger et al., 2014), NCT01153009 (Mahableshwarkar et al., 2015b), NCT01163266 (Jacobsen et al., 2015b), and NCT01179516 (Mahableshwarkar et al., 2015a) studies.

Based on the increase in placebo response and a decrease in treatment response in clinical trials over the past 20 to 30 years, as well as to address any potential issues of regionality or heterogeneity, two separate patient populations datasets were evaluated in the AD meta-analysis – a total population analysis utilizing aggregated study-level data from all 11 trials in adults and a second which only utilizing data from the 6 trials conducted primarily outside the US (NCT00839423, NCT00635219, NCT01140906, NCT01422213, NCT01255787, and NCT00735709). The dedicated trial with vortioxetine in elderly patients (NCT00811252 (Katona et al., 2012)) was not included in any of the present meta-analyses, as it only enrolled patients aged 65 years and above.

2.2. Clinical outcomes

The predefined primary efficacy endpoints in the individual studies were either the MADRS total score, HAM-D_{24} (Williams, 2001) total score, or a composite z-score of Digit Symbol Substitution Test (DSST) and Rey Auditory Verbal Learning Test (RAVLT) score, with the MADRS total score as a predefined secondary endpoint in those trials that utilized the HAM-D_{24} total score or DSST/RAVLT composite score. Secondary efficacy variables included MADRS response and remission, and the CGI-S and Clinical Global Impressions – Improvement (CGI-I) (Guy, 1976) scores. In the 6-week studies (NCT00839423 (Alvarez et al., 2012) and NCT00672958 (Jain et al., 2013)), participants were examined every week from Screening to Completion, for a total of eight scheduled visits. In the 8-week studies, participants were examined every week from Screening to Week 2, and thereafter every second week to completion, for a total of nine scheduled visits.

2.3. Statistical analysis

The vortioxetine clinical development program utilized two different methodologies for conducting primary statistical analyses – MMRM in 5 studies (NCT01140906 (Boulenger et al., 2014), NCT01422213 (McIntyre et al., 2014), NCT00735709 (Henigsberg et al., 2012), NCT01153009 (Mahableshwarkar et al., 2015b), and NCT01179516 (Mahableshwarkar et al., 2015a)) with ANCOVA, LOCF utilized in 6 studies (NCT00839423 (Alvarez et al., 2012), NCT00635219 (Baldwin et al., 2012), NCT01255787 (Takeda, 2013), NCT00672958 (Jain et al., 2013), NCT00672620 (Mahableshwarkar et al., 2013), and NCT01163266 (Jacobsen et al., 2015b)). However, all studies have been analyzed using both methodologies (data provided directly from study sponsors). In order to provide the most reliable estimates of treatment effect, an aggregated data (AD) meta-analytic approach based on study level results using common methodology was chosen. The AD meta-analytic approach was selected because it efficiently and robustly manages heterogeneity of results over studies and avoids potentially misleading results arising from not having all dosages in all studies. A random effects AD meta-analytic approach was used to account for heterogeneity in the results between studies thus broadening the confidence interval (CI) for the meta-analysis compared to a fixed effects model. The level of heterogeneity was expressed in terms of I^2 (Higgins et al., 2003), which describes the percentage of total variation of the treatment effect across studies that is due to heterogeneity rather than to chance.

For 7 of the 11 individual studies (not including NCT00672958 (Jain et al., 2013), NCT00672620 (Mahableshwarkar et al., 2013), NCT01422213 (McIntyre et al., 2014), and NCT00735709 (Henigsberg et al., 2012)), as well as for this AD meta-analysis, the primary outcome measure was defined as the change from baseline in MADRS total score at the end of the treatment period. MMRM has specific attributes suited to the data structure of acute-phase neuropsychiatric clinical studies and has been compared extensively to ANCOVA, LOCF methodology (Siddiqui et al., 2009). Research based on actual data (Mallinckrodt et al., 2004) as well as data simulation (Siddiqui et al., 2009) indicates that, in many scenarios, analyses based on the MMRM provide estimates that have less bias, as well as superior control over both type I (false positive) and type II (false negative) errors. This makes the MMRM analysis better suited for investigations of potential dose response relations. In the current meta-analysis, results from ANCOVA, LOCF is utilized as a separate sensitivity analysis to the analysis based on MMRM results. Standard methodology for MMRM and ANCOVA, LOCF meta-analysis was applied for each study (Armitage and Colton, 1998).

The MMRM model had a completely unstructured covariance matrix and included terms for site, baseline score by visit interaction, and treatment by visit interaction. The ANCOVA, LOCF sensitivity analysis utilized treatment and site as fixed factors and the baseline scale score as a covariate. All analyses were performed on the Full Analysis Set (FAS), which was previously defined for each study.

Secondary endpoints in this meta-analysis were MADRS single-item scores, MADRS response rate (defined as a decline of at least 50% from baseline in MADRS total score), MADRS remission rate (defined as MADRS total score less than or equal to 10), CGI-S score, and CGI-I score. The endpoints were analyzed using MMRM and ANCOVA, LOCF (as described above) except for the MADRS response and remission, where logistic regression was used to provide odds ratios as input for the meta-analysis.

Results represent the least squares (LS) mean differences or odds ratios versus placebo (95% CI). All statistical tests are two-sided with a 0.05 significance level. The numbers needed to treat (NNTs) were calculated as the reciprocal of the risk difference between vortioxetine and placebo. The 95% CIs for the NNTs were calculated as the reciprocals of the limits from the 95% CIs for the risk differences. Standardized effect sizes (SES; also referred to as standardized mean differences), were interpreted as Cohen's *d* statistics.

An exploratory analysis of individual participant data (IPD), often referred to as a pooled data meta-analysis, was also conducted on the primary efficacy variable of change from baseline versus placebo in MADRS total score (LOCF) using a random-effects modeling approach, acknowledging the potential bias of this analysis due to the comparison of dosages that were only included in some of the studies to an overall placebo population that includes patients from all studies. The IPD approach has a tendency to produce confidence intervals that are too narrow and therefore the IPD analysis may be regarded as a less conservative approach. Although IPD has been considered the "gold standard" for meta-analyses, research has found relatively little difference in the summary level conclusions drawn from IPD and AD when using the same pool of studies and in the absence of confounding factors (Angelillo and Villari, 2003; Lyman and Kuderer, 2005; Mathew and Nordstrom, 1999; Olkin and Sampson, 1996). Due to convergence issues, MMRM modeling could not be performed using IPD.

3. Results

Figure 1 depicts a flow diagram of study eligibility and reasons for study exclusion. This AD meta-analysis of 11

Table 1 Summary characteristics of the 11 short-term, placebo-controlled studies of vortioxetine in patients with MDD included in the meta-analysis (FAS).

NCT identifier	Treatment period	Dose mg/day (n[a])	Key inclusion criteria for MDD	Primary efficacy endpoint	Reference
NCT00839423	6 weeks	VOR 5 (108) VOR 10 (100) VEN 225 (112) PBO (105)	MADRS ≥ 30 MDE ≥ 3 months and <12 months	MADRS	(Alvarez et al., 2012)
NCT00635219	8 weeks	VOR 2.5 (155) VOR 5 (155) VOR 10 (151) DUL 60 (149) PBO (145)	MADRS ≥ 26 MDE ≥ 3 months	MADRS	(Baldwin et al., 2012)
NCT00735709	8 weeks	VOR 1 (124) VOR 5 (129) VOR 10 (122) PBO (128)	MADRS ≥ 26 MDE ≥ 3 months	HAM-D_{24}	(Henigsberg et al., 2012)
NCT01140906	8 weeks	VOR 15 (149) VOR 20 (151) DUL 60 (146) PBO (158)	MADRS ≥ 26 CGI-S ≥ 4 MDE >3 months recurrent	MADRS	(Boulenger et al., 2014)
NCT01153009	8 weeks	VOR 15 (145) VOR 20 (147) DUL 60 (146) PBO (153)	MADRS ≥ 26 CGI-S ≥ 4 MDE ≥ 3 months recurrent	MADRS	(Mahableshwarkar et al., 2015a)
NCT01163266	8 weeks	VOR 10 (154) VOR 20 (150) PBO (155)	MADRS ≥ 26 CGI-S ≥ 4 MDE ≥ 3 months recurrent	MADRS	(Jacobsen et al., 2015b)
NCT01422213	8 weeks	VOR 10 (193) VOR 20 (204) PBO (194)	MADRS ≥ 26 MDE ≥ 3 months recurrent	DSST and RAVLT composite	(McIntyre et al., 2014)
NCT01255787	8 weeks	VOR 5 (142) VOR 10 (147) VOR 20 (149) PBO (150)	MADRS ≥ 26 CGI-S ≥ 4 MDE ≥ 3 months	MADRS	(Takeda, 2013)
NCT00672958	6 weeks	VOR 5 (292) PBO (286)	MADRS ≥ 30 MDE ≥ 3 months	HAM-D_{24}	(Jain et al., 2013)
NCT00672620	8 weeks	VOR 2.5 (146) VOR 5 (153) DUL 60 (149) PBO (149)	MADRS ≥ 22 MDE ≥ 3 months	HAM-D_{24}	(Mahableshwarkar et al., 2013)
NCT01179516	8 weeks	VOR 10 (143) VOR 15 (142) PBO (149)	MADRS ≥ 26 CGI-S ≥ 4 MDE ≥ 3 months recurrent	MADRS	(Mahableshwarkar et al., 2015b)

CGI-S: Clinical Global Impressions-Severity of Illness; DSST: Digit Symbol Substitution Test; DUL: duloxetine; HAM-D_{24}: Hamilton Anxiety Rating Scale-24 item; MADRS: Montgomery-Åsberg Depression Rating Scale; MDE: major depressive episode; PBO: placebo; RAVLT: Rey Auditory Verbal Learning Test; VEN: venlafaxine XR; VOR: vortioxetine.

[a] n represents all randomized participants who took at least one dose of study medication and had at least one valid post-baseline measurement of the primary efficacy variable.

trials included 1824 patients treated with placebo and 3304 treated with vortioxetine 5–20 mg/day (5 mg/day: $n=1001$; 10 mg/day: $n=1042$; 15 mg/day: $n=449$; 20 mg/day: $n=812$) for duration of up to eight weeks. Summary demographic and baseline characteristics for participants in the FAS are shown in Table 2. The placebo and vortioxetine groups had similar characteristics, including moderate to severe depression (as indicated by mean baseline MADRS total scores of approximately 32) and mild to moderate anxiety (as indicated by mean Hamilton Anxiety Rating Scale total scores of approximately 20).

3.1. MADRS total scores

In the individual studies of vortioxetine in patients with MDD, a consistent dose relationship was seen demonstrating a greater change from baseline in MADRS total score for each dosage group. The meta-analysis supported this dose-dependent trend (Figure 2). Specifically, in studies where different doses of vortioxetine were investigated, the higher dose demonstrated a greater treatment response from baseline. Seven of the 11 trials found evidence that at least one dosage of vortioxetine treatment was associated with significantly greater reductions in mean MADRS total score versus placebo. The MMRM meta-analysis (Figure 2A) showed that treatment with vortioxetine was associated with significantly greater reductions in mean MADRS total score compared to placebo in patients receiving 5 mg ($n=840$, Δ −2.27 points, $p=0.007$), 10 mg ($n=877$, Δ −3.57 points, $p<0.001$), and 20 mg ($n=671$, Δ −4.57 points, $p<0.001$) (FAS, MMRM). Although the 15-mg arm ($n=344$) had a numerically greater reduction in mean MADRS total score versus placebo (Δ −2.60 points), the difference was not statistically significant ($p=0.105$). Similar results were obtained when the meta-analysis was performed using the ANCOVA, LOCF method (Figure 2B); however, the dose relationship was less pronounced within individual studies with more than one dose of vortioxetine. In the MMRM meta-analysis of non-US studies, all vortioxetine dosage groups had significantly greater mean reductions in MADRS total scores compared to placebo, with a more pronounced dose relationship (vortioxetine 5 mg, $n=476$, Δ −3.20 points, $p=0.001$; 10 mg, $n=630$, Δ −4.24 points, $p<0.001$; 15 mg, $n=118$, Δ −5.53 points, $p<0.001$; 20 mg, $n=437$, Δ −5.41 points, $p<0.001$; FAS, MMRM). Heterogeneity was slightly lower in the non-US meta-analysis for vortioxetine 5 mg and 10 mg but higher for 20 mg compared to the overall meta-analysis (MMRM and ANCOVA, LOCF), as demonstrated by the I^2 value for heterogeneity (Figure 2A and B).

The exploratory meta-analysis of MADRS total score using IPD from all available clinical trials demonstrated a significant treatment response for all vortioxetine doses (5 mg, Δ −2.10 points, SE±0.68, $p=0.007$; 10 mg, Δ −2.64 points, SE±0.64, $p<0.001$; 15 mg, Δ −2.26 points, SE±0.93, $p=0.027$; and

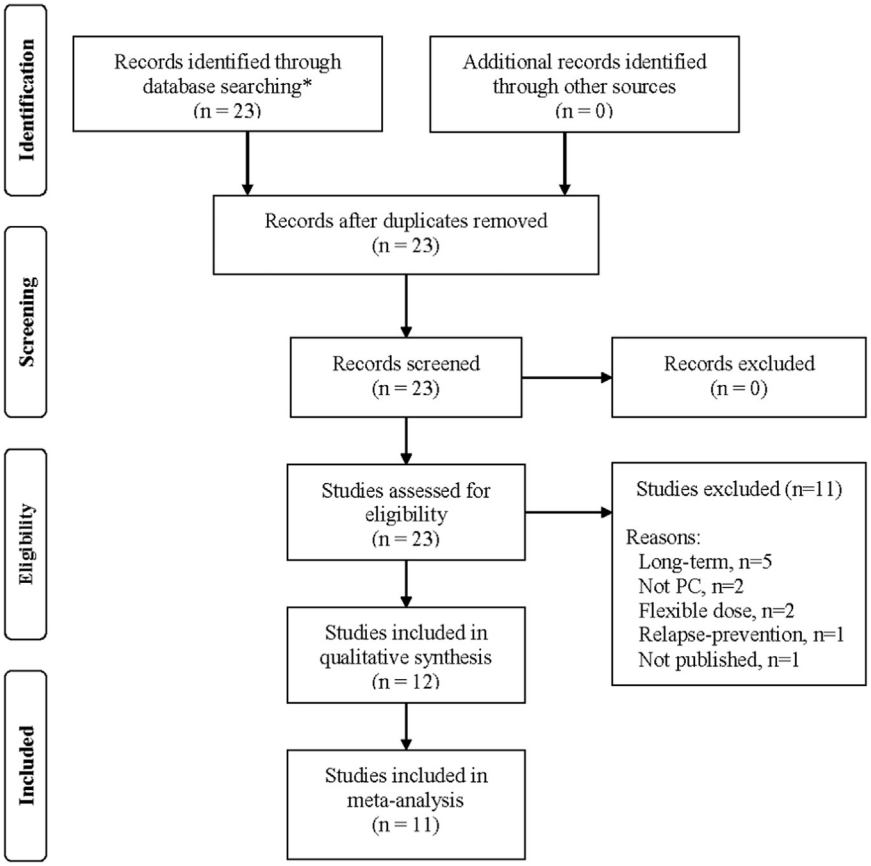

Figure 1 PRISMA Flow Diagram for Study Inclusion. * ClinicalTrials.gov search components: vortioxetine (intervention); major depressive disorder (condition); completed (recruitment); results posted (study results); phase 2 or 3 (phase); updated on or before to 1 March 2015 (last updated) (US National Institutes of Health (NIH), 2015). PC: placebo-controlled.

Table 2 Summary of demographics, baseline characteristics, and baseline efficacy parameters for patients included in the meta-analysis of 11 short-term, placebo-controlled clinical studies of vortioxetine in patients with MDD (FAS).

	Placebo (*N* = 1784)	Vortioxetine 5 mg (*N* = 989)	Vortioxetine 10 mg (*N* = 1028)	Vortioxetine 15 mg (*N* = 436)	Vortioxetine 20 mg (*N* = 800)
Age, years, mean (SD)	44.0 (12.46)	44.1 (12.79)	44.9 (12.24)	44.9 (13.61)	44.7 (12.49)
Sex, female, *n* (%)	1146 (64.2)	644 (65.1)	696 (67.7)	300 (68.8)	528 (66.0)
Race, *n* (%)					
Caucasian[a]	1454 (81.5)	752 (76.0)	812 (79.0)	360 (82.6)	648 (81.0)
Black	216 (12.1)	122 (12.3)	90 (8.8)	68 (15.6)	89 (11.1)
Asian	107 (6.0)	110 (11.1)	112 (10.9)	6 (1.4)	53 (6.6)
Other[b]	7 (0.4)	5 (0.5)	14 (1.4)	2 (0.5)	10 (1.3)
BMI, kg/m^2					
Mean (SD)	28.5 (6.99)	27.9 (7.34)	27.5 (6.75)	29.2 (7.18)	28.0 (6.63)
Mean duration of current MDE, *n* (%)					
<24 weeks	855 (47.9)	494 (49.9)	565 (55.0)	194 (44.5)	377 (47.1)
≥ 24 weeks	929 (52.1)	495 (50.1)	459 (44.6)	242 (55.5)	423 (52.9)
Number of previous MDEs					
N	1613	802	914	436	753
Mean (SD)	2.7 (2.24)	2.8 (3.05)	2.6 (2.12)	2.7 (1.90)	2.7 (2.30)
Region, *n* (%)					
United States	925 (51.8)	445 (45.0)	332 (32.3)	287 (65.8)	333 (41.6)
Non-United States	859 (48.2)	544 (55.0)	696 (67.7)	149 (34.2)	467 (58.4)
MADRS total score					
Mean (SD)	32.1 (4.00)	32.4 (4.04)	32.3 (4.03)	32.5 (4.09)	31.8 (3.88)
CGI-S total score					
Mean (SD)	4.7 (0.68)	4.8 (0.70)	4.7 (0.67)	4.7 (0.61)	4.6 (0.62)
HAM-A total score[c]					
Mean (SD)	19.7 (6.32)	20.1 (6.23)	20.6 (6.46)	19.4 (6.11)	18.9 (6.12)

BMI: body mass index; CGI-S: Clinical Global Impressions-Severity of Illness, HAM-A: Hamilton Anxiety Rating Scale, MADRS: Montgomery-Åsberg Depression Rating Scale, MDE: major depressive episode

[a]Caucasian (or white, including Hispanic)

[b]Other: including American Indian/Alaska Native, Native Hawaiian (or other Pacific Islander), and missing.

[c]Study NCT01422213 did not measure HAM-A as an outcome measure; therefore, *n*-values for the HAM-A analysis set are: 1586 (placebo), 983 (vortioxetine 5 mg), 830 (10 mg), 436 (15 mg), and 596 (20 mg).

20 mg, Δ −3.71 points, SE ±0.73, $p<0.001$; LS means, LOCF), with a pattern similar to that seen in the primary (MMRM) and sensitivity (ANCOVA, LOCF) analyses. As expected, the IPD produced smaller standard errors, and therefore smaller and less conservative confidence intervals.

3.2. MADRS single-item scores

The MMRM meta-analysis of individual MADRS single-item scores showed that vortioxetine 10 and 20 mg/day were associated with significantly greater mean reductions from baseline in MADRS single-item scores versus placebo, with a similar overall dose relationship as with the reduction in mean MADRS total score (Figure 3). The meta-analysis of MADRS single-item scores using ANCOVA, LOCF yielded similar results and overall dose-relationship to the MMRM meta-analysis (Supplemental Figure 1).

3.3. Response rates

The percentage of patients in each trial achieving a responding to treatment (defined as at least a 50% reduction in MADRS total score from baseline to the end of treatment) is shown in Figure 4A. The 5-, 10-, and 20-mg vortioxetine groups had significantly higher rates of response compared to the placebo group (placebo, $n=655/1783$ [36.7%]; vortioxetine 5 mg, $n=496/989$ [50.2%], $p=0.002$; 10 mg, $n=501/1026$ [48.8%], $p<0.001$; 15 mg, $n=202/436$ [46.3%], $p=0.080$; 20 mg, $n=412/799$ [51.6%], $p<0.001$; FAS, LOCF; *p*-values are from the odds ratios using logistic regression). When only considering clinical trials conducted outside the US, the meta-analysis was significant for all vortioxetine doses (placebo, $n=200/547$ [36.6%]; vortioxetine 5 mg, $n=221/402$ [55.0%], $p<0.001$; 10 mg, $n=223/389$ [57.3%], $p<0.001$; 15 mg, $n=85/149$ [57.0%], $p<0.001$; 20 mg, $n=93/151$ [61.6%], $p<0.001$; FAS, LOCF).

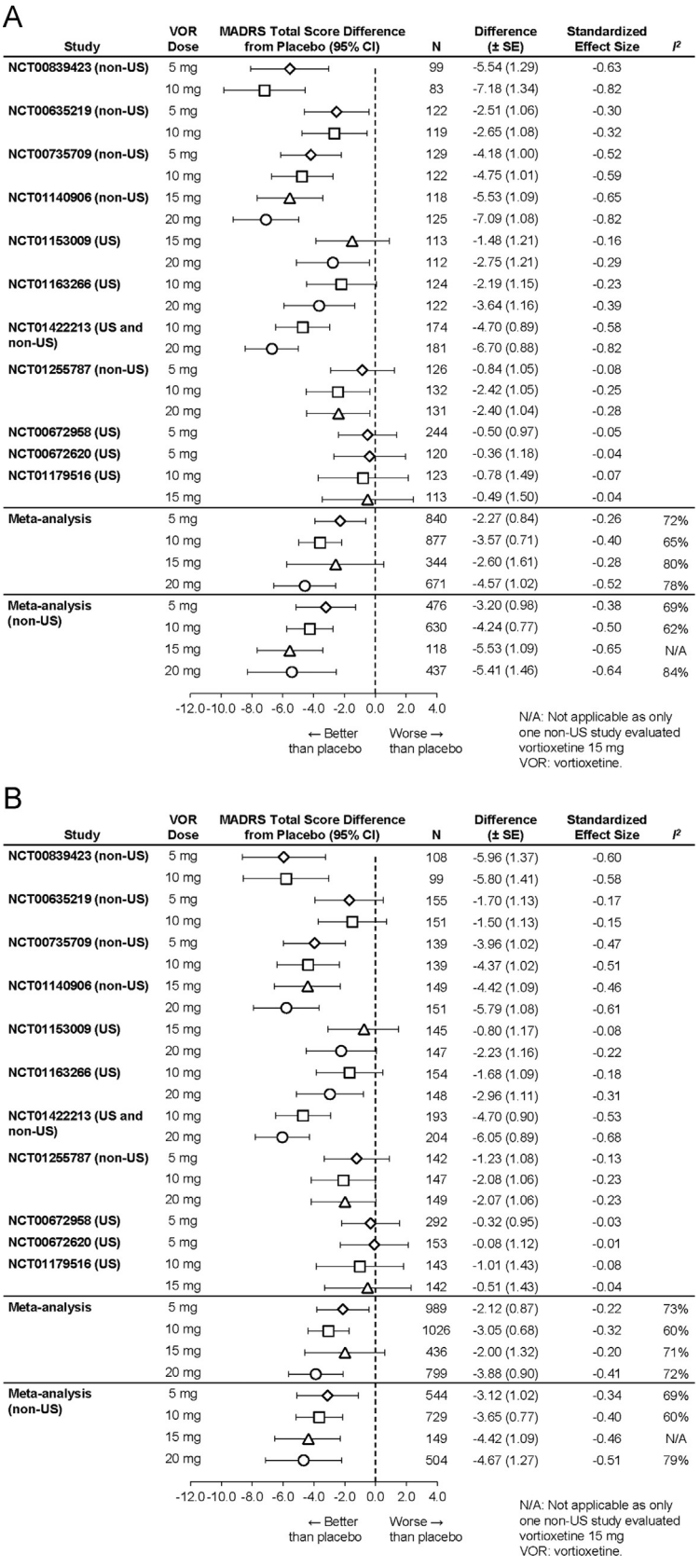

Figure 2 A. Difference from Placebo in Change from Baseline in MADRS Total Score (FAS, MMRM) B. Difference from Placebo in Change from Baseline in MADRS Total Score (FAS, ANCOVA, LOCF).

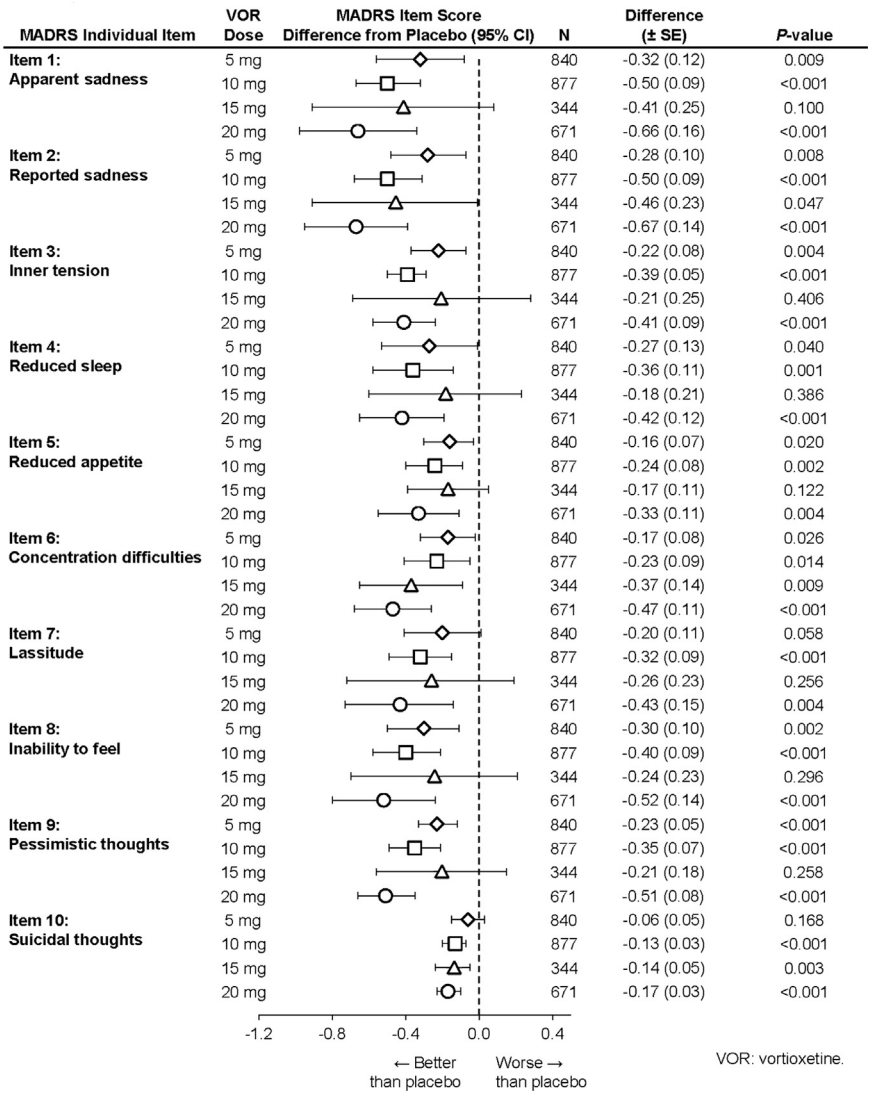

Figure 3 Difference from Placebo in Change from Baseline in MADRS Single-Item Scores (FAS, MMRM).

3.4. Remission rates

The percentage of patients in each trial achieving remission, defined as a MADRS total score of less than or equal to 10 at the end of the treatment period, is shown in Figure 4B. The vortioxetine 10 mg ($p<0.001$) and 20 mg ($p<0.05$) groups had significantly higher remission rates than did the placebo group (placebo, $n=425/1783$ [23.8%]; vortioxetine 5 mg, $n=304/989$ [30.7%], $p=0.188$; 10 mg, $n=310/1026$ [30.2%], $p<0.001$; 15 mg, $n=125/436$ [28.7%], $p=0.189$; 20 mg, $n=258/799$ [32.3%], $p=0.002$; FAS, LOCF; p-values are from the odds ratios using logistic regression). In the meta-analysis of clinical trials conducted outside the US, vortioxetine demonstrated a significant effect on remission in all treatment groups (placebo, $n=130/547$ [23.8%]; vortioxetine 5 mg, $n=148/402$ [36.8%], $p=0.029$; 10 mg, $n=139/389$ [35.7%], $p=0.043$; 15 mg, $n=52/149$ [34.9%], $p=0.002$; 20 mg, $n=58/151$ [38.4%], $p<0.001$; FAS, LOCF).

3.5. CGI-I and CGI-S scores

The MMRM meta-analysis of CGI-I and CGI-S supported the results of the overall analysis of the MADRS total score. The meta-analysis of the CGI-I demonstrated a dose-related clinical improvement similar to that seen in the individual clinical trials when compared to placebo (vortioxetine 5 mg, $n=839$, Δ -0.28, $p<0.001$; 10 mg, $n=876$, Δ -0.42, $p<0.001$; 15 mg, $n=344$, Δ -0.29, $p=0.165$; 20 mg, $n=670$, Δ -0.50, $p=0.002$; FAS, MMRM). The analysis of the CGI-I in clinical studies conducted outside the US demonstrated a clinical improvement for all doses, similar to that seen in the analysis of the MADRS total score (vortioxetine 5 mg, $n=475$, Δ -0.36, $p<0.001$; 10 mg, $n=630$, Δ -0.52, $p<0.001$; 15 mg, $n=118$, Δ -0.69, $p<0.001$; 20 mg, $n=437$, Δ -0.67, $p=0.005$; FAS, MMRM) (Figure 5). The meta-analysis using ANCOVA, LOCF yielded results similar to the meta-analysis using MMRM, but the dose relationship was less pronounced (results not shown) due to an increase in Type 1 error.

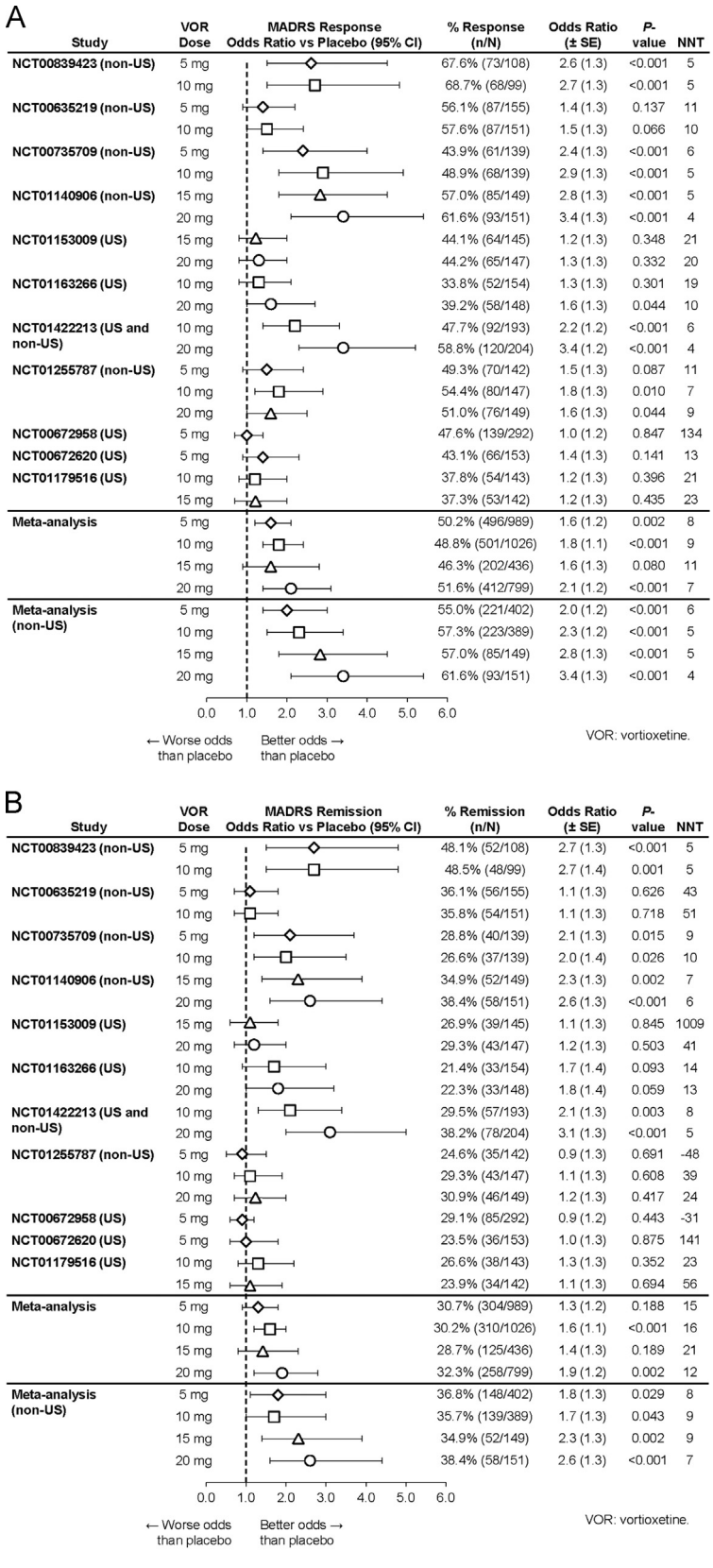

Figure 4 A. Response Rates (Defined as $\geq$ 50% Decrease in MADRS) at Week 6/8 (FAS, LOCF) B. Remission Rates (Defined as MADRS $\leq$ 10) at Week 6/8 (FAS, LOCF).

The MMRM meta-analysis of the CGI-S demonstrated a similar dose-related response to the response seen in the individual clinical trials (vortioxetine 5 mg, $n=838$, $\Delta -0.29$, $p=0.012$; 10 mg, $n=877$, $\Delta -0.46$, $p<0.001$; 15 mg, $n=344$, $\Delta -0.36$, $p=0.128$; 20 mg, $n=670$, $\Delta -0.55$, $p=0.001$; FAS, MMRM), with a greater clinical response seen in non-US clinical studies (vortioxetine 5 mg, $n=474$, $\Delta -0.42$, $p=0.004$; 10 mg, $n=630$, $\Delta -0.60$, $p<0.001$; 15 mg, $n=118$, $\Delta -0.82$, $p<0.001$; 20 mg, $n=437$, $\Delta -0.76$, $p<0.001$; FAS, MMRM) (Figure 6). The meta-analysis using ANCOVA, LOCF yielded results similar to the meta-analysis using MMRM, but the dose relationship was less pronounced (results not shown), again due to an increase in Type 1 error.

4. Discussion

The current meta-analysis of aggregated study-level data includes 11 short-term placebo-controlled trials in adults using efficacy data of the approved dose range of vortioxetine, 5–20 mg/day. Vortioxetine was found to be an efficacious antidepressant, as shown by the reduction of the MADRS total and single-item scores, and supported by a larger proportion of responders and remitters compared to placebo and by improvements on the global clinical impression scales (CGI-I and CGI-S). For patients treated with vortioxetine 10 mg/day (the recommended starting dose), the mean difference from placebo in change from baseline in MADRS total score was −3.57 points; a reduction of at least 2 points on the MADRS total score versus placebo is usually considered clinically meaningful (Melander et al., 2008; Montgomery and Moller, 2009).

For most outcome measures, the effects of vortioxetine therapy showed a general dose-dependent trend, with improvements in depression-related outcomes increasing as vortioxetine dose increased from 5 mg/day to 10 mg/day and again to 20 mg/day. The dose relationship was observed in both the MMRM and ANCOVA, LOCF meta-analyses – as well as the exploratory IPD analysis – and was more pronounced when using MMRM, particularly within individual studies. The individual studies that utilized the higher doses of vortioxetine also demonstrated a greater difference to placebo on the MADRS total score, which was confirmed by the meta-analysis. Furthermore, when conducting the meta-analysis using data from the six non-US studies, the dose response effect was more pronounced compared to the meta-analysis of all 11 studies. Although results for vortioxetine 15 mg/day defied this trend in the meta-analysis, this dose had the smallest sample size (as it was only utilized in three clinical trials) with substantially wider CIs compared to the other doses, and two of the three clinical trials were conducted exclusively in the US (regionality discussed later on). The efficacy of vortioxetine treatment in the individual studies and the meta-analysis

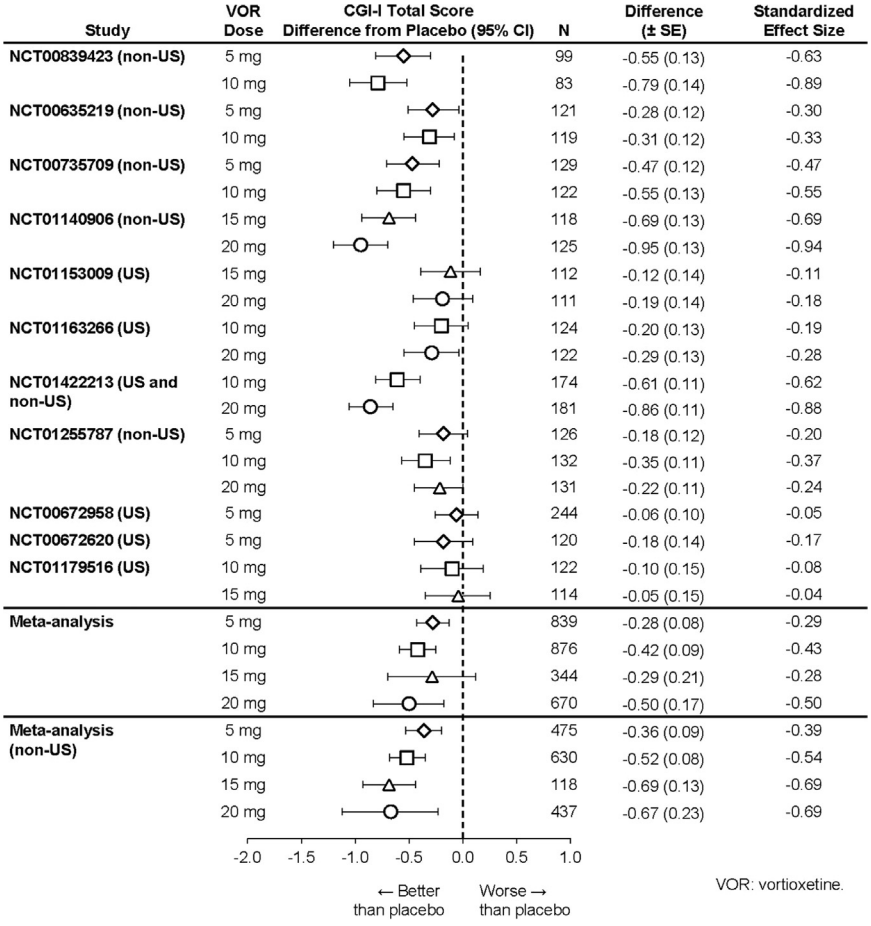

Figure 5 Difference from Placebo in Change from Baseline in CGI-I Total Score (FAS, MMRM).

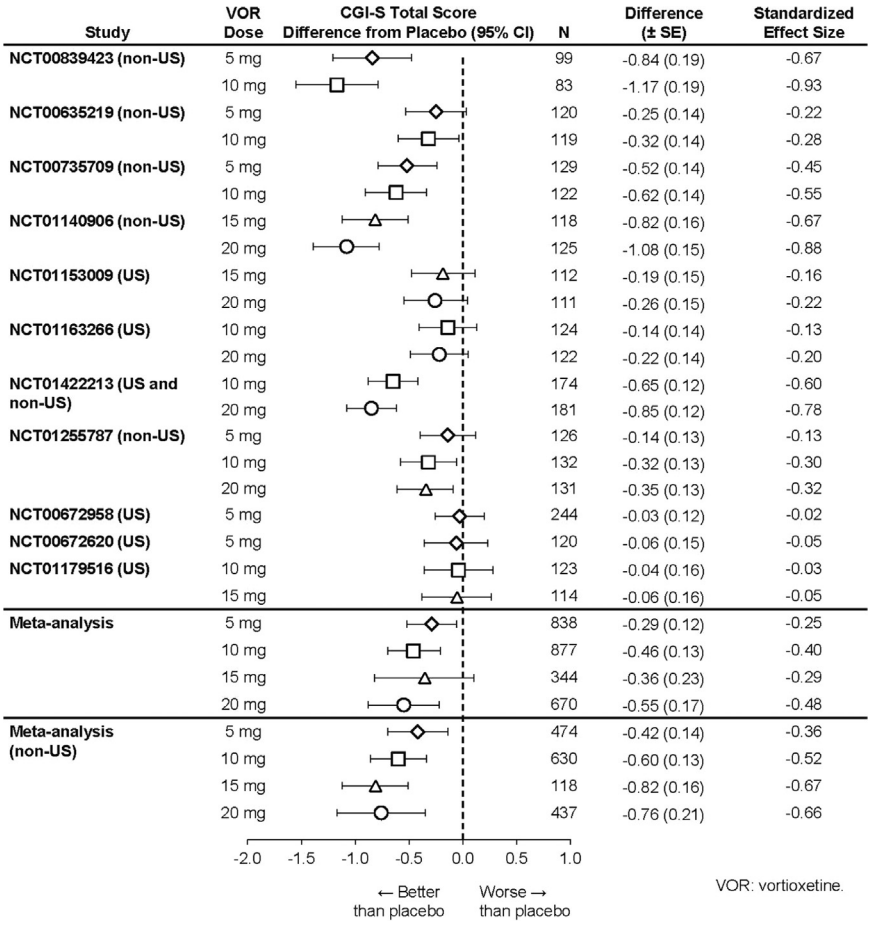

Figure 6 Difference from Placebo in Change from Baseline in CGI-S Total Score (FAS, MMRM).

is also supported by the trial in elderly patients with MDD (Katona et al., 2012); in that trial, vortioxetine 5 mg/day for eight weeks was associated with mean reductions in MADRS total score and rates of remission and response that were significantly better than placebo.

The lack of a clear dose-response relationship in the evaluation of overall response rate and remission rate should also be noted, highlighting the lack of sensitivity of these secondary assessments to identify a clinically meaningful change over time. Although response remission rates were predefined in the overall statistical testing hierarchy, the individual clinical trials were not specifically designed to detect differences to placebo in response or remission rates; rather, the studies were powered to analyze overall change from baseline, a more time-sensitive measure of clinical response. Furthermore, the dose response was also less pronounced partly due to the LOCF being applied and partly due to the dichotomization involved in the responder definition, where a large amount of information is lost.

This AD meta-analysis supports the findings of the four published meta-analyses of vortioxetine (Behzadifar et al., 2015; Berhan and Barker, 2014; Meeker et al., 2015; Pae et al., 2015), which identified a therapeutic and clinically relevant benefit of vortioxetine for patients with MDD. Each of the previous meta-analyses of vortioxetine used study-level data from peer-reviewed clinical trial reports, congress presentations, the FDA evaluation of vortioxetine, or from ClinicalTrials.gov. In addition to the similar results of antidepressant effects, these studies identified a substantial level of heterogeneity in the meta-analyses. A number of methodological differences between the previous meta-analyses and that reported here can be identified. Three of the previous meta-analyses included all doses of vortioxetine (1, 2.5, 5, 10, 15, and 20 mg/day) and included the vortioxetine trial in elderly patients (Berhan and Barker, 2014; Meeker et al., 2015; Pae et al., 2015). In one of the meta-analyses, the input used was a combination of both MMRM and ANCOVA, LOCF results, depending on which analysis was used as the primary efficacy analysis in the individual trial (Meeker et al., 2015); one meta-analysis only included seven trials (Berhan and Barker, 2014), and one used both MADRS total score and HAM-D_{24} total score as the endpoint using LOCF and with all doses of vortioxetine collapsed (Pae et al., 2015). In addition, two of the previous meta-analyses also compared the antidepressant effect of vortioxetine directly to that of the active references used in six of the trials (Meeker et al., 2015; Pae et al., 2015). One meta-analysis utilized a mix of MMRM and ANCOVA, LOCF to evaluate only trials evaluating vortioxetine 20 mg/day (Behzadifar et al., 2015). In contrast to the four previous meta-analyses of vortioxetine (Behzadifar et al., 2015; Berhan and Barker, 2014; Meeker et al., 2015; Pae et al., 2015), this aggregated meta-analysis utilized robust and consistent statistical methodology to evaluate clinical data

from all available placebo-controlled studies of vortioxetine in adult patients with moderate to severe MDD.

The observation of a dose relationship in the current meta-analysis is in contrast to one of the previous meta-analyses, which did not find a dose relationship. The methodological differences between the previous meta-analysis and the current one may have contributed to the differences in conclusions on whether a dose relationship is present. For example, the analysis by Meeker et al. (2015) also included the 1-and 2.5-mg doses and inconsistently used MMRM or ANCOVA, LOCF values as input to the analysis. It has been reported that the use of ANCOVA, LOCF may mask the presence of a dose relationship, which may be identified if using MMRM (Preskorn, 2008; Siddiqui et al., 2009). In addition, Meeker et al. (2015) utilized a statistical output from a meta-regression analysis as the main determinant of dose-response, with $p > 0.05$ resulting in the conclusion of no dose relationship for response to treatment. To accurately determine if a dose relationship is present, multiple factors must be taken into consideration, with results of the individual studies as well as those of the meta-analysis taken into consideration. The observation of a dose relationship for vortioxetine 5–20 mg/day is relevant from a therapeutic and clinical perspective, as this has not been reported for other antidepressants.

This meta-analysis centers on the comparison between vortioxetine and placebo in the 11 individual studies and does not evaluate differences between vortioxetine and the active references (duloxetine and venlafaxine XR). The results of the active references can be found in the publications for the individual studies. In two of the previous meta-analyses of the vortioxetine data, direct comparisons between vortioxetine and the active reference were included (Meeker et al., 2015; Pae et al., 2015). Direct comparison of vortioxetine and the active reference is not appropriate, as the individual studies were not designed or powered to enable this comparison. Rather, the rationale for including an active reference in these studies was for the internal validation of the study design (i.e., assay sensitivity). To evaluate the efficacy of vortioxetine relative to another antidepressant would require a study that is specifically designed for that purpose, that is, an active-comparator study (Jacobsen et al., 2015a; Montgomery et al., 2014; Wang et al., 2015). In addition, in the six studies that include an active reference, patients were excluded – for ethical reasons – if they had known hypersensitivity or a history of lack of response to previous treatment with the active reference, which introduces the potential for bias in favor of the active reference (ICH, 2000; Jin et al., 2013; Perlis et al., 2010).

The results of this meta-analysis are consistent with those seen in the individual trials, which identified a dose-dependent efficacy of vortioxetine for depression-related outcomes. However, some of the vortioxetine dosage groups (5–20 mg/day) in individual trials failed to show significant benefit of treatment versus placebo, consistent with other trials of effective antidepressants, especially in recent decades (Khin et al., 2011). Given that other effective approved antidepressants have encountered difficulties demonstrating efficacy (even in well-designed placebo-controlled clinical trials) (Khin et al., 2011), it is perhaps not surprising that clinical trials with vortioxetine have also had mixed success. Various explanations for failed antidepressant trials have been proposed, although studies have not identified a consistent cause or set of causes (Dunlop et al., 2012; Khan et al., 2010; Khin et al., 2011). Analyses into reasons of non-consistency have not been investigated, but differences in clinical trial setting and geographic location may have influenced the success or failure of specific trials. The trials included in the current meta-analysis used differing MADRS baseline total scores as entry criteria. This difference might be expected to lead to differing outcomes, as patients with higher MADRS total scores (hence worse depression) may present a greater therapeutic opportunity. However, there was no consistent trend relating the entry criteria to the magnitude or significance of vortioxetine effects on MADRS total score during treatment, even at higher doses. Furthermore, although the entry criteria differed across the trials, the baseline MADRS total scores were similar.

Clinical study results included in meta-analyses are usually heterogeneous, which is also observed in the vortioxetine clinical development program, despite the very similar study design across the studies (Armitage and Colton, 1998). Variation in responses was identified in this meta-analysis, as well as in previous meta-analyses of the vortioxetine trials (Behzadifar et al., 2015; Berhan and Barker, 2014; Meeker et al., 2015; Pae et al., 2015). This type of heterogeneity can be introduced due to, for example, regional differences and differences in clinical practice. Because of this potential source of variability, it was relevant to analyze the effect of vortioxetine based on the trials conducted outside the US in addition to the meta-analysis of all trials. The incidence of heterogeneity is slightly less pronounced with the lower doses of vortioxetine when the meta-analysis only includes trials conducted outside the US, as compared to the meta-analysis of all trials.

Several factors have been suggested to affect the outcome of MDD trials, including the setting (academic versus non-academic), the number of active treatment arms, the number of assessments, type of raters used (centralized versus non-centralized), inflation of depression rating scores at inclusion, number of previous treatment episodes, previous treatments used, treatment compliance, and region (Dunlop et al., 2012; Jain et al., 2013; Khan et al., 2003; Kobak et al., 2010; Mallinckrodt et al., 2011; Mundt et al., 2007; Shen et al., 2008; Vieta et al., 2011). In addition, there has been a steady decline in the antidepressant-placebo difference in clinical studies (Khin et al., 2011), with this decline appearing to be particularly pronounced in studies conducted in the US, thought primarily due to the higher placebo response (Vieta et al., 2011). None of these factors have been identified as clearly contributing to the outcome of the clinical trials with vortioxetine. No single causative factor can be isolated to explain the differences between 5 studies conducted in the US and those conducted outside the US. It appears, however, that issues around study conduct, including patient selection, adherence to the protocol, and investigational medicinal product regimen, are critical. This analysis shows that trials conducted outside the US were more likely to report significant vortioxetine efficacy than were US trials. Other studies have reported important differences between the US and other countries with regard to patient and disease characteristics, diagnostic and clinical

practices, and the conduct of clinical trials (Chang et al., 2008; Khin et al., 2011; Niklson and Reimitz, 2001). For example, studies NCT01140906 and NCT01153009 were identical in study design, both in terms of duration, doses, inclusion and exclusion criteria, and study endpoints, but with the difference that NCT01140906 was conducted outside the US and NCT01153009 was conducted exclusively in the US (Boulenger et al., 2014; Mahableshwarkar et al., 2015b). The non-US NCT01140906 study was a positive study, with vortioxetine 15 and 20 mg/day separating from placebo and with a relatively large standardized effect sizes. This is in contrast to the US study NCT01153009, where only the 20-mg/day dose separated from placebo and with a lower standardized effect size than the non-US study. The explanation for differences in the outcomes of vortioxetine trials is not entirely understood, but a population-based pharmacokinetic/pharmacodynamic analysis of the vortioxetine clinical development program identified that 15% of patients in the US phase 3 trials of vortioxetine had lower and more variable plasma drug concentrations than did patients on corresponding vortioxetine doses in the non-US phase 3 trials (3–5%) (Areberg et al., 2013). In contrast, patients in phase 1 trials, where compliance is monitored more closely, had similar plasma drug concentrations regardless of study location. Such differences could explain the greater difficulty in demonstrating a significant treatment effect of vortioxetine in US trials compared with non-US trials.

This meta-analysis of aggregated study-level data from 11 randomized, placebo-controlled, short-term studies with vortioxetine (5–20 mg/day) in adult MDD patients supports the efficacy profile demonstrated in the individual studies, with an overall increasing effect size associated with increasing dose, not seen with other antidepressants. The broad clinical efficacy profile of vortioxetine – as demonstrated by the effect on the primary endpoint of change from baseline in MADRS total score – is supported by the effect on other depression endpoints as well as overall clinical improvement.

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Conflict of interest statements

The authors of this manuscript have the following competing interests: M. Thase and E. Vieta are consultants to H. Lundbeck A/S and the Takeda Pharmaceutical Company Ltd. Professor Thase also has received research funding from both companies. Professor Thase discloses similar relationships with other pharmaceutical companies. A.R. Mahableshwarkar is an employee of Takeda Development Center Americas. M Dragheim and H Loft are employees of H.Lundbeck A/S.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2016.03.007.

References

Alvarez, E., Perez, V., Dragheim, M., Loft, H., Artigas, F., 2012. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. Int. J. Neuropsychopharmacol. 15, 589–600.

American Psychiatric Association (APA), 2010. Work Group on Major Depressive Disorder. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, third ed. American Psychiatric Association, Arlington, VA.

Angelillo, I.F., Villari, P., 2003. Meta-analysis of published studies or meta-analysis of individual data? Caesarean section in HIV-positive women as a study case. Public Health 117, 323–328.

Areberg, J., Chan, S., Vakilynejad, M., Chen, G., Mahableshwarkar, L.H., Naik H, A., 2013. A population pharmacokinetic (PK)-pharmacodynamic (PD) meta-analysis of vortioxetine in patients with major depressive disorder (MDD). Int. J. Psychiatry Clin. Pract. 17, 13.

Armitage, P., Colton, T., 1998. Meta-analysis of clinical trials. In: Armitage, P., Colton, T. (Eds.), Encyclopedia of Biostatistics. John Wiley & Sons Ltd., Chichester, England, pp. 2570–2579.

Baldwin, D.S., Loft, H., Dragheim, M., 2012. A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). Eur. Neuropsychopharmacol. 22, 482–491.

Bang-Andersen, B., Ruhland, T., Jorgensen, M., Smith, G., Frederiksen, K., Jensen, K.G., Zhong, H., Nielsen, S.M., Hogg, S., Mork, A., Stensbol, T.B., 2011. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel

multimodal compound for the treatment of major depressive disorder. J. Med. Chem. 54, 3206–3221.
Behzadifar, M., Dehghan, H., Saki, K., Behzadifar, M., Keshavarzi, A., Saran, M., Sari, A., 2015. Evaluation efficacy and safety of vortioxetine 20 mg/d versus placebo for treatment major depressive disorder: a systematic review and meta-analysis of randomized controlled trials. Pharmacol. Pharm. 6, 221–231.
Berhan, A., Barker, A., 2014. Vortioxetine in the treatment of adult patients with major depressive disorder: a meta-analysis of randomized double-blind controlled trials. BMC Psychiatry 14, 276.
Boulenger, J.P., Loft, H., Olsen, C.K., 2014. 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. Int. Clin. Psychopharmacol. 29, 138–149.
Chang, S.M., Hahm, B.J., Lee, J.Y., Shin, M.S., Jeon, H.J., Hong, J. P., Lee, H.B., Lee, D.W., Cho, M.J., 2008. Cross-national difference in the prevalence of depression caused by the diagnostic threshold. J. Affect. Disord. 106, 159–167.
Dunlop, B.W., Thase, M.E., Wun, C.C., Fayyad, R., Guico-Pabia, C. J., Musgnung, J., Ninan, P.T., 2012. A meta-analysis of factors impacting detection of antidepressant efficacy in clinical trials: the importance of academic sites. Neuropsychopharmacology 37, 2830–2836.
Guy, W., 1976. Clinical global impressions (028-CGI). In: Guy, W. (Ed.), ECDEU Assessment Manual for Psychopharmacology. U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, Rockville, MD.
H. Lundbeck A/S, 2015. European Medicines Agency Summary of Product Characteristics: Brintellix.
Henigsberg, N., Mahableshwarkar, A.R., Jacobsen, P., Chen, Y., Thase, M.E., 2012. 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 73, 953–959.
Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560.
ICH, 2000. ICH Harmonised Tripartite Guideline Choice of Control Group and Related Issues in Clinical Trials. July 2000.
Jacobsen, P.L., Mahableshwarkar, A.R., Chen, Y., Chrones, L., Clayton, A.H., 2015a. Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-Induced sexual dysfunction. J. Sex. Med. 12, 2036–2048.
Jacobsen, P.L., Mahableshwarkar, A.R., Serenko, M., Chan, S., Trivedi, M., 2015b. 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 76, 575–582.
Jain, R., Mahableshwarkar, A.R., Jacobsen, P., Chen, Y., Thase, M. E., 2013. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. Int. J. Neuropsychopharmacol. 16, 313–321.
Jin, H., Shih, P.A., Golshan, S., Mudaliar, S., Henry, R., Glorioso, D. K., Arndt, S., Kraemer, H.C., Jeste, D.V., 2013. Comparison of longer-term safety and effectiveness of 4 atypical antipsychotics in patients over age 40: a trial using equipoise-stratified randomization. J. Clin. Psychiatry 74, 10–18.
Katona, C., Hansen, T., Olsen, C.K., 2012. 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. Int. Clin. Psychopharmacol. 27, 215–223.
Khan, A., Bhat, A., Kolts, R., Thase, M.E., Brown, W., 2010. Why has the antidepressant-placebo difference in antidepressant clinical trials diminished over the past three decades? CNS Neurosci. Ther. 16, 217–226.
Khan, A., Detke, M., Khan, S.R., Mallinckrodt, C., 2003. Placebo response and antidepressant clinical trial outcome. J. Nerv. Ment. Disord. 191, 211–218.
Khin, N.A., Chen, Y.F., Yang, Y., Yang, P., Laughren, T.P., 2011. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J. Clin. Psychiatry 72, 464–472.
Kobak, K.A., Leuchter, A., DeBrota, D., Engelhardt, N., Williams, J. B., Cook, I.A., Leon, A.C., Alpert, J., 2010. Site versus centralized raters in a clinical depression trial: impact on patient selection and placebo response. J. Clin. Psychopharmacol. 30, 193–197.
Lyman, G.H., Kuderer, N.M., 2005. The strengths and limitations of meta-analyses based on aggregate data. BMC Med. Res. Methodol. 5, 14.
Mahableshwarkar, A.R., Jacobsen, P., Serenko, M., Chen, Y., Trivedi, M., 2015a. A randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of vortioxetine in adults with major depressive disorder. J. Clin. Psychiatry 76, 583–591.
Mahableshwarkar, A.R., Jacobsen, P.L., Chen, Y., 2013. A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. Curr. Med. Res. Opin. 29, 217–226.
Mahableshwarkar, A.R., Jacobsen, P.L., Chen, Y., Serenko, M., Trivedi, M., 2015b. 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 232, 2061–2070.
Mallinckrodt, C.H., Raskin, J., Wohlreich, M.M., Watkin, J.G., Detke, M.J., 2004. The efficacy of duloxetine: a comprehensive summary of results from MMRM and LOCF_ANCOVA in eight clinical trials. BMC Psychiatry 4, 26.
Mallinckrodt, C.H., Tamura, R.N., Tanaka, Y., 2011. Recent developments in improving signal detection and reducing placebo response in psychiatric clinical trials. J. Psychiatr. Res. 45, 1202–1207.
Mathew, T., Nordstrom, K., 1999. On the equivalence of meta-analysis using literature and using individual patient data. Biometrics 55, 1221–1223.
McIntyre, R.S., Lophaven, S., Olsen, C.K., 2014. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. Int. J. Neuropsychopharmacol. 17, 1557–1567.
Meeker, A.S., Herink, M.C., Haxby, D.G., Hartung, D.M., 2015. The safety and efficacy of vortioxetine for acute treatment of major depressive disorder: a systematic review and meta-analysis. Syst. Rev. 4, 21.
Melander, H., Salmonson, T., Abadie, E., van Zwieten-Boot, B., 2008. A regulatory Apologia-a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. Eur. Neuropsychopharmacol. 18, 623–627.
Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.
Montgomery, S.A., Moller, H.J., 2009. Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? Int. Clin. Psychopharmacol. 24, 111–118.
Montgomery, S.A., Nielsen, R.Z., Poulsen, L.H., Häggström, L., 2014. A randomised, double-blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor treatment switched to vortioxetine or agomelatine. Hum. Psychopharmacol. Clin. Exp. 29, 470–482.

Mork, A., Pehrson, A., Brennum, L.T., Moller, N.S., Zhong, H., Lassen, A.B., Miller, S., Westrich, L., Boyle, N.J., Sanchez, C., Weide, F.C., Liebenberg, N., Wegener, G., Bundgaard, C., Hogg, S., Bang-Andersen, B., Bryan, S.T., 2012. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. J. Pharmacol. Exp. Ther. 340, 666–675.

Mundt, J.C., Greist, J.H., Jefferson, J.W., Katzelnick, D.J., DeBrota, D.J., Chappell, P.B., Modell, J.G., 2007. Is it easier to find what you are looking for if you think you know what it looks like? J. Clin. Psychopharmacol. 27, 121–125.

Niklson, I.A., Reimitz, P.E., 2001. Baseline characteristics of major depressive disorder patients in clinical trials in Europe and United States: is there a transatlantic difference? J. Psychiatr. Res. 35, 71–81.

Olkin, I., Sampson, A., 1996. Olkin I, Sampson A. Analysis of variance of individual patient data. Technical Report No. 315.

Pae, C.U., Wang, S.M., Han, C., Lee, S.J., Patkar, A.A., Masand, P.S., Serretti, A., 2015. Vortioxetine: a meta-analysis of 12 short-term, randomized, placebo-controlled clinical trials for the treatment of major depressive disorder. J. Psychiatry Neurosci. 40, 174–186.

Papakostas, G.I., 2010. The efficacy, tolerability, and safety of contemporary antidepressants. J. Clin. Psychiatry 71 (Suppl. E1), e03.

Perlis, R.H., Ostacher, M., Fava, M., Nierenberg, A.A., Sachs, G.S., Rosenbaum, J.F., 2010. Assuring that double-blind is blind. Am. J. Psychiatry 167, 250–252.

Preskorn, S.H., 2008. Flat dose–response curves for efficacy: what do they mean to the clinician? J. Psychiatr. Pract. 14, 232–236.

Rosenzweig-Lipson, S., Beyer, C.E., Hughes, Z.A., Khawaja, X., Rajarao, S.J., Malberg, J.E., Rahman, Z., Ring, R.H., Schechter, L.E., 2007. Differentiating antidepressants of the future: efficacy and safety. Pharmacol. Ther. 113, 134–153.

Shen, J., Kobak, K.A., Zhao, Y., Alexander, M.M., Kane, J.M., 2008. Use of remote centralized raters via live 2-way video in a multicenter clinical trial for schizophrenia. J. Clin. Psychopharmacol. 28, 691–693.

Siddiqui, O., Hung, H.M., O'Neill, R., 2009. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. J. Biopharm. Stat. 19, 227–246.

Takeda, 2013. A multinational, randomized, double-blind, placebo-controlled, dose ranging study to assess the efficacy and safety of Lu AA21004 in patients with major depressive disorder. U.S. National Institutes of Health, In: ClinicalTrials.gov [Internet], p. NCT01255787.

Takeda Pharmaceuticals America Inc., 2014. Brintellix [package insert], Deerfield, IL.

Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M., 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am. J. Psychiatry 163, 28–40.

US National Institutes of Health (NIH), 2015. ClinicalTrials.gov Advanced Search. National Library of Medicine (US), Bethesda, MD.

Vieta, E., Pappadopulos, E., Mandel, F.S., Lombardo, I., 2011. Impact of geographical and cultural factors on clinical trials in acute mania: lessons from a ziprasidone and haloperidol placebo-controlled study. Int. J. Neuropsychopharmacol. 14, 1017–1027.

Wang, G., Gislum, M., Filippov, G., Montgomery, S., 2015. Comparison of vortioxetine versus venlafaxine XR in adults in Asia with major depressive disorder: a randomised, double-blind study. Curr. Med. Res. Opin. 31, 785–794.

Warden, D., Rush, A.J., Trivedi, M.H., Fava, M., Wisniewski, S.R., 2007. The STAR*D Project results: a comprehensive review of findings. Curr. Psychiatry Rep. 9, 449–459.

Westrich, L., Pehrson, A., Zhong, H., Nielsen, S.M., Frederiksen, K., Stensbol, T.B., Boyle, N.J., Hentzer, M., Sanchez, C., 2012. In vitro and in vivo effects for the multimodal antidepressant vortioxetine (Lu AA21004) at human and rat targets. Int. J. Psychiatry Clin. Pract. 16, 47.

Williams, J.B., 2001. Standardizing the Hamilton Depression Rating Scale: past, present, and future. Eur. Arch. Psychiatry Clin. Neurosci. 251 (Suppl. 2), Ii6-12.