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CADTH COMMON DRUG REVIEW

Clinical Review Report

VORTIOXETINE HYDROBROMIDE (TRINTELLIX)

(Lundbeck Canada Inc.)

Indication: The treatment of major depressive disorder in adults.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

ANCOVA	analysis of covariance
ASEX	Arizona Sexual Experiences Scale
BP	bodily pain
CDR	CADTH Common Drug Review
CGI-I	Clinical Global Impression – Improvement
CI	confidence interval
CrI	credible interval
CDFQ	Changes in Sexual Functioning Questionnaire
CDFQ-14	Changes in Sexual Functioning Questionnaire Short-Form
CANMAT	Canadian Network for Mood and Anxiety Treatments
C-SSRS	Columbia Suicide Severity Rating Scale
DESS	Discontinuation-Emergent Signs and Symptoms
DSST	Digit Symbol Substitution Test
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels
FAS	full analysis set
GH	general health
HAM-D	Hamilton Depression Rating Scale
HAM-D17	17-item Hamilton Depression Rating Scale
HAM-D24	24-item Hamilton Depression Rating Scale
HRQoL	health-related quality of life
ITC	indirect treatment comparison
ITT	intention-to-treat
LOCF	last observation carried forward
MADRS	Montgomery–Åsberg Depression Rating Scale
MCID	minimum clinically important difference
MCS	mental component summary
MD	mean difference
MDAO	Hope + Me-Mood Disorders Association of Ontario
MDD	major depressive disorder

MDE	major depressive event
MDSC	Mood Disorders Society of Canada
MH	mental health
MMRM	mixed-effect model for repeated measures
NICE	National Institute for Health and Clinical Excellence
NMA	network meta-analysis
OR	odds ratio
PCS	physical component summary
PDQ-D20	20-item Perceived Deficits Questionnaire
PF	physical functioning
PPS	per-protocol set
RAVLT	Rey Auditory Verbal Learning Test
RCT	randomized controlled trial
RE	role emotional
RP	role physical
SF	social functioning
SDS	Sheehan Disability Scale
SFS	Stigma-Free Society
SF-36	Short-Form (36) Health Survey
SMD	standard mean difference
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUCRA	surface under the cumulative ranking curve
UPSA	University of San Diego Performance-Based Skills Assessment
UPSA-B	University of San Diego Performance-Based Skills Assessment – Brief
VAS	visual analogue survey
VT	vitality
WAIS	Wechsler Adult Intelligence Scale
WLQ	Work Limitations Questionnaire
XR	extended release

Drug	Vortioxetine (Trintellix)
Indication	Treatment of major depressive disorder in adults
Reimbursement request	As per indication
Dosage form(s)	5 mg, 10 mg, 15 mg, and 20 mg tablets
NOC date	October 22, 2014
Manufacturer	Lundbeck Canada Inc.

Executive Summary

Introduction

Major depressive disorder (MDD) is one of the most prevalent chronic conditions in Canada, with an annual prevalence reaching 4.7% and a lifetime prevalence of 11.3% of the population.[1] The prevalence of MDD is twice as high for women compared with men, and MDD is the second-leading cause of disability worldwide.[1-2] Both impaired function in the workplace (presenteeism) and high levels of absenteeism have been shown to contribute to economic losses.[3] The clinical manifestation of MDD is heterogeneous and may include dysphoria (any or a combination of feeling sad, helpless, hopeless, irritable or angry, agitated or anxious), anhedonia (displeasure in previously enjoyed activities), a sense of worthlessness or guilt, inability to concentrate, loss of appetite, insomnia or sleep disturbances, and suicidal thoughts or ideation, as well as somatic (physical) symptoms. The duration of major depressive episodes can also vary significantly in length, ranging from weeks to even years.[3]

Vortioxetine is an antidepressant that is thought to act through the modulation of serotonin transmission in the brain. It is approved for use in Canada for the treatment of MDD in adults.[4] The recommended starting dosage is 10 mg per day for adults younger than 65 years of age, and 5 mg per day in adults 65 and older.[4] The maximum daily dose is 20 mg.[4]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of vortioxetine 5 mg, 10 mg, and 20 mg oral tablets for the treatment of MDD in adults.

Results and Interpretation

Included Studies

A total of 22 randomized controlled trials (RCTs) met the inclusion criteria for the systematic review. All trials evaluated the efficacy and safety of vortioxetine (5 mg to 20 mg daily) in adults with MDD over six to 12 weeks of therapy (21 short-term trials) or up to 64 weeks (one relapse prevention study). The trials were designed to test the difference between vortioxetine and placebo (17 RCTs), venlafaxine (one noninferiority study), or escitalopram (three RCTs). One other trial was designed to compare vortioxetine as add-on therapy to a selective serotonin reuptake inhibitor (SSRI) or vortioxetine as monotherapy, with SSRI monotherapy. Seven placebo-controlled trials also included an active-reference group (duloxetine, venlafaxine, or paroxetine).

Fourteen short-term efficacy trials assessed the impact of vortioxetine on depression symptom severity, measured as the change from baseline to week 6 or 8 for either the Montgomery–Åsberg Depression Rating Scale (MADRS) or the 24-item Hamilton Depression Rating Scale (HAM-D24). Four short-term trials examined cognitive function as the primary outcome, which was assessed using the Digit Symbol Substitution Test (DSST) or a composite of the DSST and the Rey Auditory Verbal Learning Test (RAVLT). The other studies evaluated sexual function (Study 318) and the Clinical Global Impression – Improvement scale (Liebowitz et al.) and one study did not specify the primary outcome (Levada et al.) One trial (11985A) used a withdrawal design, in which patients who had achieved remission of their MDD with 12 weeks of vortioxetine therapy were randomized to placebo or continuation of vortioxetine; time to relapse over 24 weeks was the primary outcome. The number of patients enrolled per study ranged from 40 to 766 with a median of 458 patients per study.

The patients enrolled in the studies had a mean age per treatment group that ranged from 38.8 to 50.6 years, except for Study 12541A, which enrolled patients aged 65 years and older and had a mean age of 70.6 years. The proportion of females ranged from 29% to 79% across the trial treatment groups. At baseline, the mean MADRS scores ranged from 27.8 to 34.2 points except for studies 318 and 15905A, which had lower depression severity scores (mean MADRS scores ranged from 4.7 to 8.3 in Study 318; mean 17-item Hamilton Depression Rating Scale scores ranged from 5.6 to 6.1 in Study 15905A) as these patients were receiving antidepressant therapy prior to enrolment. In the relapse prevention study (11985A), baseline MADRS scores were 32.3; however, only those in remission at the end of the 12-week, open-label vortioxetine treatment period entered the double-blind phase (MADRS score 4.7 to 4.9).

Key limitations of the reviewed studies included the short duration of most trials (up to eight weeks), possible unblinding that may have biased subjective outcomes, and the magnitude of withdrawals (i.e., greater than 19% in seven studies) or differential losses to follow-up (four studies). Data comparing vortioxetine to other antidepressants was limited and, considering the inclusion and exclusion criteria of the trials, the generalizability of the findings is applicable to a select MDD patient population.

Efficacy

Although health-related quality of life (HRQoL) and disability were identified as key efficacy outcomes of interest to patients, none of the included studies were designed or powered to test for these outcomes. Eight trials included HRQoL as a secondary or exploratory outcome, and the findings were inconsistent between trials. Placebo and active-treatment groups generally showed improvement in HRQoL scores; however, statistically significant differences were observed for vortioxetine versus placebo only in some studies, with other trials showing no differences between groups.

The change from baseline in the Sheehan Disability Scale (SDS) was reported as a secondary outcome in 13 short-term trials and the relapse prevention study. The SDS is scored from 0 to 30, with higher scores indicating more severe impairment of patients' work, family, and social life. Most studies found no statistically significant difference between the vortioxetine and control groups. Meta-analysis of disability data from 11 short-term trials showed statistically significant differences between vortioxetine 10 mg and 20 mg versus placebo with a mean difference (MD) of −1.4 (95% confidence interval [CI], −2.0 to −0.8) for the 10 mg dose, and −1.8 points (95% CI, −2.8 to −0.9) for the 20 mg dose. Vortioxetine 5 mg and 15 mg doses did not show statistically significant differences compared with

placebo in the pooled analysis. However, the clinical importance of these findings is unclear given the uncertain validity of the SDS and the lack of a minimum clinically important difference (MCID).

With regard to depression symptom severity, six of the 13 short-term placebo-controlled trials did not demonstrate statistically significant differences between vortioxetine and placebo in the primary outcome of depression symptom severity (change from baseline to end of treatment in MADRS or HAM-D24 scores), four studies showed statistically significant differences between vortioxetine and placebo, and in three trials statistically significant differences were observed for the highest dose of vortioxetine tested (20 mg or 10 mg per day), but not for the lower vortioxetine doses included in those studies. Pooled data on the change from baseline in the MADRS or HAM-D24 total score showed vortioxetine (5 mg, 10 mg, and 20 mg) were statistically significantly different than placebo (Table 1). The differences favouring vortioxetine were generally small (the pooled primary outcome standardized mean difference [SMD] was −0.24 to −0.40) but exceeded the MCID of 2 for the MADRS score (MD −2.4 to −3.7), with substantial between-study heterogeneity (I^2 > 50%). Although the CADTH meta-analysis of all short-term efficacy trials showed statistically significant differences for most vortioxetine doses compared with placebo, the generally small differences observed and the variable treatment effects across studies make the clinical significance of the differences unclear. As well, the variability in treatment effects and heterogeneity across studies reduced confidence in the findings. The meta-analysis of secondary outcomes, response, and remission showed results similar to those of the primary outcome, with some vortioxetine doses showing statistically significant differences versus placebo, but with substantial between-study heterogeneity (Table 1).

Seven of the short-term efficacy studies included an active control group, although only one trial (13926A) was powered to compare active treatments (venlafaxine versus vortioxetine) for changes in depressive symptom severity. Compared with placebo, the SMD in the change from baseline in MADRS or HAM-D24 scores was −0.53 and −0.63 for duloxetine and venlafaxine, respectively; whereas the pooled data for vortioxetine versus placebo showed an SMD from −0.24 to −0.40. When data were pooled from the duloxetine-controlled studies, statistically significant differences were observed favouring duloxetine over vortioxetine 5 mg, 15 mg, and 20 mg doses for the primary outcome (change from baseline in MADRS or HAM-D24). In the meta-analysis, the SMDs for vortioxetine versus duloxetine were 0.17 (95% CI, 0.03 to 0.32) for vortioxetine 5 mg, 0.37 (95% CI, 0.18 to 0.55) for vortioxetine 15 mg, and 0.21 (95% CI, 0.03 to 0.39) for vortioxetine 20 mg. No statistically significant differences were found for vortioxetine 10 mg versus duloxetine (one study). Study 13926A found vortioxetine to be noninferior to venlafaxine as the upper bounds of the 95% CIs did not exceed the noninferiority margin of +2.5 points on the MADRS scale (MD −1.2; 95% CI, −3.03 to 0.63 for the full analysis set, and 0.19; 95% CI, −1.61 to 1.99 for the per-protocol set). This noninferiority margin may be overly large, considering that the MCID of the MADRS is estimated at 2 points, and pooled data from a number of antidepressant trials[5] showed a MD of 2 points between active treatments and placebo. This trial was also limited by the extent of withdrawals, which were also imbalanced between groups (vortioxetine 18% and venlafaxine 27%), and the use of the last observation carried forward approach to impute missing outcome data. While the available head-to-head data are suggestive of a smaller treatment effect for vortioxetine relative to venlafaxine and duloxetine, definitive conclusions cannot be made.[6] The CADTH pooled analysis suggests that vortioxetine may be less effective than duloxetine in reducing depression symptom severity; however, the observed differences were small and of unclear clinical significance.

Although the effect of vortioxetine on cognitive function tests was measured in six studies, the findings were heterogeneous and the impact of vortioxetine on cognition was unclear. Cognitive functioning was measured using the DSST, and a composite z score of the change in DSST and RAVLT. The DSST is a timed task requiring patients to match geometric symbols to corresponding numbers as designated by an answer key. It is unclear how a change in DSST scores relates to how patients function at home or at work. While the composite z score of the DSST and RAVLT covers a broader range of cognitive functions, the validity and clinical importance of a change in score in this composite measure is not known. Study 14122A reported statistically significant improvement in the composite z score of the DSST and RAVLT for patients receiving vortioxetine compared to patients receiving placebo (Table 2). However, three other studies (15905A, 15906A, and 15907A) found no statistically significant differences between vortioxetine and control groups (SSRI, escitalopram, or placebo) in change from baseline in the DSST (the primary outcome in these studies). Three trials (15905A, 15906A, and 15907A) measured the change from baseline in the University of San Diego Performance-Based Skills Assessment – Brief (UPSA-B), and no statistically significant difference was found between vortioxetine and control groups (SSRI, escitalopram, or placebo). While UPSA-B includes financial and communication skills and was developed to assess everyday living skills, the clinical expert consulted for this review stated that such skills are better aligned with impairments observed in people with serious mental illness (such as schizophrenia) rather than in outpatients with depression.

Among patients who responded to treatment with vortioxetine during a 12-week open-label period in the relapse prevention study (11985A), those who were randomized to vortioxetine were statistically significantly less likely to experience a relapse compared to those who received placebo over the course of a 24-week double-blind period (Table 2). Although there was a risk of patient and investigator unblinding after randomization (due to the occurrence of withdrawal symptoms or rebound depression symptoms), the findings were similar among sensitivity analyses that excluded early relapses and used different definitions of relapse.

In addition to the evidence provided by the pivotal and other RCTs included in the systematic review, there is evidence from six extension studies (Appendix 7), five non-randomized studies (Appendix 8) and five indirect treatment comparisons (ITCs) (Appendix 9). While the extension data and non-randomized studies provide some evidence on the effects of longer-term use of vortioxetine, or report outcomes such as hospitalizations that were not assessed in clinical trials, the potential selection bias, lack of control groups, or lack of blinding, limit the utility of these studies. One published ITC (Cipriani et al.) and one manufacturer-submitted analysis provided evidence used to inform the pharmacoeconomic analysis.[7,8] Cipriani et al.[8] based their analysis on evidence drawn from 522 double-blind, short-term RCTs that evaluated treatment response and acceptability of 21 antidepressant drugs. In this analysis, all approved dosages of antidepressants were pooled, whereas in the manufacturer-submitted analysis, dosage data from Cipriani et al. were divided and analyzed separately as high- and low-dosage groups, based on the WHO defined daily dose. Vortioxetine was found to be more efficacious than placebo in achieving a response of least at 50% reduction in the total score on a standardized observer-rating scale for depression (odds ratio [OR] 1.66; 95% credible interval [CrI], 1.45 to 1.92). Vortioxetine was also deemed to be as acceptable as placebo (OR 1.01; 95% CrI, 0.86 to 1.19), based on the proportion of patients who withdrew from the study for any reason. A primary analysis that included placebo and active-controlled trials found the response rate and acceptability of vortioxetine were similar to those of other antidepressants. Data from the manufacturer-

submitted analysis by dose showed similar results. These ITCs support a general finding that most drugs used for the acute treatment of MDD have a similar efficacy and all are more efficacious than placebo.

Harms

The overall frequency of adverse events was higher among those receiving vortioxetine than placebo; nausea was the most common adverse event in the vortioxetine groups. Withdrawals due to adverse events were also reported more frequently among for those on the higher doses of vortioxetine (15 mg and 20 mg) compared with placebo. The incidence of serious adverse events, including suicidal behaviour and serotonin syndrome, was low and similar between groups, although the studies were not powered to detect differences in rare adverse events. Moreover, the duration of most studies was limited to 6 to 8 weeks. Data from open-label extension studies did not reveal any new safety signals, but these studies lacked a control group and thus cannot provide information of comparative safety.

With regards to sexual function, vortioxetine was found to statistically significantly improve treatment-related sexual dysfunction based on the change from baseline to week 8 in the 14-item Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) scores, compared with escitalopram, among patients with SSRI-related sexual dysfunction at baseline. Both groups showed improvement in their CSFQ-14 scores and although the between-group differences favoured vortioxetine, the clinical significance of the change score is unknown (Table 2). It is unclear how changes on the CSFQ-14 scores correlate to changes in day-to-day patient functioning. Moreover, no statistically significant differences were detected between treatments in the odds of achieving normal sexual functioning based on the established thresholds on the CSFQ-14 for normal sexual functioning. Treatment-emergent sexual dysfunction was reported more frequently among those receiving vortioxetine 10 mg to 20 mg per day, compared with placebo or vortioxetine 5 mg, based on data from the Arizona Sexual Experiences Scale instrument. Self-reported sexual dysfunction was low and likely under-reported.

No substantial increases in body weight were observed in the short-term studies, and in the longer-term relapse prevention trial, the proportion of patients with clinically important weight gain was similar between vortioxetine and placebo. Abrupt cessation of vortioxetine was associated with an increased incidence of adverse events, including headaches, sudden outbursts of anger, mood swings, increased dreaming or nightmares, muscle tension or stiffness, dizziness, confusion or trouble concentrating, insomnia, and runny nose. The product monograph recommends a gradual reduction in dose rather than abrupt cessation of therapy.[4]

The ITC by Cipriani et al.[8] found no difference in the odds of stopping therapy for vortioxetine versus other antidepressants or placebo. However, patients who received vortioxetine were more likely to stop treatment due to adverse events compared with placebo (OR 1.64; 95% CI, 1.25 to 2.14).[8]

Patients report that the adverse effects of antidepressants are often difficult to manage, and they affect patients' abilities to remain on therapy. The network meta-analysis did not examine specific adverse events; therefore, no comment can be made on the relative incidence of adverse events such as nausea, sexual dysfunction, or suicide ideation and behaviour. Additional longer-term safety data are needed to determine the comparative safety of vortioxetine.

Potential Place in Therapy[a]

The first-line agents recommended for the treatment of MDD include several SSRIs, a few serotonin-norepinephrine reuptake inhibitors, bupropion, mirtazapine, and vortioxetine.[9] Medications with different mechanisms of action show different treatment effects and safety profiles. According to the clinical expert, approximately 30% of patients experience a remission of a major depressive episode with the first selected antidepressant medication.[10] This means that most people following a single trial of an antidepressant medication will either be nonresponsive, or partly responsive with remaining symptoms. Vortioxetine is a potentially useful treatment with a core SSRI action and a variety of additional serotonergic receptor effects. It can be prescribed in inpatient, outpatient, community, specialty clinic, and family-practice clinic settings. Vortioxetine is likely to be used as a first-line antidepressant agent. It is unclear whether satisfactory data are available for the use of vortioxetine as a second- or third-line agent.

Clinically meaningful outcomes when assessing treatment effect of an antidepressant include reduction in the number, frequency, and severity of depression symptoms, improvement in quality of life, and return to baseline functioning in a variety of domains (e.g., work, school, interpersonal, and recreational). In the maintenance phase, prevention of relapse or recurrence of depressive episodes is the key outcome. Ideally, during acute outpatient treatment, treatment response will be assessed frequently (e.g., every one to two weeks), and periodically during maintenance treatment. There is a general alignment between clinical practice and clinical trials in the way response to treatment is determined, in that both practice and trials rely on questions to determine how much change has occurred in key depression symptoms. However, in clinical practice, symptomatic change is usually evaluated somewhat informally without reliance on standardized rating scales, and standardized scales are not consistently adopted for mental health outcome assessment.

Treatment with vortioxetine may be discontinued due to adverse events or lack of effectiveness, or when the pre-scheduled recommended maintenance treatment interval is complete.

Conclusions

Twenty short-term, double-blind RCTs, one short-term, open-label RCT, and one double-blind, randomized withdrawal study provided evidence on the efficacy and safety of vortioxetine 5 mg to 20 mg daily compared with placebo, venlafaxine, or escitalopram.

Overall, vortioxetine showed statistically significant differences over placebo in reducing depression symptom severity after six to eight weeks of therapy. However, treatment effects varied substantially across trials, with approximately half of the short-term efficacy trials reporting no statistically significant differences between vortioxetine and placebo for the primary outcome (MADRS or HAM-D24 scales). Vortioxetine was noninferior to venlafaxine in one trial for the change from baseline to week 8 in the MADRS score, but pairwise meta-analysis suggests vortioxetine may be less effective than duloxetine in reducing depression symptom severity in the short-term. The differences between duloxetine and vortioxetine were small and the clinical significance was unclear.

[a] This information is based on information provided in draft form by the clinical expert consulted by CADTH for the purpose of this review.

Vortioxetine may be more effective in preventing relapse than placebo based on data from one trial. No conclusions can be drawn on the impact of vortioxetine on HRQoL, disability, and cognitive function, or in reducing SSRI-related sexual dysfunction due to methodological issues or questions regarding the clinical relevance of the outcome measures utilized.

Serious adverse events, including suicidal behaviour, were reported infrequently in all treatment groups, although the studies were not powered to detect differences in rare adverse events, and treatment duration was eight weeks or less for most RCTs. Withdrawals due to adverse events occurred more frequently in the higher-dose vortioxetine groups compared to the placebo groups. No new safety signals were identified in the longer-term, open-label extension studies.

Indirect evidence suggests that the drugs used for the acute treatment of MDD, including vortioxetine, other second-generation antidepressants, tricyclic antidepressants, and trazodone, have similar efficacy and acceptability (in terms of treatment response and withdrawal frequency) compared with each other, and all are more effective than placebo.

The available evidence was limited by the short duration of the trials (six to eight weeks), possible unblinding that may have biased subjective outcomes, and concerns with the generalizability of the findings. Direct evidence comparing vortioxetine with other antidepressants available in Canada was limited.

Table 1: Summary of Meta-Analysis of Placebo-Controlled Short-Term Trials

Outcome	Comparison versus placebo						
	VOR 5 mg	VOR 10 mg	VOR 15 mg	VOR 20 mg	DUL 60 mg	PAR 10 mg	VEN 225 mg
Primary depression scale (MADRS or HAM-D24)							
N trials	8	8	3	5	5	NA	1
SMD (95% CI)	**−0.24 (−0.38 to −0.10)**	**−0.27 (−0.40 to −0.13)**	−0.28 (−0.65 to 0.08)	**−0.40 (−0.61 to −0.19)**	**−0.53 (−0.83 to −0.24)**		**−0.63 (−0.90 to −0.36)**
I^2	66	58	84	75	86		0
Response							
N trials	8	10	3	6	5	1	1
RD (95% CI)	**12% (6 to 18)**	**14% (9 to 19)**	11% (−2 to 25)	**17% (9 to 25)**	**23% (12 to 34)**	**32% (15 to 48)**	**28% (15 to 40)**
I^2	57	45	77	73	81	0	0
Remission							
N trials	8	10	3	6	5	1	1
RD (95% CI)	6% (−0 to 11)	**9% (6 to 12)**	6% (−4 to 16)	**11% (5 to 17)**	**14% (1 to 27)**	**21% (6 to 35)**	**29% (16 to 41)**
I^2	**61**	**13**	**67**	**62**	**87**	**0**	**0**
Adverse events							
N trials	8	10	3	6	5	1	1
RD (95% CI)	**5.2% (1.5 to 9.0)**	**7.0% (3.5 to 10.5)**	**6.0% (0.1 to 11.9)**	**10.5% (6.3 to 14.7)**	**15.2% (10.7 to 19.7)**	5.0% (−13.9 to 4.1)	**15.0% (3.0 to 27.4)**
I^2	0	12	0	0	7	0	0
SAEs							
RD (95% CI)	0.0% (−0.8 to 0.9)	0.1% (−0.7 to 0.8)	0.1% (−0.9 to 1.0)	0.3% (−0.4 to 1.0)	−0.0% (−1.1 to 1.0)	1.6% (−4.8 to 8.1)	0.9% (−1.6 to 3.4)
I^2	0	0	0	0	12	0	0
WDAEs							
RD (95% CI)	−0.0% (−1.5 to 1.1)	**1.5% (0.1 to 3.0)**	**4.0% (0.9 to 7.0)**	**2.7% (0.9 to 4.5)**	**3.6% (1.1 to 6.1)**	3.5% (−3.9 to 10.8)	**10.3% (3.0 to 17.7)**
I^2	0	0	0	4	0	0	0

CI = confidence interval; DUL = duloxetine; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; NA = not applicable; PAR = paroxetine; RD = risk difference; SAE = serious adverse events; SMD = standardized mean difference; VEN = venlafaxine extended release; VOR = vortioxetine; WDAE = withdrawal due to adverse events.

Note: Comparisons in bold had a 95% CI that excluded the null.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Clinical Study Report.[11-30]

Table 2: Summary of Other Primary End Points

Study	Outcome	Treatment group	Total N	End of treatment results	Treatment difference
Cognitive function				**Mean change from baseline to week 8, (SE)**	**MD (95% CI) VOR versus control[a]**
14122A	Composite z score for DSST and RAVLT	PBO	194	−0.235 (0.053)	Reference
		VOR 10 mg	193	0.128 (0.052)	0.36 (0.22 to 0.50)
		VOR 20 mg	204	0.095 (0.051)	0.33 (0.19 to 0.47)
Relapse				**Relapse at 24 weeks, n (%)**	**HR (95% CI) PBO versus VOR[b]**
11985A	Time to relapse	PBO	192	50 (26)	2.01 (1.26 to 3.21)
		VOR 5 mg or 10 mg	204	27 (13)	Reference
Sexual functioning				**LS mean change from baseline to week 8, (SE)**	**MD (95% CI) VOR versus control[c]**
318	CSFQ-14	ESC 10 mg or 20 mg	207	6.6 (0.6)	Reference
		VOR 10 mg or 20 mg	217	8.8 (0.6)	2.2 (0.48 to 4.02)

CI = confidence interval; CSFQ-14 = Changes in Sexual Functioning Questionnaire Short-Form; DSST = Digit Symbol Substitution Test; ESC = escitalopram; FAS = full analysis set; HR = hazard ratio; LS = least squares; MD = mean difference; MMRM = mixed-effect model for repeated measures; PBO = placebo; RAVLT = Rey Auditory Visual Learning Test; SE = standard error; VOR = vortioxetine.

[a] Change from baseline to week 8 in the composite z score (comprising the DSST, RAVLT acquisition, and RAVLT delayed recall). Based on the FAS, using the MMRM controlling for grouped site, baseline composite z score, and interaction terms (baseline composite z score by visit; treatment by visit).

[b] During the first 24 weeks of the double-blind period (i.e., after the 12-week open-label period). Based on Cox proportional hazards model.

[c] Change from baseline to week 8. Analysis was based on the FAS and MMRM controlling for site, week, treatment, baseline score by week, and week by treatment.

Source: Clinical Study Report.[16,22,24]

Introduction

Disease Prevalence and Incidence

Major depressive disorder (MDD) is characterized by the occurrence of one or more major depressive episodes (MDEs) that persist for at least two weeks and are characterized by a depressed mood (most of the day, nearly every day) and/or markedly diminished interest or pleasure in all, or almost all, activities (most of the day, nearly every day).[3] During the same two-week period, the presence of a minimum of five criterion symptoms (inclusive of depressed mood and/or loss of interests) are required for a diagnosis of MDD. The clinical manifestation of MDD is heterogeneous and may include dysphoria (any or a combination of feeling sad, helpless, hopeless, irritable or angry, agitated or anxious), anhedonia (displeasure in previously enjoyed activities), a sense of worthlessness or guilt, inability to concentrate, loss of appetite, insomnia or sleep disturbances, suicidal thoughts or ideation, as well as somatic (physical) symptoms. The duration of MDEs can also vary significantly in length, ranging from weeks to even years.[3]

MDD is one of the most prevalent chronic conditions in Canada, with an annual prevalence reaching 4.7% and a lifetime prevalence of 11.3% of the population.[1] The prevalence of MDD is twice as high for women versus men, but this difference declines with age.[1] According to the Global Burden of Disease study, MDD is the second-leading cause of disability worldwide.[2] Both impaired function in the workplace (presenteeism) and high levels of absenteeism have been shown to contribute to economic losses.[3]

Standards of Therapy

The goals of the acute phase of treatment in patients with MDD (8 to 12 weeks) are the resolution of symptoms (remission), improvement in health-related quality of life (HRQoL), and restoration of psychosocial and occupational functioning.[3] The goals of the maintenance phase, which typically lasts six to 24 months (though it may be longer), are to prevent recurrence of depressive episodes, return to full functioning, and restore HRQoL.[3] Psychoeducation, self-management, and psychological treatments (e.g., cognitive-behavioural therapy and interpersonal therapy) are recommended as first-line therapies for patients with mild depression.[9] For patients with moderate or severe depression, pharmacotherapy with most second-generation antidepressants is recommended as first-line therapy. First-line treatments available in Canada include: selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline); serotonin-norepinephrine reuptake inhibitors (SNRIs) (desvenlafaxine, duloxetine, and venlafaxine); a noradrenaline-dopamine reuptake inhibitor (bupropion); an alpha-2-adrenergic agonist or 5-HT2 antagonist (mirtazapine); and vortioxetine.[9] Second-line drugs include a reversible inhibitor of monoamine oxidase-A (moclobemide) and tricyclic antidepressants (e.g., amitriptyline, levomilnacipran, trazodone, vilazodone, and quetiapine).[9]

Drug

Vortioxetine is an antidepressant that is thought to act through the modulation of serotonin neurotransmission in the central nervous system, including the inhibition of serotonin reuptake (5-HT) at the 5-HT transporter (5-HTT) and activity at several 5-HT receptors including 5-HT1A receptor agonism, 5-HT1B receptor partial agonism, and 5-HT3, 5-HT1D,

and 5-HT7 receptor antagonism.[4] It is approved for use in Canada for the treatment of MDD in adults.[4] The recommended starting dosage is 10 mg per day for adults younger than 65 years of age, and 5 mg per day for adults 65 and older.[4] The maximum daily dose is 20 mg.[4] It is available as 5 mg, 10 mg, and 20 mg oral tablets.

Table 3: Characteristics of Key Drugs for Major Depressive Disorder in Canada

Drug Class	Vortioxetine	SSRIs	SNRIs	NDRIs
Mechanism	Serotonin modulator: Serotonin reuptake inhibition (5-HT) at the 5-HT transporter (5-HTT) and activity at several 5-HT receptors including 5-HT1A receptor agonism, 5-HT1B receptor partial agonism, and 5-HT3, 5-HT1D, and 5-HT7 receptor antagonism	Serotonin reuptake inhibition	Serotonin-norepinephrine reuptake inhibition	Norepinephrine-dopamine reuptake inhibition
Drug, usual oral dose	Adult (< 65 years): starting dosage 10 mg once daily, range 5 mg to 20 mg Geriatric (> 65 years): Starting dosage 5 mg, range 5 mg to 10 mg	Citalopram 20 to 40 mg Escitalopram 10 to 20 mg Fluoxetine 20 to 60 mg Fluvoxamine 100 to 300 mg Paroxetine 20 to 50 mg (25 to 62.5 mg CR) Sertraline 50 to 200 mg	Desvenlafaxine 50 to 100 mg Duloxetine 60 mg Venlafaxine XR 75 to 225 mg	Bupropion 150 to 300 mg XR
Safety issues	Nausea, constipation, vomiting, sexual dysfunction, serotonin syndrome	Nausea, dry mouth, sweating, insomnia, anorexia, tremor, somnolence, headache, dizziness, diarrhea, constipation, sexual dysfunction, serotonin syndrome	Nausea, insomnia, somnolence, headache, dizziness, nervousness, diarrhea, dry mouth, constipation, sexual dysfunction, sweating, anorexia, serotonin syndrome	Nausea, dry mouth, headache, insomnia
Other	Drug interactions with agents metabolized by certain cytochrome P450 isoenzymes, MAOIs	Drug interactions with agents metabolized by certain cytochrome P450 isoenzymes, MAOIs	Drug interactions with agents metabolized by certain cytochrome P450 isoenzymes, MAOIs	Contraindicated in anorexia, bulimia, or seizure disorders.

CR = controlled release; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; NDRI = noradrenaline-dopamine reuptake inhibitor; XR = extended release.

Source: Trintellix product monograph,[4] Canadian Network for Mood and Anxiety Treatments guidelines.[9]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of vortioxetine 5 mg, 10 mg, 15 mg, and 20 mg orally for the treatment of MDD in adults.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CADTH Common Drug Review (CDR) and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adults with MDD
Intervention	Vortioxetine at the Health Canada–recommended dosage of 5 mg to 20 mg daily[a]
Comparators	Antidepressant(s) to treat MDD (e.g., SNRIs, SSRIs, NRIs, NDRIs, TCAs, MAOIs, mirtazapine, trazodone, vilazodone)[a] Placebo[a]
Outcomes	**Efficacy outcomes:** HRQoL (e.g., SF-36, EQ-5D)[b] Function/disability (e.g., SDS)[b] Remission Response Hospitalizations or emergency room visits for depression Symptom severity score rated by patients (e.g., BDI, PHQ-9, IDS-SR)[b] Symptom severity score rated by physician (e.g., HAM-D24, MADRS) Relapse Withdrawals or discontinuation of treatment (all-cause or due to lack of efficacy) **Harms outcomes:** Mortality (all-cause and suicide) Suicidality (ideation or attempts) Serious adverse events Withdrawals or discontinuation of treatment due to adverse events Adverse events Notable adverse events: weight gain,[b] sexual dysfunction,[b] withdrawal symptoms, serotonin syndrome
Study design	Published and unpublished phase III and IV RCTs

BDI = Beck Depression Inventory; EQ-5D = EuroQol 5-Dimensions questionnaire; HAM-D24 = 24-item Hamilton Depression Rating Scale; HRQoL = health-related quality of life; IDS-SR = Inventory of Depressive Symptomatology – Self-Reported; MADRS = Montgomery–Åsberg Depression Rating Scale; MAOIs = monoamine oxidase inhibitors; MDD = major depressive disorder; NDRIs = norepinephrine-dopamine reuptake inhibitors; NRIs = norepinephrine reuptake inhibitors; PHQ-9 = Patient Health Questionnaire; RCT = randomized controlled trial; SDS = Sheehan Disability Scale; SF-36 = Short-Form (36) Health Survey; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs= selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

[a] May be used in combination with psychotherapy (e.g., cognitive-behavioural therapy, mindfulness, or interpersonal therapy).

[b] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press).[31] Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH

(Medical Subject Headings), and keywords. The main search concepts were Trintellix (vortioxetine). Clinical trial registries searched included the US National Institutes of Health's clinicaltrials.gov and the WHO International Clinical Trials Registry Search Portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for detailed search strategies.

The initial search was completed on May 30, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on September 18, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters),[32] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

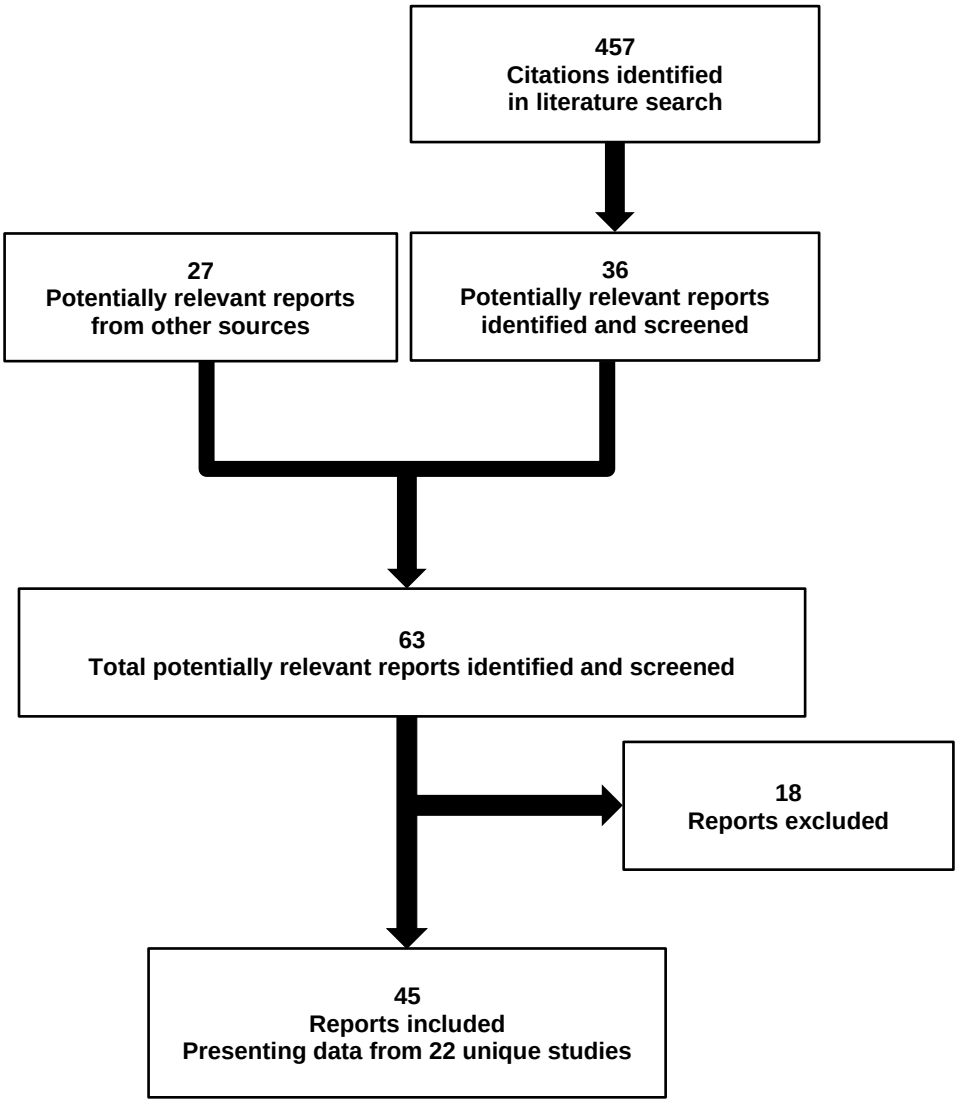
A meta-analysis using Comprehensive Meta-Analysis software (version 2) was conducted for the trials that included similar patient populations, outcome definitions, and follow-up time. Each dose of vortioxetine was pooled separately.

Results

Findings from the Literature

Twenty-two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



Literature Search Update January 10, 2020: Three potential reports were identified in the literature search updates. This included the study by Inoue et al.,[33] which is the published report for study CCT-004, and two other potentially relevant RCTs (Wang et al.[34] and Tovilla-Zárate et al.[35]). Data from these reports have not been included in this formulary review.

Table 5: Details of Included Studies

		305	303	316	317	CCT-002	CCT-003
Designs and Populations	**Study design**	DB RCT phase III pivotal	DB RCT phase III pivotal	DB RCT phase III pivotal	DB RCT phase III pivotal	DB RCT phase II/III pivotal	DB RCT phase III
	Locations	Europe, South Africa, Asia, Australia	US	US	US	Europe, Asia	Japan
	Randomized (N)	560	600	462	469	600	366
	Inclusion criteria	• MDD (DSM-IV-TR criteria) • Current MDE ≥ 3-month duration • MADRS total score ≥ 26 (except 303) • Age ≥ 18 and ≤ 75 years (except CCT-002 and CCT-003)					
		--	MADRS total score ≥ 30	• Recurrent MDD • CGI-S score ≥ 4	• Recurrent MDD • CGI-S score ≥ 4	• Age ≥ 20 and ≤ 64 years • CGI-S score ≥ 4	• Age ≥ 20 and ≤ 75 years • CGI-S score ≥ 4
	Exclusion criteria	• Current psychiatric disorder other than MDD • History of manic or hypomanic episode, schizophrenia, any other psychotic, mental or neurological disorder (other than MDD) • Current substance abuse • Significant risk of suicide, attempted suicide in past 6 months, or score ≥ 5 on MADRS item 10 (suicidal thoughts) • Treatment-resistant depression (defined as non-response to 2 adequate antidepressant treatments of at least 6-week duration) • Currently receiving cognitive or behavioural therapy or systematic psychotherapy					
Drugs	**Intervention** (daily dose)	VOR 1 mg VOR 5 mg VOR 10 mg	VOR 5 mg	VOR 10 mg VOR 20 mg	VOR 10 mg VOR 15 mg	VOR 5 mg VOR 10 mg VOR 20 mg	VOR 5 mg VOR 10 mg
	Comparator(s)	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Duration	**Phase**						
	DB	8 weeks	6 weeks	8 weeks	8 weeks	8 weeks	8 weeks
	Discontinuation	--	2 weeks (no treatment)	2 weeks (SB)[a]	--	2 weeks (SB)[a]	2 weeks (SB)[a]
	Follow-up[b]	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks

		305	303	316	317	CCT-002	CCT-003
Outcomes	**Primary end point**	Change from baseline to week 8 in HAM-D24	Change from baseline to week 6 in HAM-D24, and at each week of treatment	Change from baseline to weeks 8 in MADRS	Change from baseline to week 8 in MADRS	Change from baseline to week 8 in MADRS	Change from baseline to week 8 in MADRS
	Other end points	• Response • Remission • MADRS • SF-36 • SDS • Harms • C-SSRS	• Response • Remission • MADRS • SF-36 • SDS • Harms • C-SSRS	• Response • Remission • SDS • Harms • DESS • ASEX • C-SSRS	• Response • Remission • SDS • Harms • ASEX • C-SSRS	• Response • Remission • SDS • Harms • DESS • C-SSRS	• Response • Remission • HAM-D17 • SDS • Harms • DESS • C-SSRS
	Publications	Henigsberg et al. (2012)[36]	Jain et al. (2013)[37]	Jacobsen et al. (2015)[38]	Mahableshwarkar et al. (2015)[39]	Nishimura et al. (2018)[40]	Inoue et al. (2018)[41]

ASEX = Arizona Sexual Experiences Scale; DB = double blind; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia Suicide Severity Rating Scale;
DB = double-blind; DESS = Discontinuation-Emergent Signs and Symptoms checklist; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Scale; MDD = major depressive disorder; MDE = major depressive episode; RCT = randomized controlled trial; SB = single-blind; SDS = Sheehan Disability Scale; SF-36 = Short-Form (36) Health Survey;
VOR = vortioxetine.

Note: Four additional reports were included (FDA Medical and Statistical Reports, Health Canada Reviewer's Report, CADTH Common Drug Review submission).[6,7,57,58]

[a] Patients in the placebo and vortioxetine groups received placebo.

[b] The follow-up period includes the one or two weeks during the drug discontinuation period.

Source: Clinical Study Report,[11-30] Henigsberg et al., (2017)[36] Jain et al. (2013),[37] Baldwin et al. (2012),[42] Mahableshwarkar et al. (2015),[39] Mahableshwarkar et al. (2013),[43] Mahableshwarkar et al. (2015),[44] Boulenger et al. (2014)[45], Katona et al. (2012),[46] Alvarez et al. (2012),[47] Wang et al. (2015),[48] McIntyre et al. (2014),[49] Boulenger et al. (2012),[50] Jacobsen et al. (2015),[51] Baune et al. (2018),[52] Nierenberg et al. (2019),[53] Vieta et al. (2018),[54] Levada et al. (2019),[55] Liebowitz et al. (2017),[56] Inoue et al. (2018),[41] Jacobsen et al. (2015),[38] and Nishimura et al. (2018).[40]

Table 5: Details of Included Studies (continued)

		11984A	304	13267A	315	12541A	11492A	13926A
Designs and Populations	**Study design**	DB RCT phase III pivotal	DB RCT phase III pivotal	DB RCT phase III pivotal	DB RCT phase III pivotal	DB RCT phase III pivotal	DB RCT phase II pivotal	DB RCT phase III noninferiority
	Locations	Europe, Asia, Canada, Australia	US	Europe, South Africa	US	Europe, Canada, US	Europe, Asia, Canada, Australia	Asia
	Randomized (N)	766	611	608	614	453	429	437
	Inclusion criteria	• MDD (DSM-IV-TR criteria) • Current MDE ≥ 3-month duration (exception 12541A) • MADRS total score ≥ 26 (exception 304, 11492A) • Age ≥ 18 and ≤ 75 years (except 12541A, 11492A, and 13926A)						
			MADRS total score ≥ 22	• Recurrent MDD • CGI-S score ≥ 4	• Recurrent MDD • CGI-S score ≥ 4	• Elderly ≥ 65 years of age • MDE ≥ 4 weeks in duration • At least 1 MDE before age of 60 years	• Age ≥ 18 and ≤ 65 years • MADRS total score ≥ 30 • Current MDE < 12 months	• Recurrent MDD • Age ≥ 18 and ≤ 65 years • CGI-S score ≥ 4
	Exclusion criteria	• Current psychiatric disorder other than MDD • History of manic or hypomanic episode, schizophrenia, any other psychotic, mental or neurological disorder (other than MDD) • Current substance abuse • Significant risk of suicide, attempted suicide in past 6 months, or score ≥ 5 on MADRS item 10 (suicidal thoughts) • Treatment-resistant depression (defined as non-response to 2 adequate antidepressant treatments of at least 6-week duration) • History of lack of response to duloxetine (11984A, 13267A, 304, 315, 12541A) or venlafaxine (11492A, 13926A) • Currently receiving cognitive or behavioural therapy or systematic psychiatry						
		--	--	--	--	• AMI in past 6 months • Mini-Mental State Exam < 24	--	--
Drugs	**Intervention**	VOR 2.5 mg VOR 5 mg VOR 10 mg	VOR 2.5 mg VOR 5 mg	VOR 15 mg VOR 20 mg	VOR 15 mg VOR 20 mg	VOR 5 mg	VOR 5 mg VOR 10 mg	VOR 10 mg
	Comparator(s)	Placebo DUL 60 mg	Placebo DUL 60 mg	Placebo DUL 60 mg	Placebo DUL 60 mg	Placebo DUL 60 mg	Placebo	VEN 150 mg

		11984A	304	13267A	315	12541A	11492A	13926A
							VEN 225 mg	
DURATION	**Phase**							
	DB	8 weeks	8 weeks	8 weeks	8 weeks	8 weeks	6 weeks	8 weeks
	Discontinuation	1 week (DB)[a]	1 week (DB)[a]	2 weeks (DB)[a]	2 weeks (DB)[a]	1 week (DB)[a]	2 weeks (DB)[b]	1 week (DB)[c]
	Follow-up[d]	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks
OUTCOMES	**Primary end point**	Change from baseline to week 8 in MADRS	Change from baseline to week 8 in HAM-D24	Change from baseline to week 8 in MADRS	Change from baseline to week 8 in MADRS	Change from baseline to week 8 in HAM-D24	Change from baseline to week 6 in MADRS	Change from baseline to week 8 in MADRS
	Other end points	• Response • Remission • HAM-D24 • SDS • SF-36 • Harms • ASEX	• Response • Remission • SDS • MADRS • Harms • C-SSRS • ASEX	• Response • Remission • SDS • Q-LES-Q SF • Harms • C-SSRS • ASEX • DESS	• Response • Remission • SDS • Harms • C-SSRS • ASEX • DESS	• Cognitive function (RAVLT, DSST) • MADRS • Response • Remission • Harms • C-SSRS	• Response • Remission • HAM-D24 • SF-36 • Harms	• Response • Remission • SDS • Q-LES-Q SF • Harms •
	Publications	Baldwin et al. (2012)[42]	Mahableshwarkar et al. (2013)[43]	Boulenger et al. 2014[45]	Mahableshwarkar et al. (2015)[44]	Katona et al. (2012)[46]	Alvarez et al. (2012)[47]	Wang et al. (2015)[48]

AMI = acute myocardial infarction; ASEX = Arizona Sexual Experiences Scale; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia Suicide Severity Rating Scale; DB = double-blind; DESS = Discontinuation-Emergent Signs and Symptoms checklist; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DUL = duloxetine; DSST = Digit Symbol Substitution Test; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Scale; MDD = major depressive disorder; MDE = major depressive episode; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; RAVLT = Rey Auditory Verbal Learning Test; RCT = randomized controlled trial; SB = single-blind; SDS = Sheehan Disability Scale; SF-36 = Short-Form (36) Health Survey; VEN = venlafaxine extended release; VOR = vortioxetine.

Note: Four additional reports were included (FDA Medical and Statistical Reports, Health Canada Reviewer's Report, CADTH Common Drug Review submission).[6,7,57,58]

[a] Patients in the DUL group received DUL 30 mg per day; placebo and vortioxetine groups received placebo for one week. In trials with a two-week discontinuation period, all groups received placebo for the second week.

[b] The VOR 5 mg per day group switched to placebo; the VOR 10 mg per day group switched to 5 mg per day VOR for one week, then placebo for one week; the VEN group received 150 mg per day for one week then 75 mg per day for one week; the placebo group received placebo for two weeks.

[c] Patients in the VEN group received 75 mg per day for one week and those in the VOR group received placebo.

[d] The follow-up period includes the one or two weeks during the drug discontinuation period.

Source: Clinical Study Report,[11-30] Henigsberg et al., (2017)[36] Jain et al. (2013),[37] Baldwin et al. (2012),[42] Mahableshwarkar et al. (2015),[39] Mahableshwarkar et al. (2013),[43] Mahableshwarkar et al. (2015),[44] Boulenger et al. (2014)[45], Katona et al. (2012),[46] Alvarez et al. (2012),[47] Wang et al. (2015),[48] McIntyre et al. (2014),[49] Boulenger et al. (2012),[50] Jacobsen et al. (2015),[51] Baune et al. (2018),[52] Nierenberg et al. (2019),[53] Vieta et al. (2018),[54] Levada et al. (2019),[55] Liebowitz et al. (2017),[56] Inoue et al. (2018),[41] Jacobsen et al. (2015),[38] and Nishimura et al. (2018).[40]

Table 5: Details of Included Studies (continued)

		CCT-004	11985A	318	Liebowitz et al.
Designs and Populations	**Study design**	DB phase III RCT	DB phase III RCT withdrawal design	DB phase III RCT	DB RCT single-centre phase IV
	Locations	Japan	Australia, Europe, Canada, India, Korea, South Africa, Taiwan, Thailand	Canada, US	US
	Randomized (N)	493	OL period: 639, DB period: 400	447	42
	Inclusion criteria	• MDD (DSM-IV-TR criteria) • Age 20 to 75 year • Current MDE 3 to 12 months in duration • MADRS ≥ 26 • HAM-D17 ≥ 18 • CGI-S ≥ 4	**OL Period:** • Recurrent MDD (DSM-IV-TR criteria) • MADRS total score ≥ 26 • Current MDE ≥ 4 weeks duration • Age ≥ 18 and ≤ 75 years • Inpatient or outpatient **DB period:** • MADRS total score ≤ 10 at week 10 and 12 of the OL period.	• MDD (DSM-IV-TR criteria) • Receiving treatment with SSRI (citalopram, paroxetine, or sertraline) for ≥ 8 weeks • Stable and well-treated MDD with CGI-S ≤ 3 • Experiencing SSRI treatment-emergent sexual dysfunction and suitable for switching antidepressant medication (sexual dysfunction defined as CSFQ-14 ≤ 41 for women, ≤ 47 for men) • Age ≥ 18 and ≤ 55 years • Sexually active prior to the current MDE ≥ 2 times per week	• MDD and SAD diagnosed according to DSM-V criteria • Outpatients aged 18 to 70 years • LSAS ≥ 60 • MADRS ≥ 20 • CGI-S ≥ 4 based on composite of MDD and SAD • SAD that was ongoing for ≥ 6 months and observable when not experiencing MDD
	Exclusion criteria	• Current psychiatric disorder other than MDD • History of manic or hypomanic episode, schizophrenia, any other psychotic, mental or neurological disorder (other than MDD) • Current substance abuse • Significant risk of suicide, attempted suicide in past 6 months, or score ≥ 5 on MADRS item 10 (suicidal thoughts) • Receiving or plans to receive formal cognitive or behavioural therapy or psychotherapy during the study (exception 318) • MDD resistant to two antidepressant treatments (≥ 6 weeks of duration) (exception 318)			• History of bipolar, schizophrenia, obsessive-compulsive disorder, eating disorder, or body dysmorphic disorder • Current substance abuse, panic disorder, PTSD • Treatment refractory MDD or SAD (inadequate response to two drug treatments ≥ 6 weeks in duration) • Clinically significant risk of suicide • Treated with antidepressants or other psychotropic medications within the past 2 to 4 weeks • Started psychotherapy in the past six months
		• MADRS score improved or worsened by ≥ 25 during placebo run-in • Non-adherent during run-in	--	• Sexual dysfunction from other causes (i.e., not related to SSRI) • Not sexually active or anticipated a decrease in sexual activity during the study period • Initiation of formal CBT or psychotherapy ≤ 6 months before	

		CCT-004	11985A	318	Liebowitz et al.
				study, or plans to initiate therapy during the study	
DRUGS	**Intervention (daily dose)**	VOR 10 mg VOR 20 mg	VOR 5 mg or10 mg	VOR 10 mg or 20 mg	VOR 10 mg or 20 mg
	Comparators	Placebo	Placebo	ESC 10 mg/20 mg	Placebo
DURATION	**Phase**				
	Run-in	1 week	12 weeks[a]	None	None
	DB	8 weeks	24 to 64 weeks[a]	8 weeks[b]	12 weeks
	Discontinuation		2 weeks (no treatment)[c]	1 week (DB)[d]	
	Follow-up	4 weeks	4 weeks	4 weeks	4 weeks (including 1-week taper)
OUTCOMES	**Primary end point**	Change from baseline to week 8 in MADRS	Time to relapse (MADRS ≥ 22 or lack of efficacy) during first 24 weeks of DB period	Change from baseline to week 8 in CSFQ-14	CGI responder for MDD and SAD
	Other end points	• Response • Remission • HAM-D17 • SDS • DSST	• Response • Remission • MADRS • HAM-D17 • SDS • SF-36 • Harms	• Remission • MADRS • Harms • C-SSRS	• MADRS • LSAS • Remission (SAD and MDD) • Response (MDD) • Harms
	Publications	--	Boulenger et al. (2012)[50]	Jacobsen et al. (2015)[51]	Liebowitz et al. (2017)[56]

CBT = cognitive behaviour therapy; CGI-S = Clinical Global Inventory – Severity; CSFQ-14 = Changes in Sexual Functioning Questionnaire Short-Form; DB = double-blind; C-SSRS = Columbia Suicide Severity Rating Scale; ESC = escitalopram; DSST = Digit Symbol Substitution Test; HAM-D17 = 17-item Hamilton Depression Rating Scale; LSAS = Liebowitz Social Anxiety Scale; MADRS = Montgomery–Åsberg Depression Scale; OL = open-label; PTSD = post-traumatic stress disorder; SAD = social anxiety disorder; SDS = Sheehan Disability Scale; SRT = simple reaction time; VOR = vortioxetine.

Note: Four additional reports were included (FDA Medical and Statistical Reports, Health Canada Reviewer's Report, CADTH Common Drug Review submission).[6,7,57,58]

[a] Patients were enrolled into a 12-week OL period starting at 5 mg per day VOR for the first two weeks. Between week 2 and week 8, the dose adjustments up to 10 mg per day of VOR were allowed at the discretion of the investigator. Between weeks 8 and 12, dose was fixed. Patients who were in remission (MADRS total score ≤ 10 at week 10 and week 12) were randomized into the double-blind period. The double-blind period lasted between 24 and 64 weeks so that all patients continued in the study until the last patient enrolled had completed 24 weeks of therapy.

[b] Flexible-dose treatment. Patients received 10 mg of their respective treatment at baseline. At week 1, the dose was increased to 20 mg. At weeks 2, 4, and 6, dose adjustments were allowed at the discretion of the investigator.

[c] There were two two-week periods of discontinuation (one after randomization and one after the double-blind period).

[d] During the taper-down period, patients in the VOR group received placebo and patients in the ESC group received 10 mg of ESC.

Source: Clinical Study Report,[11-30] Henigsberg et al., (2017)[36] Jain et al. (2013),[37] Baldwin et al. (2012),[42] Mahableshwarkar et al. (2015),[39] Mahableshwarkar et al. (2013),[43] Mahableshwarkar et al. (2015),[44] Boulenger et al. (2014)[45], Katona et al. (2012),[46] Alvarez et al. (2012),[47] Wang et al. (2015),[48] McIntyre et al. (2014),[49] Boulenger et al. (2012),[50] Jacobsen et al. (2015),[51] Baune et al. (2018),[52] Nierenberg et al. (2019),[53] Vieta et al. (2018),[54] Levada et al. (2019),[55] Liebowitz et al. (2017),[56] Inoue et al. (2018),[41] Jacobsen et al. (2015),[38] and Nishimura et al. (2018).[40]

Table 5: Details of Included Studies (continued)

		14122A	15906A	15905A	15907A	Levada
Designs & Populations	**Study Design**	DB phase III RCT	DB RCT phase III	DB RCT phase III	DB RCT phase III	OL RCT single-centre
	Locations	Australia, Canada, US, Mexico, Europe, South Africa	Europe	Europe	Europe	Ukraine
	Randomized (N)	602	152	151	101	66
	Inclusion criteria	• Recurrent MDD (DSM-IV-TR criteria) • MADRS total score ≥ 26 • Current MDE ≥ 3 months duration inpatients or outpatients aged ≥ 18 and ≤ 65 years • Received prescribed treatment for previous MDE	• Recurrent MDD diagnosed according to DSM-IV-TR criteria • MADRS score ≥ 26 points • Current MDE ≥ 3 months duration • Employed full time or part-time (50% full time hours) at current job for ≥ 3 months • Outpatients aged ≥ 18 and ≤ 65 years	• MDD diagnosed according to DSM-IV-TR criteria • Treated with SSRI monotherapy for ≥ 12 weeks at licensed doses and showed a partial response or full remission of • HAM-D17 score ≤ 10 • ≥ 50% response to SSRI based on ATRQ • PDQ-D score > 25 • Inpatients or outpatients (≥ 18 and ≤ 65 years)	• MDD diagnosed according to DSM-IV-TR criteria • Treated for ≥ 6 weeks with SSRI or SNRIa and showing no response or inadequate response • Patient wants to switch therapy due to inadequate response (ATRQ < 50% response) • MADRS score ≥ 22 points • PHQ-9 score ≥ 14 • PDQ-D score > 25 • Current MDE ≤ 1 year in duration • Inpatients or outpatients aged ≥ 18 and ≤ 65 years	• Outpatients aged 18 to 65 years • MDD diagnosed according to DSM-V criteria • Current MDE ≥ 2 months in duration • Paid employee or student • MADRS ≥ 7 points • Free of psychotropic medications for at least 5 half-lived prior to baseline
	Exclusion criteria	• Current psychiatric disorder other than MDD • History of manic or hypomanic episode, schizophrenia, any other psychotic, mental or neurological disorder (other than MDD) • History of moderate-to-severe head trauma • Current substance abuse • Significant risk of suicide, attempted suicide in past 6 months, or score ≥ 5 on MADRS item 10 (suicidal thoughts) • Receiving or plans to receive formal cognitive or behavioural therapy or psychotherapy during the study • Prior MDE considered treatment-resistant (inadequate response to two antidepressant treatments ≥ 6 weeks in duration) (exception 15905A)				• Current psychiatric disorder other than MDD • History of manic or hypomanic episode, or neurological disorder, head trauma, personality disorder endocrine disease, or unstable medical condition • High suicide risk defined by clinician • Substance dependence or abuse over the past year
		• Score ≥ 70 on DSST or score ≥ 42 on the RAVLT (learning) or score ≥ 14 on RAVLT (memory)	• Baseline DSST score ≥ 70 • History of lack of response to VOR or PAR	• Baseline DSST score ≥ 70	• Baseline DSST score ≥ 70 • History of lack of response to VOR or ESC	
Drugs	**Intervention (daily dose)**	VOR 10 mg VOR 20 mg	VOR 10 mg	VOR 10 mg or 20 mg + placebo	VOR 10 mg or 20 mg	VOR 10 mg to 20 mg

		14122A	15906A	15905A	15907A	Levada
				VOR 10 mg or 20 mg + SSRI[b]		
	Comparator(s)	Placebo	Placebo Paroxetine 20 mg	SSRI[b] + placebo	ESC 10 mg or 20 mg	ESC 10 mg or 20 mg
DURATION	**Phase**					
	DB	8 weeks	8 weeks	8 weeks	8 weeks	OL: 8 weeks
	Follow-up	4 weeks	4 weeks[c]	4 weeks[c]	4 weeks[c]	NR
OUTCOMES	**Primary end point**	Change from baseline to week 8 in composite z score for RAVLT and DSST[d]	Change from baseline to week 8 for DSST	Change from baseline to week 8 for DSST	Change from baseline to week 8 for DSST	Not specified
	Other end points	• Response • Remission • MADRS • Harms • C-SSRS	• UPSA-B • Other cognitive function measures (TMT, reaction time, STROOP score) • EQ-5D-3L • MADRS • Response • Remission • Harms • C-SSRS	• UPSA-B • Other cognitive function measures (RAVLT, TMT, reaction time, STROOP score) • SDS • HAM-D17 • Harms • C-SSRS	• UPSA-B • Other cognitive function measures (RAVLT, TMT, reaction time, STROOP score) • Harms • C-SSRS	• RAVLT • DSST • MADRS • Response • Remission • Harms
	Publications	McIntyre et al. (2014)[49]	Baune et al. (2018)[52]	Nierenberg et al. (2019)[53]	Vieta et al. (2018)[54]	Levada et al. (2019)[55]

ATRQ = Antidepressant Treatment Response Questionnaire; C-SSRS = Columbia Suicide Severity Rating Scale; DB = double-blind; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSST = Digit Symbol Substitution Test; ESC = escitalopram; HAM-D17 = 17-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Scale; MDD = major depressive disorder; MDE = major depressive episode; NR = not reported; OL = open-label; PDQ-D = Perceived Deficits Questionnaire – Depression; PHQ-9 = Patient Health Questionnaire-9; RAVLT = Rey Auditory Verbal Learning Test; RCT = randomized controlled trial; SDS = Sheehan Disability Scale; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; STROOP = Stroop Colour Naming Test; TMT = Trail Making Test; UPSA-B = University San Diego Performance-Based Sills Assessment – Brief; VOR = vortioxetine.

Note: Four additional reports were included (FDA Medical and Statistical Reports, Health Canada Reviewer's Report, CDR submission).[6,7,57,58]

[a] SSRI monotherapy at licensed dosages (escitalopram 5 mg, 10 mg, 15 mg, or 20 mg per day; citalopram 10 mg, 20 mg, 30 mg, or 40 mg per day; sertraline 50 mg, 100 mg, 150 mg, or 200 mg per day). At screening, patients had to have been treated with a SSRI for at least 12 weeks, plus the dose had to be stable for at least the last eight weeks.

[b] Prior antidepressant monotherapy could include citalopram, paroxetine, sertraline, duloxetine, or venlafaxine at licensed doses.

[c] Includes one-week DB taper-down period.

[d] Composite z score: DSST (0.5 weight) and RAVLT (0.25 for acquisition subtest; 0.25 for the delayed-recall subtest).

Source: Clinical Study Report,[11-30] Henigsberg et al., (2017)[36] Jain et al. (2013),[37] Baldwin et al. (2012),[42] Mahableshwarkar et al. (2015),[39] Mahableshwarkar et al. (2013),[43] Mahableshwarkar et al. (2015),[44] Boulenger et al. (2014)[45], Katona et al. (2012),[46] Alvarez et al. (2012),[47] Wang et al. (2015),[48] McIntyre et al. (2014),[49] Boulenger et al. (2012),[50] Jacobsen et al. (2015),[51] Baune et al. (2018),[52] Nierenberg et al. (2019),[53] Vieta et al. (2018),[54] Levada et al. (2019),[55] Liebowitz et al. (2017),[56] Inoue et al. (2018),[41] Jacobsen et al. (2015),[38] and Nishimura et al. (2018).[40]

Included Studies

Description of Studies

A total of 22 randomized controlled trials (RCTs) met the inclusion criteria for the systematic review (Table 5). All trials evaluated the efficacy and safety of vortioxetine in adults with MDD after six to 12 weeks of therapy (21 short-term trials) or up to 64 weeks (one relapse prevention study[25]). The trials were designed to test differences between vortioxetine and placebo (17 RCTs), venlafaxine (one noninferiority study)[25] or escitalopram (three studies).[24,28,55] One other trial was designed to compare vortioxetine as add-on therapy to a selective serotonin reuptake inhibitor (SSRI) or vortioxetine as monotherapy, with SSRI monotherapy.[30] Seven placebo-controlled trials also included an active-reference group (duloxetine,[13,15,17,18,21] venlafaxine,[11] or paroxetine[29]).

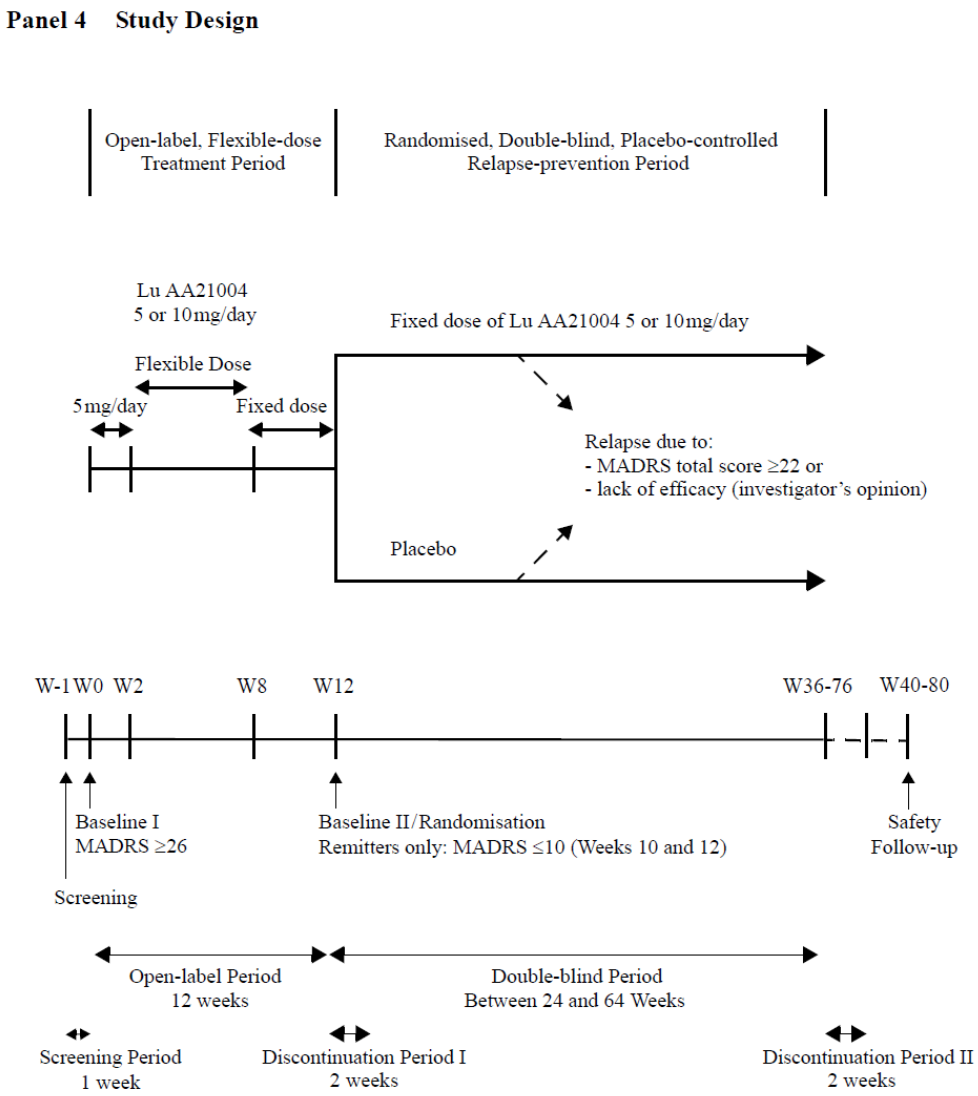
All but one of the trials were double-blind.[55] Fourteen short-term efficacy trials assessed the impact of vortioxetine on depression symptom severity, measured as the change from baseline to week 6 or 8 for either the Montgomery–Åsberg Depression Scale (MADRS) or the 24-item Hamilton Depression Rating Scale (HAM-D24) (studies 305, 303, 316, 317, CCT-002, CCT-003, 11984A, 304, 13267A, 315, 12541A, 11492A, 13926A, and CCT-004). Four trials examined cognitive function as the primary outcome, which was assessed using the Digit Symbol Substitution Test (DSST) or a composite of the DSST and the Rey Auditory Verbal Learning Test (RAVLT) (15905A, 15906A, 15907A, and 14122A).[22,28-30] The other studies evaluated sexual function (Study 31824) and the Clinical Global Impression – Improvement Scale (CGI-I) (Liebowitz et al.[56]) and one did not specify the primary outcome (Levada et al.[55]). One trial (11985A)[16] used a withdrawal design, in which patients who had achieved remission of their MDD with 12 weeks of vortioxetine therapy were randomized to placebo or continuation of vortioxetine: time to relapse was the primary outcome (Figure 2).

Study CCT-004 used an enrichment design, and excluded any patients who showed substantial improvement or worsening of depression symptoms or who were non-adherent to placebo during the single-blind one-week run-in phase.[27] All other studies used a parallel design.

In 15 trials, patients were randomized 1:1 to treatment groups using an interactive voice or web response system. Four trials used sealed envelopes containing the treatment allocation code (11984A, 12541A, 11492A, and 11985A), and three trials did not fully describe the methods used to allocate patients to treatments (Liebowitz et al., Levada et al., and CCT-004). Randomization was stratified by site in 13 trials (315, 316, 317, 11984A, 13267A, 12541A, 11492A, 318, 14122A, 11985A, 15905A, 15906A, and 15907A) and by baseline sexual function in three studies (315, 316, and 317). The number enrolled ranged from 40 patients[56] to 766 patients,[15] with a median of 457.5 per study.

Twenty trials were multi-centre, manufacturer-sponsored studies (either Lundbeck or Takeda),[11-30] while two single-centre randomized controlled trials (RCTs)[55,56] had other sponsors. A high-level summary of the included studies is provided in Table 6.

Figure 2: Schematic of the Relapse Prevention Study (11985A)



Source: Clinical Study Report.[16]

Table 6: Included Studies Summary

Study	MDD population	Primary outcome[a]	N	Duration (weeks)	PBO	VOR					Active-treatment group
						5 mg	10 mg	15 mg	20 mg	Other[b]	
Manufacturer-sponsored trials											
305	Adults	HAM-D24	560	8	x	x	x			1 mg	
303	Adults	HAM-D24	600	6	x	x					
316	Adults	MADRS	462	8	x		x		x		
317	Adults	MADRS	469	8	x		x	x			
CCT-002	Adults	MADRS	600	8	x	x	x		x		
CCT-003	Adults	MADRS	366	8	x	x	x				
11984A	Adults	MADRS	766	8	x	x	x			2.5 mg	DUL 60 mg
304	Adults	HAM-D24	611	8	x	x				2.5 mg	DUL 60 mg
13267A	Adults	MADRS	608	8	x			x	x		DUL 60 mg
315	Adults	MADRS	614	8	x			x	x		DUL 60 mg
12541A	Elderly	HAM-D24	453	8	x	x					DUL 60 mg
11492A	Adults	MADRS	429	6	x	x	x				VEN 225 mg
13926A	**Adults**	**MADRS**	**437**	**8**			**x**				**VEN 150 mg**
CCT-004	Adults	MADRS	453	8	x		x		x		
14122A	Adults	Cognitive function (DSST/RAVLT)[c]	602	8	x		x		x		
15906A	Employed adults	Cognitive function (DSST)	158	8	x		x				PAR 20 mg
15905A	**Adults with full or partial remission of with SSRI**	**Cognitive function (DSST)**	**151**	**8**			**VOR 10 mg or 20 mg monotherapy, or VOR 10 mg or 20 mg + SSRI**				**SSRI**
15907A	**Adults with inadequate response to SSRI or SNRI**	**Cognitive function (DSST)**	**101**	**8**			**VOR 10 mg or 20 mg**				**ESC 10 mg or 20 mg**

Study	MDD population	Primary outcome[a]	N	Duration (weeks)	PBO	VOR					Active-treatment group
						5 mg	10 mg	15 mg	20 mg	Other[b]	
318	**Adults with SSRI-related sexual dysfunction**	**Sexual function (CSFQ-14)**	**447**	**8**			**10 mg or 20 mg**				**ESC 10 mg or 20 mg**
11985A	Adults	Time to relapse	400	24 to 64	x	VOR 5 mg or 10 mg					
Other trials											
Liebowitz et al. (2017)	Adults with comorbid social anxiety disorder	CGI-I	40	12	x		10 mg or 20 mg				
Levada et al. (2019)	**Adults**	**Unclear**	**56**	**8**			**10 mg or 20 mg**				**ESC 10 mg or 20 mg**

CGI-I = Clinical Global Impression – Improvement; CSFQ-14 = Changes in Sexual Functioning Questionnaire Short-Form; DSST = Digit Symbol Substitution Test; DUL = duloxetine; ESC = escitalopram; HAM-D24 = 24-item Hamilton Depression Rating Scale; MDD = major depressive disorder; MADRS = Montgomery–Åsberg Depression Rating Scale; PAR = paroxetine; PBO = placebo; RAVLT = Rey Auditory Verbal Learning Test; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; VEN = venlafaxine extended release; VOR = vortioxetine.

Note: Studies in bold were designed as active-controlled trials.

[a] The primary outcome was the change from baseline to the treatment period (six or eight weeks) for all studies except 11985A.

[b] Doses classified as “other” were not consistent with the Health Canada–recommended dosing range and have not been summarized in this report.

[c] Composite outcome.

Source: Clinical Study Report,[11-30] Levada et al. (2019),[55] Liebowitz et al. (2017).[56]

Populations

Inclusion and Exclusion Criteria

All trials enrolled adult patients diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) or Fifth Edition (DSM-V) (two trials). Eight studies enrolled those with recurrent MDD, in which patients were required to have at least one MDE prior to the current episode. In one trial, the patients enrolled had comorbid social anxiety disorder.[56]

Fifteen short-term trials used similar inclusion and exclusion criteria, enrolling patients with a current major depressive episode of at least three months, with a baseline MADRS total score of at least 22, 26, or 30, and who were between 18 and 75 years of age (305, 303, 316, 317, CCT-002, CCT-004, 11984A, 304, 13267A, 315, 11492A, 13926A, CCT-004, 14122A, and 15906A). Six studies had an upper age restriction of 65 years (Table 5). Study 15906A had additional inclusion criteria that patients had to be working full time or part-time to be eligible for enrolment. In study CCT-004, patients underwent a one-week, single-blind, placebo run-in period and any patients who showed an increase or decrease of at least 25 points in MADRS score, or were non-adherent to the study drug, were excluded from the study.

Study 12541A enrolled elderly patients aged 65 years and older with a current MDE of at least four weeks' duration and a MADRS score of 26 or greater. Study 318 enrolled patients with an MDD between 18 and 55 years of age who were experiencing sexual dysfunction because of at least eight weeks of treatment with citalopram, paroxetine, or sertraline. Study 15905A enrolled patients in full or partial remission of their MDD with SSRI monotherapy (escitalopram, citalopram, or sertraline) at licensed doses. In Study 15907A, patients were eligible if their MDD was only partially responsive or they had shown no response to at least six weeks of therapy of citalopram, paroxetine, sertraline, duloxetine, or venlafaxine at licensed doses. Study 11985A enrolled patients with MDD in whom their current MDE was at least four weeks in duration, who had a baseline MADRS score of 26 or greater, and were aged 18 to 75 years, into the open-label treatment period. At the end of 12 weeks of vortioxetine therapy, patients with a maximum MADRS score of 10 (i.e., in remission for a minimum of two weeks) were eligible for the double-blind phase to assess relapse.

The study by Liebowitz et al.[56] enrolled patients aged 18 to 70 years with MDD and social anxiety disorder that met the DSM-V criteria. Other inclusion criteria were a MADRS score of 20 or greater and social anxiety disorder that was ongoing for at least six months and observable when not experiencing MDD. Levada et al.[55] enrolled patients aged 18 to 65 years with MDD according to DSM-V criteria with a MADRS score of 7 or more points, and who were paid employees or students and had stopped any psychotropic medications for at least five half-lives prior to baseline.

Six trials were conducted in US patients only (303, 316, 317, 304, 315, and Liebowitz et al.) and three enrolled only Asian patients (CCT-003, 13926A, and CCT-004). All other studies enrolled patients from multiple countries, and five studies included patients from Canada (12541A, 11492A, 11984A, 11985A, and 318). Inpatients and outpatients were enrolled in nine studies (13267A, 13926A, 12541A, 14122A, 11985A, 11984A, CCT-002, 15905A, and 15907A), and 10 studies enrolled only outpatients (11492A, 305, 303, 304, 315, 316, 317, 15906A, Levada et al., and Liebowitz et al.). Studies CCT-003, CCT-004, and 318 did not state if enrolment included inpatients or outpatients.

All trials listed numerous exclusion criteria, such as patients with another psychiatric, mental, or neurological disorder (other than MDD), substance abuse disorder, clinically unstable illness, treatment-resistant depression, or who were at significant risk of suicide. Patients receiving or who planned to receive formal cognitive or behavioural therapy or other psychotherapy were excluded. In studies with an active comparator, patients with a history of non-response to that drug were excluded. The four trials that evaluated cognitive function as the primary outcome (14122A, 15905A, 15906A, and 15907A) also excluded patients with a DSST score of at least 70 points as these patients were not expected to be able to improve their neuropsychological test performance.

Baseline Characteristics

Among the 20 manufacturer-sponsored trials, the baseline characteristics were generally similar across treatment groups within studies (Table 7). However, there were a few notable between-study differences. The mean age per treatment group ranged from 38.8 to 50.6 years, except for study 12541A, which enrolled patients older than 65 years and had a mean age of 70.6 years. The proportion of females ranged from 29% to 79% across the trial treatment groups. There appears to be some variation between groups in the baseline characteristics of patients enrolled in the five trials; specifically, the proportion of patients with prior pharmacotherapy (Liebowitz et al.), number of prior MDEs and duration of current MDEs (Levada et al.), and the proportion of females (15906A and 15905A) and mean age (15905A and 15907A). These trials had a small sample size (20 to 54 patients per group).

Patients in Study 318 were receiving citalopram, paroxetine, or sertraline for MDD at enrolment (Table 8). Their baseline MADRS scores (7.9 to 8.3) were therefore lower than all other studies (27.8 to 34.2). Similarly, in Study 15905A, the patients enrolled had a full or partial remission at baseline with SSRI therapy, and their 17-item Hamilton Depression Rating Scale (HAM-D17) scores were low at the start of the study (mean score of 5.6 to 6.1 points) and were reported to be high functioning based on a mean DSST score of 47 points and a University of San Diego Performance-Based Skills Assessment – Brief (UPSA-B) score of 81 points.

In Study 11985A, baseline MADRS scores were 32.3; however, only those in remission at the end of the 12-week, open-label vortioxetine treatment period entered the double-blind phase (MADRS score 4.7 to 4.9).

Eleven studies enrolled patients with recurrent MDD (316, 317, 13267A, 315, 12541A, 13926A, 14122A, 11985A, 15905A, 15906A, and 15907A), whereas approximately 60% to 80% of patients had at least one prior MDE in seven studies (305, 303, CCT-002, 11984A, 304, 11492A, and 318), and roughly 40% had recurrent major depressive episodes in Study CCT-003.

Table 7: Summary of Baseline Characteristics

Characteristic	305			303		316			317		
	PBO	VOR 5 mg	VOR 10 mg	PBO	VOR 5 mg	PBO	VOR 10 mg	VOR 20 mg	PBO	VOR 10 mg	VOR 15 mg
N	**140**	**140**	**140**	**300**	**300**	**157**	**155**	**150**	**160**	**157**	**152**
Age, mean (SD)	46.4 (12.3)	47.3 (12.0)	46.4 (12.3)	42.4 (12.7)	42.5 (13.0)	42.3 (11.6)	43.1 (12.0)	43.1 (13.1)	46.2 (11.8)	45.2 (11.9)	43.8 (13.5)
Female, N (%)	86 (61)	87 (62)	85 (61)	164 (55)	186 (62)	110 (70)	118 (76)	107 (71)	108 (68)	113 (72)	108 (71)
Mean baseline HAM-D24 score (SD)	32.7 (4.4)	32.1 (5.0)	33.1 (4.8)	32.2 (5.5)	32.7 (5.4)	NR	NR	NR	NR	NR	NR
Mean baseline MADRS score (SD)	30.6 (2.9)	30.6 (2.8)	31.6 (3.4)	34.0 (3.4)	34.1 (3.4)	32.0 (4.0)	32.3 (4.5)	32.4 (4.3)	33.4 (4.5)	34.1 (4.1)	33.7 (4.5)
Median duration of current MDE, weeks (range)	[redacted]										
Proportion of patients with 1 or more prior MDE, N (%)	[redacted]										
Prior pharmacotherapy for MDD, N (%)	[redacted]										

Table 7: Summary of Baseline Characteristics (continued)

Characteristic	CCT-002				CCT-003			11984A			
	PBO	VOR 5 mg	VOR 10 mg	VOR 20 mg	PBO	VOR 5 mg	VOR 10 mg	PBO	VOR 5 mg	VOR 10 mg	DUL 60 mg
N	**152**	**144**	**150**	**154**	**124**	**119**	**123**	**148**	**157**	**151**	**155**
Age, mean (SD)	43.6 (11.6)	44.2 (11.9)	45.7 (10.9)	44.0 (11.8)	37.6 (10.7)	38.8 (10.9)	38.8 (11.0)	43.4 (12.5)	44.7 (13.1)	45.2 (13.1)	45.3 (12.0)
Female, N (%)	91 (60)	98 (68)	93 (62)	93 (60)	67 (54)	50 (42)	54 (44)	103 (70)	104 (66)	100 (66)	105 (68)
Mean baseline HAM-D24 score (SD)	NR	NR	NR	NR	21.5 (4.5)[a]	20.9 (4.1)[a]	21.2 (4.4)[a]	29.8 (5.1)	31.3 (5.8)	30.4 (5.4)	29.9 (5.8)
Mean baseline MADRS score (SD)	31.6 (3.6)	31.6 (3.7)	31.8 (4.0)	31.7 (3.7)	32.5 (4.5)	32.2 (4.8)	32.5 (4.9)	31.7 (4.3)	32.7 (4.8)	31.8 (3.9)	31.4 (4.2)
Median duration of current MDE, weeks (range)	[redacted]										

Characteristic	CCT-002				CCT-003			11984A			
	PBO	VOR 5 mg	VOR 10 mg	VOR 20 mg	PBO	VOR 5 mg	VOR 10 mg	PBO	VOR 5 mg	VOR 10 mg	DUL 60 mg
Proportion of patients with 1 or more prior MDE, N (%)	[redacted]										
Prior pharmacotherapy for MDD, N (%)	[redacted]										

Table 7: Summary of Baseline Characteristics (continued)

Characteristic	304			13267A				315			
	PBO	VOR 5 mg	DUL 60 mg	PBO	VOR 15 mg	VOR 20 mg	DUL 60 mg	PBO	VOR 15 mg	VOR 20 mg	DUL 60 mg
N	**153**	**153**	**152**	**158**	**151**	**151**	**147**	**161**	**147**	**154**	**152**
Age, mean (SD)	42.6 (13.8)	43.1 (13.9)	42.7 (14.4)	48.1 (13.1)	47.0 (14.6)	46.2 (13.4)	45.6 (13.6)	42.4 (12.6)	43.1 (12.3)	42.8 (12.4)	43.4 (12.2)
Female, N (%)	93 (61)	106 (69)	91 (60)	110 (70)	97 (64)	91 (60)	102 (69)	116 (72)	104 (71)	114 (74)	119 (78)
Mean baseline HAM-D24 score (SD)	29.5 (6.1)	29.8 (5.6)	28.7 (5.1)	NR	NR	NR	NR	NR	NR	NR	NR
Mean baseline MADRS score (SD)	30.0 (4.4)	30.1 (4.5)	29.4 (4.3)	31.5 (3.6)	31.8 (3.4)	31.2 (3.4)	31.2 (3.5)	31.5 (4.2)	31.9 (4.1)	32.0 (4.4)	32.8 (4.3)
Median duration of current MDE, weeks (range)	[redacted]										
Proportion of patients with 1 or more prior MDE, N (%)	[redacted]										
Prior pharmacotherapy for MDD, N (%)	[redacted]										

Table 7: Summary of Baseline Characteristics (continued)

Characteristic	12541A			11492A				13926A	
	PBO	VOR 5 mg	DUL 60 mg	PBO	VOR 5 mg	VOR 10 mg	VEN 225 mg	VOR 10 mg	VEN 150 mg
N	**145**	**156**	**151**	**105**	**108**	**100**	**113**	**211**	**226**
Age, mean (SD)	70.3 (4.4)	70.5 (4.8)	70.9 (5.5)	42.0 (10.9)	43.8 (11.6)	42.3 (13.1)	45.0 (10.3)	39.6 (12.4)	40.7 (12.3)
Female, N (%)	90 (62)	107 (69)	100 (66)	69 (66)	70 (65)	66 (66)	62 (55)	123 (58)	139 (62)
Mean baseline HAM-D24 score (SD)	29.4 (5.1)	29.2 (5.0)	28.5 (4.9)	29.7 (5.0)	29.9 (5.4)	29.3 (5.6)	29.4 (5.0)	NR	NR
Mean baseline MADRS score (SD)	30.3 (3.2)	30.7 (3.6)	30.4 (3.1)	33.9 (2.7)	34.1 (2.6)	34.0 (2.8)	34.2 (3.1)	32.3 (4.6)	32.3 (4.5)
Median duration of current MDE, weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with 1 or more prior MDE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior pharmacotherapy for MDD, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: Summary of Baseline Characteristics (continued)

Characteristic	CCT-004			11985A			318	
	PBO	VOR 10 mg	VOR 20 mg	Open-label period	Double-blind period		ESC 10 mg/ 20 mg	VOR 10 mg/ 20 mg
				VOR 5 mg/10 mg	PBO	VOR 5 mg/10 mg		
N	**164**	**165**	**164**	**639**	**192**	**204**	**222**	**225**
Age, mean (SD)	39.5 (10.5)	40.0 (10.6)	40.4 (11.3)	44.6 (12.4)	45.1 (12.1)	44.8 (12.4)	40.2 (10.0)	39.3 (10.0)
Female, N (%)	72 (44)	72 (44)	80 (49)	397 (62)	120 (63)	130 (64)	135 (61)	128 (57)
Mean baseline HAM-D17 score (SD)	22.0 (3.2)	22.1 (3.1)	22.2 (3.1)	22.8 (4.5)	4.0 (3.2)	4.5 (3.3)	NR	NR
Mean baseline MADRS score (SD)	30.5 (3.9)	30.8 (3.7)	30.6 (3.6)	32.3 (4.1)	4.7 (3.2)	4.9 (3.0)	8.3 (6.5)	7.9 (6.3)

Characteristic	CCT-004			11985A			318	
	PBO	VOR 10 mg	VOR 20 mg	Open-label period	Double-blind period		ESC 10 mg/ 20 mg	VOR 10 mg/ 20 mg
				VOR 5 mg/10 mg	PBO	VOR 5 mg/10 mg		
Median duration of current MDE, weeks (range)	NR	NR	NR	16 (4 to 213)	16 (4 to 144)	16 (4 to 135)	46 (0 to 938)	59 (0 to 1683)
Number of previous MDE								
1 to 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 to 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of previous MDE, median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior pharmacotherapy for MDD, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: Summary of Baseline Characteristics (continued)

Characteristic	14122A			Liebowitz et al.		Levada et al.	
	PBO	VOR 10 mg	VOR 20 mg	PBO	VOR 10 mg/20 mg	VOR 10 mg/20 mg	ESC 10mg/20 mg
N	**196**	**195**	**207**	**20**	**20**	**36**	**20**
Age, mean (SD)	45.6 (12.1)	45.4 (12.2)	46.1 (11.8)	42.2 (12.6)	40.8 (14.5)	37.3 (11.0)	37.2 (12.4)
Female, N (%)	129 (66)	134 (69)	133 (64)	12 (60)	12 (60)	21 (58)	12 (60)
Mean baseline HAM-D17 score (SD)	NR	NR	NR	NR	NR	NR	NR
Mean baseline MADRS score (SD)	31.3 (3.8)	31.6 (3.8)	31.7 (3.5)	30.7 (5.9)	28.1 (4.9)	28.6 (6.2)	27.8 (10.2)
Median duration of current MDE, weeks (range)	[redacted]	[redacted]	[redacted]	NR	NR	Mean 32.2 (SD 49.7)[c]	Mean 47.0 (SD 85.7)[c]
Number of previous MDE, median (range)	[redacted]	[redacted]	[redacted]	NR	NR	Mean 2.1 (SD 1.9)[c]	Mean 1.4 (SD 2.0)[c]
Prior pharmacotherapy for MDD, N (%)	[redacted]	[redacted]	[redacted]	16 (80)	8 (40)	NR	NR

Table 7: Summary of Baseline Characteristics (continued)

Characteristic	15906A			15905A			15907A	
	PBO	VOR 10 mg	PAR 20 mg	VOR 10 mg/20 mg + SSRI	VOR 10mg/20 mg	SSRI	VOR 10 mg/ 20 mg	ESC 10 mg/ 20 mg
N	**48**	**48**	**54**	**52**	**50**	**46**	**50**	**49**
Age, mean (SD)	45.0 (12.7)	47.3 (12.0)	46.3 (11.5)	45.9 (12.7)	50.6 (10.0)	47.9 (11.5)	46.7 (10.7)	49.7 (10.4)
Female, N (%)	29 (60)	35 (73)	36 (67)	41 (79)	34 (68)	34 (69)	39 (78)	35 (71)
Mean baseline HAM-D17 score (SD)	NR	NR	NR	5.6 (2.3)	6.1 (2.4)	5.6 (2.1)	NR	NR
Mean baseline MADRS score (SD)	31.8 (3.3)	30.6 (3.3)	31.3 (3.4)	NR	NR	NR	29.3 (3.1)	28.9 (3.0)
Median duration of current MDE, weeks (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of previous MDE, median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior pharmacotherapy for MDD, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DUL = duloxetine; ESC = escitalopram; 17-item HAM-D17 = Hamilton Depression Rating Scale; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Scale; MDD = major depressive disorder; MDE = major depressive episode; NR = not reported; PBO = placebo; SD = standard deviation; VEN = venlafaxine extended release; VOR = vortioxetine.

[a] HAM-D17 total score.

[redacted]

[c] Mean (SD) reported because median was not reported.

Source: Clinical Study Report,[11-30] Levada et al. (2019),[55] Liebowitz et al. (2017).[56]

Table 8: Prior Treatments for Current Major Depressive Episode (Studies 318, 15906A, and 15907A)

	Study 318		15906A			15907A	
	ESC 10 mg/20 mg	VOR 10 mg/20 mg	VOR 10 mg/20 mg + PBO	SSRI + PBO	VOR 10 mg/ 20 mg + SSRI	VOR 10 mg/ 20 mg	ESC 10 mg/ 20 mg
N	**222**	**225**	**50**	**46**	**52**	**50**	**49**
Received pharmacotherapy, n (%)							
Citalopram	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Escitalopram	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paroxetine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sertraline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duloxetine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venlafaxine			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Received psychotherapy, n (%)							
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ESC = escitalopram; NR = not reported; PBO = placebo; SSRI = selective serotonin reuptake inhibitor; VOR = vortioxetine.

Source: Clinical Study Report.[24,28,29]

Interventions

All manufacturer-sponsored trials and Liebowitz et al.[56] used identical-looking intervention and control tablets or capsules to maintain blinding to the treatment received. The study by Levada et al. was open-label.[55]

Across the included studies, the dose of vortioxetine tested ranged from 1 mg to 20 mg per day; but only the Health Canada–approved doses (5 mg to 20 mg) are summarized in this report. Most trials used fixed dosing regimens of 5 mg daily (eight trials), 10 mg daily (11 trials), 15 mg daily (three trials), or 20 mg daily (six trials) (Table 7). In six trials, variable dosing of vortioxetine was used (5 mg or 10 mg per day for Study 11985A and 10 mg or 20 mg per day for studies 318, 15905A, 15907A, Levada et al., and Liebowitz et al.).

Seventeen trials compared vortioxetine with placebo. Of these, seven also included an active comparator that was either duloxetine 60 mg per day, venlafaxine extended release (XR) 225 mg per day, or paroxetine 20 mg daily. The head-to-head trials compared vortioxetine 10 mg daily with venlafaxine XR 150 mg per day (13926A) or vortioxetine 10 mg to 20 mg with escitalopram 10 mg to 20 mg per day (318, 15907A, and Levada et al.). One trial (15905A) compared vortioxetine 10 mg or 20 mg daily as adjunctive therapy to an SSRI, and vortioxetine as monotherapy, with monotherapy with an SSRI in patients with full or partial remission of the MDE. In this study, patients randomized to an SSRI or SSRI plus vortioxetine continued to take the SSRI they were prescribed prior to enrolment, which was either escitalopram 5 mg to 20 mg per day, citalopram 10 mg to 40 mg daily, or sertraline 50 mg to 200 mg daily (Table 8). Patients randomized to the vortioxetine monotherapy group discontinued their SSRI at baseline.

In Study CCT-004, all patients received single-blind placebo tablets during the one-week run-in period. Those patients who were adherent to therapy and did not show an increase or decrease of at least 25% in MADRS score were eligible for randomization to placebo, VOR 10 mg, or VOR 20 mg groups.

In 12 trials, antidepressants were started at lower doses and titrated up to the randomized dose over the first week. This included vortioxetine 15 mg or 20 mg groups in studies 14122A, 13267A, 315, 316, 317, CCT-002, CCT-004, 15905A, 15906A, and 15907A; duloxetine in studies 13267A and 315; and venlafaxine in studies 11492A and 13926A. Patients randomized to the vortioxetine group in Study 11985A continued on the dosage they were on at the end of the open-label phase (either 5 mg per day or 10 mg per day). In Study 318, patients randomized to the vortioxetine and escitalopram groups received 10 mg per day during the first week,
20 mg per day during the second week, and flexible dosing of 10 mg or 20 mg per day for the rest of the study period.

Sixteen studies had a one- or two-week discontinuation period during which some active treatments were tapered off at the end of the six- to eight-week double-blind study period or at study withdrawal (303, 316, CCT-002, CCT-003, 11984A, 304, 13267A, 315, 12541A, 11492A, 13926A, 11985A, and 318, 15905A, 15906A, and 15907A). During the discontinuation period, either no study drug was administered (303 and 11985A), or the taper was placebo-controlled (double-blind: 11984A, 304, 13267A, 315, 12541A, 11492A, 13926A, and 318; single-blind: 316, CCT-002, CCT-003, 15905A, 15906A, and 15907A). In placebo-controlled trials, patients on placebo continued with placebo and those on active-treatment were either tapered to a lower dose or switched to placebo. In 16 studies,

patients receiving vortioxetine were switched abruptly to placebo (316, CCT-002, CCT-003, 11984A, 304, 13267A, 315, 12541A, 13926A, 318, and 11492A, 5 mg dose) or no treatment (305, 303, 317, 14122A, and 11985A), with no tapering. Tapering of duloxetine or venlafaxine dosages is described in the footnotes in Table 5.

Patients could use zolpidem, zopiclone, zaleplon, or in Study 318, eszopiclone, for severe insomnia for a maximum of two days per week (305, 303, 316, 317, CCT-002, CCT-003, CCT-004, 11984A, 13267A, 11492A, 13926A, 304, 315,12541A, 14122A, 11985A, 318, 15905A, 15906A, and 15907A). Specific medications that were not allowed during the study included monoamine oxidase inhibitors, SSRIs, SNRIs, tricyclic antidepressants, drugs used for augmentation of antidepressants, antipsychotic drugs, anti-manic drugs, dopamine antagonists, and anxiolytics. Other exclusions included anticonvulsants, narcotic analgesics, anti-inflammatory drugs, anti-migraine drugs, oral anticoagulants, anti-platelet drugs, systemic steroids, and specific anti-arrhythmic drugs. In Study 11492A, diuretics, proton-pump inhibitors, antihypertensives, and antilipidemic drugs were not allowed. Diuretics were not allowed in Study 11984A, and in studies 315 and 13267A only select beta-blockers could be used. Proton-pump inhibitors and histamine-2 blockers were prohibited in studies 316 and 13267A. The trial by Liebowitz et al.[56] excluded patients taking antidepressants or other psychotropic medications, but zolpidem was allowed up to three times per week.

Outcomes

Health-Related Quality of Life

The Short-Form (36) Health Survey (SF-36) is a generic, HRQoL measure that includes eight domains: physical functioning, bodily pain, vitality, social functioning, mental health, general health, and role limitations due to physical or emotional problems. Each domain is scored from 0 to 100, with higher scores indicating better health status. The minimal clinically important difference (MCID) is not known for patients with depression, although there is evidence to support the validity of the SF-36 in this population (Appendix 6). The SF-36 was reported in five studies (305, 303, 11984A, 11492A, and 11985A).

The EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire was reported as an exploratory outcome in Study 15906A. It consists of five domains (mobility, self-care, usual activities, pain or discomfort, and depression or anxiety), each rated on a three-point index from 1 (no problems) to 3 (extreme problems). Estimates of MCIDs for the EQ-5D-3L index score in general have ranged from 0.033 to 0.074.[59] It also includes a 20 cm visual analogue scale (VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.” Respondents are asked to rate their health by drawing a line from an anchor box to the point on the VAS that best represents their health on that day. No MCID for the VAS in patients with depression was identified.

Data from the Quality of Life Enjoyment and Satisfaction Questionnaire – Short-Form (Q-LES-Q SF) were reported in two RCTs (13267A and 13926A). This questionnaire is a patient-reported measure designed to assess the degree of enjoyment and satisfaction experienced by patients in various areas of daily life.[60] The short-form consists of 14 items from the General Activities section of the full, 93-item version of the questionnaire, and each item is rated on a five-point scale (1 = very poor and 5 = very good).[6] The short-form total scores range from 14 to 70, with higher scores indicating better quality of life. The short-form also includes two general questions on medication use and overall life

satisfaction that are not included in the total score. The Q-LES-Q SF, including the General Activities subscale, was reported to be reliable and valid in patients with depression.[60] No MCID was identified.

Depression Severity

Among the 14 short-term efficacy trials, the primary outcome was either the change from baseline to week 6 or 8 (end of the treatment period) in the MADRS total score (316, 317, CCT-002, CCT-003, CCT-004, 11984A, 13267A, 315, 11492A, and 13926A) or the HAM-D24 total score (305, 303, 304, and 12541A). In addition, the change from baseline in MADRS, HAM-D24, or HAM-D17 score was reported as a secondary or exploratory outcome in 11 trials. Both the MADRS and HAM-D scales are physician-rated measures of the severity of depression symptoms. The MADRS includes 10 items with a maximum total score of 60, the HAM-D24 includes 24 items with a maximum of 76 points, and the HAM-D17 has 17 items with a maximum of 53 points. For these instruments, higher MCID scores indicate more severe symptoms. There is evidence to support the validity of the MADRS, with an MCID of 2. The validity of the HAM-D24 is not known, although the HAM-D17, which is the core of the HAM-D24, has evidence of validity and an MCID of 2 or 3 (Appendix 6).

Response was defined as a decrease of at least 50% from baseline in MADRS score (316, 317, CCT-002, CCT-003, CCT-004, 11984A, 13267A, 315, 11492A, 13926A, 14122A, 11985A, and 15906A) or HAM-D24 (305, 303, 304, and 12541A) at the end of the treatment period (week 6 or 8). Remission was defined as a MADRS total score of no more than 10 (305, 303, 316, 317, CCT-002, CCT-003, CCT-004, 11984A, 304, 13267A, 315, 11492A, 13926A, 14122A, 11985A, and 15906A) or a HAM-D17 total score of no more than 7 (12541A). There is evidence to support these thresholds for remission (see Appendix 6). If a trial reported results for multiple definitions of response or remission, the definition based on the MADRS or a HAM-D listed among the key secondary outcomes (i.e., part of hierarchical testing procedure) was summarized in this review. In the relapse prevention study (11985A), the time to relapse over the first 24 weeks of double-blind treatment was the primary outcome. In this study relapse was defined as a MADRS score of at least 22 or lack of efficacy as judged by investigator opinion. Depression symptom severity was assessed every two weeks during the open-label period, and at randomization, weeks 1, 2, and 4, then every four weeks during the double-blind period for all patients.

In the Liebowitz et al. trial,[56] which enrolled patients with MDD and social anxiety disorder, the primary outcome was the proportion of responders on the CGI-I scale. The CGI-I responder was defined as a score of 2, “much improved,” or 1, “very much improved,” for MDD and social anxiety disorder. To be rated as “much improved” on the overall CGI-I, individuals had to show at least moderate benefit in both MDD and social anxiety disorder features or marked benefit in one of the two domains if there was only minimal or no benefit in the other. To achieve a rating of “very much improved” on the combined CGI-I, individuals had to show marked benefit in both MDD and social anxiety disorder.

Functioning and Disability

Thirteen trials reported scores on the Sheehan Disability Scale (SDS), which measures the extent to which the patient’s global functioning is impaired by depressive symptoms. With this self-reported, three-item scale, patients rate the extent to which their work, social life or leisure activities, and home life or family responsibilities are impaired by symptoms (0

indicates no disability; 10 indicates extreme disability). Total scores range from 0 to 30, with higher scores indicating more severe disability. The MCID is not known (Appendix 6).

Three studies (15905A, 15906A, and 15907A) reported data for the UPSA-B, which is a performance-based measure of functional capacity that has been used to assess functional skill deficits in psychotic and other disorders, including major depression. It evaluates performance accuracy on everyday tasks that are considered necessary for independent functioning in the community. The UPSA-B consists of two subscales: managing finances (for example, counting correct change, writing a check to pay a bill) and communication with others (for example, calling an emergency telephone number, rescheduling a medical appointment). Raw scores of the two subscales are converted to scaled scores from 0 to 100, with higher scores indicating greater functional capacity.[30] An increase of 6.4 points (distribution-based method) or 7.0 points (anchor-based method) on the UPSA-B summary score was determined to be the clinically important difference to show a treatment response in patients with MDD;[61] however, an MCID for UPSA-B was not reported in the literature.

Cognitive function was assessed with several different tests, including the DSST and RAVLT, which were selected as primary outcomes in five studies (14122A, 12541A, 15905A, 15906A, and 15907A). The DSST is a measure of cognitive functioning that focuses on psychomotor speed. It is a timed task requiring patients to match geometric symbols to corresponding numbers as designated by an answer key. The number of correct symbol-number pairs given within the prescribed time limit determines the raw DSST score, which can range from 0 to 133. The RAVLT is a brief cognitive function test that assesses immediate memory span, capacity for new learning and recognition, and susceptibility to interference. Patients are asked to recall two or more lists of 15 nouns that have been read out loud to them after various lengths of time and in various formats, with one point awarded for every correctly recalled word. In Study 14122A the primary outcome was the composite z score of the DSST and RAVLT. No evidence to support the validity or MCID for the DSST, RAVLT or the composite z score of DSST and RAVLT in MDD was identified in the literature search conducted by CADTH (Appendix 6).

Harms

Reporting of adverse events included those that were observed by the investigator, spontaneously reported by the patient, or based on lab tests, vital signs, or other tests. An adverse event was any unfavourable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it was considered related to the drug. A treatment-emergent adverse event was defined as an adverse event with an onset that occurred after receiving the study drug and within 30 days after receiving the last dose of study drug, or a continuing adverse event diagnosed prior to the date of first dose of study drug that increased in severity after the start of dosing.

A serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, led to a congenital anomaly or birth defect, or was another important medical event that may have required intervention or exposed the patient to danger.

The Columbia Suicide Severity Rating Scale (C-SSRS) was used to assess suicidal ideation and behaviour in 15 studies (303, 304, 305, 13267A, 315, 316, 317, 14122A, CCT-002, CCT-003, 12541A, 318, 15905A, 15906A, and 15907A). The C-SSRS is a clinician-

rated instrument consisting of nine questions that evaluate the presence of suicidal ideation, behaviour, and severity. There is evidence to support its validity in adolescents with MDD (Appendix 6).

The Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) was used to assess changes in sexual functioning in one study (318). The CSFQ-14 consists of five domains of sexual functioning: desire/frequency (two items), desire/interest (three items), arousal/excitement (three items), orgasm/completion (three items), pleasure (one item), and two other items, for a total of 14. Each item is scored on a five-point Likert scale (1 = never and 5 = every day), with the total score ranging from 14 to 70 and higher scores representing higher sexual functioning.[54] There is evidence to support the validity of the CSFQ-14 in patients with MDD, but the MCID is not known (Appendix 6).

The Arizona Sexual Experience Scale (ASEX) was used to assess sexual dysfunction in six studies (11984A, 304, 13267A, 315, 316, and 317). ASEX is a patient-reported instrument consisting of five items that assess sexual drive, arousal, gender-specific erection or lubrication, ability to reach orgasm, and sexual satisfaction. Each item is scored from 1 to 6, with higher scores indicating greater dysfunction. Sexual dysfunction was defined as a total score of 19 or higher, a score of at least 5 on any item, or at least 4 on three or more items. There is evidence to support its validity in patients with MDD, although the MCID is not known (Appendix 6).

The Discontinuation-Emergent Signs and Symptoms checklist (DESS) was used to assess possible effects of discontinuation of antidepressant therapy. It is a clinician-rated checklist of 43 items that query for signs and symptoms that may be discontinuation-emergent.[6] A new or worsened adverse event scores 1 point, and the total score is the sum of all positive responses.[6] DESS was reported in five studies (316, CCT-002, 13267A, 315, and CCT-003).

Statistical Analysis

Thirteen short-term studies (305, 303, 316, 317, CCT-002, CCT-003, CCT-004, 11984A, 304, 13267A, 315, 12541A, and 11492A) were powered to test for differences between vortioxetine and placebo on the change from baseline to end of treatment in the MADRS or HAM-D24 total score (Table 9). Six of these trials also included an active control group (duloxetine: studies 11984A, 304, 13267A, 315, and 12541A; venlafaxine: Study 11492A) but none were powered to test for differences between the active comparators and vortioxetine.

Study 13926A used a noninferiority design to test for differences between vortioxetine 10 mg and venlafaxine XR 150 mg on the change from baseline to the end of treatment in the MADRS total score (Table 9). Vortioxetine was declared to be noninferior to venlafaxine if the upper limit of the calculated two-sided 95% confidence interval (CI) for the treatment difference at week eight between vortioxetine and venlafaxine was less than +2.5 points. The study's authors stated that +2.5 was smaller than the differences observed in superiority studies of venlafaxine versus placebo.[21]

Study 318 was powered to test for differences between vortioxetine versus escitalopram on the change from baseline to week eight for sexual function measured using the CSFQ-14 scale.

Study 14122A was powered to test for differences between vortioxetine and placebo on the change from baseline to week 8 in cognitive functioning as measured by a composite of the

DSST, RAVLT (acquisition), and RAVLT (delayed recall) scores (Table 9). The composite z score was calculated as follows: individual patient scores for each of the three measures were first standardized by subtracting the change from baseline for each individual patient score from the mean change from baseline for the sample, and then dividing by the standard deviation of the change from baseline. Each of the three standardized scores were then combined to create a composite score based on a weighting of 0.5 for the DSST, 0.25 for the RAVLT delayed recall, and 0.25 for the RAVLT acquisition.

Three studies (15906A, 15907A, and 15905A) were designed to detect differences between vortioxetine and control groups (placebo, escitalopram, or SSRI monotherapy) in the change from baseline to week 8 in the DSST. No references were provided for the mean difference and standard deviation used in the power calculations, which was the same for all three studies, despite the differences in the populations (working patients with MDD, patients in full or partial remission of MDD, or those with inadequate response to treatment), and the control treatment.

Study 11985A was powered to test for differences between vortioxetine and placebo on the time to relapse during the 24-week double-blind period of the trial (Table 9). The time to relapse was analyzed using a Cox model for the full analysis set (FAS) using two different conventions:

- Primary analysis of relapse
  - considers data up to week 24 in the double-blind period
  - all withdrawals (relapses or other reasons) occurring after week 24 (visit 16) are regarded as censored observations and are assigned the date of visit 16 as censoring time
  - withdrawals occurring before week 24 due to other reasons than lack of efficacy (relapse) are considered as non-relapsed and receive the date of withdrawal as censoring time.
- Secondary analysis of relapse
  - considers all data in the double-blind period
  - withdrawals due to other reasons than lack of efficacy (relapse) are considered as non-relapsed and receive the date of withdrawal as censoring time.

Table 9: Estimation of Sample Size

Study	Primary outcome[a]	Power, %	Withdrawal rate, %	Expected mean difference (SD)	Total planned sample size, (per group)	Significance level VOR versus PBO or control
305	HAM-D24	85	NR	3.5 (9.5)	560 (140)	5%
303	HAM-D24	85	NR	1.5 (6.0) at week 1	600 (300)	5%
316, 317	MADRS	80	[redacted]	[redacted]	[redacted]	[redacted]
CCT-002	MADRS	85	NR	3.0 (8.2)	600 - 615 (150)	5%, adjusted with the Dunnett-Hsu procedure
CCT-003	MADRS	80	NR	3.0 (8.2)	360 (120)	5%
CCT-004	MADRS	80	NR	3.5 [redacted]	480 (160)	[redacted]
11984A	MADRS	80	NR	3.5 (10.1)	660(132)	5%
304	HAM-D24	85	NR	3.5 (9.5)	560 (140)	5%

Study	Primary outcome[a]	Power, %	Withdrawal rate, %	Expected mean difference (SD)	Total planned sample size, (per group)	Significance level VOR versus PBO or control
13267A	MADRS	85	20	3.5 (9.5)	600 (150)	2.5% per VOR dose
315	MADRS	80	[redacted]	[redacted]	[redacted]	[redacted]
12541A	HAM-D24	80	NR	2.64 (8.0)	450 (150)	5%
11492A	MADRS	80	NR	3.7 (9.0)	384 (96)	5%
13926A Noninferiority	MADRS	80	20	0 (9)	410	5%[b] NI margin +2.5
14122A	Composite z score (DSST and RAVLT)	85[c]	20	0.25 (NR)	600 (200)	5% (2.5% per dose)
15905A	DSST	80	15	4.3 (7)	150 (50)	5%
15906A	DSST	80	15	4.3 (7)	150 (50)	5%
15907A	DSST	80	15	4.3 (7)	100 (50)	5%
11985A[d]	Time to relapse	91	65% drop out after OL VOR	Relapse rate PBO 0.2, VOR 0.1	OL: 650 DB: 420 (210)	5%
318	CSFQ-14	80	15	2.5 (8.5)	440 (220)	5%[e]
Liebowitz et al. (2017)	CGI-I response	79%	NR	Difference in % responders: 39%	40 (20)	5%
Levada et al. (2019)	Unclear	NR	NR	NR	NR	NR

DB = double-blind; CGI-I = Clinical Global Impression – Improvement; CSFQ-14 = Changes in Sexual Functioning Questionnaire Short-Form; DSST = Digit Symbol Substitution Test; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Scale; NI = noninferiority; NR = not reported; OL = open-label; PBO = placebo; RAVLT = Rey Auditory Verbal Learning Test; SD = standard deviation; VOR = vortioxetine.

[a] Change from baseline to end of treatment except for Study 11985A.

[b] Two-sided CI for vortioxetine versus venlafaxine; vortioxetine noninferior if the upper 95% CI was less than +2.5 points on the MADRS.

[c] 85% power for finding a specific dose significant, 90% power for at least one dose significant.

[d] The power of Study 11985A was re-evaluated during the study because a higher proportion of patients were eligible for randomization after the open-label period, and blinded data showed lower than expected number of relapses.

[e] Vortioxetine versus escitalopram.

Source: Clinical Study Report,[11-30] Levada et al. (2019),[55] Liebowitz et al. (2017).[56]

The main analyses for the primary outcomes for the manufacturer-sponsored trials are listed in Table 10. Continuous outcomes were analyzed using either an analysis of covariance (ANCOVA) model with last observation carried forward (LOCF) for missing data, or a mixed-effect model for repeated measures (MMRM) using observed case data. Continuous secondary outcomes were generally analyzed using the same model as the primary continuous outcome; however, in most trials the results of multiple sensitivity analyses were also reported for primary and secondary outcomes. These included analyses conducted using alternative statistical models (e.g., ANCOVA, MMRM), patient populations (e.g., FAS, per-protocol set [PPS]), missing data methods (e.g., observed case, LOCF), and model covariates (such as age, sex, body mass index). In 17 studies, dichotomous secondary outcomes were analyzed using logistic regression models (adjusted for key covariates) and LOCF methods for missing data (305, 303, 316, 317, CCT-002, CCT-003, CCT-004, 11984A, 304, 13267A, 315, 12541A, 13926A, 14122A, 318, 15906A, and 15907A). In studies 11492A and 11985A, dichotomous outcomes were analyzed using pairwise chi-square and Fisher's exact tests.

Liebowitz et al.[56] stated that continuous outcomes were analyzed using a two-sample independent t-test (alpha = 0.05) and group comparisons of dichotomous outcomes were conducted using an odds ratio (OR) analyses. In the study by Levada at al.[55] the differences between treatment groups at baseline and at eight weeks were analyzed using an MMRM that included 56 of 66 patients who completed the study. No power calculations were reported for this study. It is unclear which outcome was defined as primary and there was no control of inflated type I error due to multiple testing.

Table 10: Analysis of Primary Outcomes in Manufacturer-Sponsored Trials

Analysis	MADRS	HAM-D24	Composite z score (DSST and RAVLT)	DSST	CSFQ-14	Time to relapse
ANCOVA, LOCF, FAS Covariates: treatment, baseline score, site	11984A 11492A	304 12541A 303				
ANCOVA, LOCF, FAS Covariates: treatment, baseline score	CCT-003 CCT-002					
MMRM, OC[a] Covariates: treatment, site (or site group), visit, treatment by visit interaction, baseline score, baseline score by visit interaction	13267A 316 315 317 CCT-004	305	14122A	15906A 15905A 15907A	318	
ANCOVA, LOCF, FAS Covariates: treatment, baseline score, site	13926A (NI)[b]					
Cox proportional hazard model, FAS						11985A

ANCOVA = analysis of covariance; FAS = full analysis set; HAM-D24 = 24-item Hamilton Depression Rating Scale; LOCF = last observation carried forward; MADRS = Montgomery–Åsberg Depression Scale; MMRM = mixed-effect model for repeated measures; NI = noninferiority; OC = observed cases; RAVLT = Rey Auditory Verbal Learning Test.

[a] Outcomes were measured weekly for the first 2 weeks, then every 2 weeks until the end of the study. Exceptions: Study 15905A, 15906A, and 15907A; DSST was measured at baseline, week 1 and week 8.

[b] Primary analysis used the full analysis set; per-protocol set was a secondary analysis.

Source: Clinical Study Report.[11-30]

Fourteen trials used a hierarchical ordered testing strategy comprising the primary outcome and key secondary outcomes (303, 304, 305, 315, 316, 317, 11984A, 13267A, 14122A, 15905A, 15906A, and 15907A) or the primary outcome at multiple time points (12541A and 11492A) (Table 11). The strategy consisted of either one sequence or two sequences tested in parallel (usually with Bonferroni correction if two dosage regimens were tested concurrently). Study CCT-002 used the Dunnett-Hsu procedure, Study CCT-003 used the Fisher's least significant difference procedure, and CCT-004 used the Holm's step-down method to control for type I error for testing of multiple doses of vortioxetine for the primary outcome. Five studies did not mention any methods to control for multiplicity (13926A, 11985A, 318, Liebowitz et al., and Levada et al.).

Table 11: Methods to Control for Type I Error

Study	Statistical hierarchy
303	1: Change from baseline in HAM-D24 total score LOCF at week 6, significance level 0.05 2: Other efficacy end points were tested in 2 sequential orders; each sequence was tested at significance level 0.025; assuming a Bonferroni adjustment of 0.05/2 at this step: Sequence 1: • Change from baseline in HAM-D24 total score LOCF at week 5 • Change from baseline in HAM-D24 total score LOCF at week 4 • Change from baseline in HAM-D24 total score LOCF at week 3 • Change from baseline in HAM-D24 total score LOCF at week 2 • Change from baseline in HAMD-24 total score LOCF at week 1 Sequence 2 • HAM-D24 response rate LOCF at week 6 • MADRS remission rate LOCF at week 6 • CGI-I score LOCF at week 6 • Change from baseline in HAMD-24 total score LOCF at week 6 in subjects with baseline HAM-A total score > 19 • Change from baseline in MADRS-S total score LOCF at week 6 • Change from baseline in SDS total score LOCF at week 6 • Change from baseline in MADRS-S total score LOCF at week 4 • Change from baseline in MADRS-S total score LOCF at week 1 Testing stopped within each sequence with a non-significant test result
304	The testing order was as follows: • Change from baseline in HAM-D24 total score at week 8 (VOR 5 mg versus placebo, LOCF) • HAM-D24 response rate at week 8 (VOR 5 mg versus placebo, LOCF) • CGI-I at week 8 (VOR 5 mg versus placebo, LOCF) • Change from baseline in HAM-D24 total score at week 8 in subjects with baseline HAM-A total score ≥ 20 (VOR 5 mg versus placebo, LOCF) • Change from baseline in SDS total score at week 8 (VOR 5 mg versus placebo, LOCF) • MADRS remission rate at week 8 (VOR 5 mg versus placebo, LOCF) • Change from baseline in HAM-D24 total score at week 8 (VOR 2.5 mg versus placebo) The sequential testing procedure was stopped for all subsequent end points at the first occurrence of a non-significant end point (P ≥ 0.05)
305	Efficacy end points were tested in the following sequential order at significance level 0.05; as soon as an end point was non-significant at 0.05, the testing procedure stopped for all subsequent end points: • Change from baseline in HAM-D24 total score at week 8 (VOR 10 mg versus placebo, MMRM) (primary end point) • Change from baseline in SDS total score at week 8 (VOR 10 mg versus placebo, MMRM) • CGI-I at week 8 (VOR 10 mg versus placebo, MMRM) • HAM-D24 response rate at week 8 (VOR 10 mg versus placebo, LOCF) • Change from baseline in HAM-D24 total score at week 8 in subgroup of subjects with baseline HAM-A total score ≥ 20 (VOR 10 mg versus placebo, MMRM) • MADRS remission rate at week 8 (VOR 10 mg versus placebo, LOCF) • Change from baseline in HAM-D24 total score at week 8 (VOR 5 mg versus placebo, MMRM) • Change from baseline in SDS total score at week 8 (VOR 5 mg versus placebo, MMRM) • CGI at week 8 (VOR 5 mg versus placebo, MMRM) • HAM-D24 response rate at week 8 (VOR 5 mg versus placebo, LOCF) • Change from baseline in HAM-D24 total score at week 8 in subjects with baseline HAM-A ≥ 20 (VOR 5 mg versus placebo, MMRM) • MADRS remission rate at week 8 (VOR 5 mg versus placebo, LOCF)

Study	Statistical hierarchy
315	Efficacy end points were tested for each dose of VOR in the following sequential order at significance level 0.025; as soon as an end point was non-significant at 0.025, the testing procedure stopped for all subsequent end points for that dose: • Change from baseline in MADRS total score at week 8 (MMRM) • MADRS responders at week 8 (LOCF) • CGI-I at week 8 (MMRM) • Change from baseline in MADRS total score at week 8 in subjects with baseline HAM-A ≥ 20 (MMRM) • MADRS remissions at week 8 (LOCF) • Change from baseline in SDS total score at week 8 (MMRM)
316	The primary and key secondary efficacy end points were tested for each dose of VOR at a significance level of 0.025 in the sequential order as follows: • Change from baseline in MADRS total score at week 8 (MMRM) • MADRS responders at week 8 (LOCF) • Mean CGI-I at week 8 (MMRM) • Change from baseline in MADRS total score at week 8 in subjects with baseline HAM-A ≥ 20 (MMRM) • MADRS remissions at week 8 (LOCF) • Change from baseline in SDS total score at week 8 (MMRM) As soon as an end point was non-significant at 0.025, the testing procedure stopped for all subsequent end points for that dose
317	Efficacy end points for each VOR dose were tested in the following sequential order at significance level 0.025; as soon as an end point was non-significant at 0.025, the testing procedure stopped for all subsequent end points for that dose: • Change from baseline in MADRS total score at week 8 (MMRM) • MADRS responders at week 8 (LOCF) • Mean CGI-I at week 8 (MMRM) • Change from baseline in MADRS total score at week 8 in subjects with baseline HAM-A ≥ 20 (MMRM) • MADRS remissions at week 8 (LOCF) • Change from baseline in SDS total score at week 8 (MMRM)
CCT-002	The change from baseline in MADRS for each dose of VOR was tested versus placebo with adjustment for multiplicity based on the Dunnett-Hsu procedure.
CCT-003	Fisher's least significant difference procedure was used to control type I error for the different doses of VOR for the primary outcome (change from baseline in MADRS). [redacted]
CCT-004	[redacted]
11984A	To control the two-sided type I error over the primary and ordered key secondary efficacy end points, the 5 and 10 mg doses of VOR were tested separately versus placebo at a 0.025 level of significance, in the following order: 1. Mean change from baseline in MADRS total score at week 8 2. Mean change from baseline in HAM-D24 total score at week 8 3. Proportion of patients who respond to treatment (defined as a ≥ 50% decrease from baseline in MADRS total score) at week 8 4. Mean CGI-I score at week 8 5. Mean change from baseline in HAM-D24 total score in patients with a baseline HAM-A total score ≥ 20 6. Mean change from baseline in SDS total score at week 8 7. Proportion of patients who achieve remission (defined as a MADRS total score ≤ 10) at week 8 8. As soon as an end point was non-significant at the 0.025 level of significance within a dose (5 mg or 10 mg), the testing procedure was stopped for all subsequent end points for that dose.

Study	Statistical hierarchy
13267A	To adjust for multiplicity, the 15 mg and 20 mg doses of VOR were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.05/2 = 0.025. The following sequence of hierarchically ordered primary and key secondary end points was used: 1. Change from baseline at week 8 in MADRS total score (primary) 2. Response (defined as a ≥ 50% decrease from baseline in MADRS total score) at week 8 3. CGI-I score at week 8 4. Change from baseline at week 8 in MADRS total score in patients with a baseline HAM-A total score ≥ 20 5. Remission (defined as a MADRS total score ≤ 10) at week 8 6. Change from baseline at week 8 in SDS total score As soon as a hypothesis was rejected (that is, there was no statistically significant difference versus placebo at the 0.025 level of significance within a dose [15 mg or 20 mg]), the testing procedure was stopped for all subsequent end points for that dose.
12541A	For the primary efficacy analysis ANCOVA of the change from baseline in HAM-D24 total score at week 8 (FAS, LOCF), followed a hierarchically ordered hypotheses: • H1: No difference between VOR and placebo at week 8 • H2: No difference between VOR and placebo at week 6 • H3: No difference between VOR and placebo at week 4 • H4: No difference between VOR and placebo at week 2 • H5: No difference between VOR and placebo at week 1 As soon as an end point was non-significant at the 0.05 level of significance, the testing procedure was stopped for all subsequent end points.
11492A	For the primary outcome of change from baseline in MADRS total score (ANCOVA, LOCF, FAS) was tested in order as follows: • H1: No difference between 10 mg VOR and placebo at week 6 • H2: No difference between 5 mg VOR and placebo at week 6 • H3: No difference between 10 mg VOR and placebo at week 1 • H4: No difference between 5 mg VOR and placebo at week 1 The procedure stops if a null hypothesis is not rejected, and subsequent hypotheses are not tested and will consequently have the status of not showing a significant difference between VOR and placebo
13926A noninferiority	[redacted]
318	[redacted]
14122A	[redacted]

Study	Statistical hierarchy
	[redacted]
15905A	1. Change from baseline to week 8 for DSST using MMRM for VOR + SSRI versus SSRI group 2. Change from baseline to week 8 in UPSA-B using ANCOVA, LOCF for VOR + SSRI versus SSRI group 3. Change from baseline to week 8 for DSST using MMRM for VOR versus SSRI group 4. Change from baseline to week 8 in UPSA-B using ANCOVA, LOCF for VOR versus SSRI group
15906A	1. Change from baseline to week 8 for DSST using MMRM for VOR versus PBO group 2. Change from baseline to week 8 in UPSA-B using ANCOVA, LOCF for VOR versus PBO group
15907A	1. Change from baseline to week 8 for DSST using MMRM for VOR versus ESC group 2. Change from baseline to week 8 in UPSA-B using ANCOVA, LOCF for VOR versus ESC group
11985A	No control of type I error
Liebowitz et al. (2017)	No control of type I error
Levada et al. (2019)	No control of type I error

ANCOVA = analysis of covariance; CGI-I = Clinical Global Impression Scale – Improvement; DSST = Digit Symbol Substitution Test; ESC = escitalopram; FAS = full analysis set; H = hypothesis; HAM-A = Hamilton Anxiety Scale; HAM-D24 = 24-item Hamilton Depression Scale; LOCF = last observation carried forward; MADRS = Montgomery–Åsberg Depression Rating Scale; MMRM = mixed-effect model for repeated measures; OC = observed cases; PBO = placebo; PPS = per-protocol set; RAVLT = Rey Auditory Verbal Learning Test; SDS = Sheehan Disability Scale; SSRI = selective serotonin reuptake inhibitor; UPSA-B = University of San Diego Performance-Based Skills Assessment – Brief; VOR = vortioxetine.

Source: Clinical Study Report,[11-30] Levada et al. (2019),[55] Liebowitz et al. (2017).[56]

Analysis Populations

In all trials, the FAS included all randomized patients who received at least one dose of study medication and had a valid baseline value and at least one valid post-baseline value for the primary outcome. The PPS included patients in the FAS without any major protocol violations. The safety analysis included all randomized patients who received at least one dose of study drug.

Analysis of sexual dysfunction using data from the ASEX scale was limited to those with normal sexual function at baseline (11984A, 304, 13267A, 315, 316, and 317). The DESS checklist was reported for patients who completed the study and was assessed at the last treatment visit, plus one week and two weeks later. The analysis of the SDS total scores was based on patients who were employed in Study 13267A.

Patient Disposition

The disposition of participants in the included studies is presented in Table 12. Six studies did not report the number of patients screened. Among the patients screened for inclusion in the other RCTs, the percentage randomized ranged from 42% to 85%. Common reasons for screening failure were patients met exclusion criteria, did not meet inclusion criteria, or withdrew consent.

The proportion of patients who withdrew from the trials, and the reasons for withdrawal, were similar across treatment groups within studies, except in four trials (13926A, 11985A, 15906A, and Levada et al.), in which some variability was noted. In Study 13926A, 18% of patients in the vortioxetine group withdrew, compared with 27% in the venlafaxine group. Twice as many patients withdrew consent or withdrew due to adverse events from the venlafaxine group compared with the vortioxetine group. More patients in the vortioxetine and paroxetine groups withdrew from Study 15906A than placebo (14% and 16% versus

6% respectively), and in Levada et al.,[55] 25% in the escitalopram group withdrew compared with 12% for vortioxetine.

Study 11985A was a 24-week relapse prevention study in which patients were exposed to an open-label period of vortioxetine and responders were randomized to either placebo or vortioxetine. A total of 639 patients entered the open-label vortioxetine treatment period and 492 completed (77%). The main reasons for withdrawal were adverse events (8%), lack of efficacy (5%), or other reasons (10%). Of those who completed the open-label period, 92 did not qualify for randomization due to not fulfilling randomization criteria (8%), lack of efficacy (4%) adverse events (1%), or other (2%). Among the 400 patients randomized to placebo or vortioxetine, 46% of patients in the placebo group and 29% of those in the vortioxetine group withdrew from the study. Withdrawal due to lack of efficacy was reported more frequently in the placebo group than in the vortioxetine group (27% versus 14%, respectively). Most of these patients were considered relapsed (the primary outcome of the trial). Excluding the number of withdrawals due to lack of efficacy, the withdrawal rate was 19% in the placebo group and 25% in the vortioxetine group. The reasons for withdrawal are described in the Table 12.

Also notable were the withdrawals from Study CCT-004. In total, 530 patients entered the placebo run-in period, 493 (85%) of whom were randomized to treatment groups. The 47 patients who withdrew were either non-adherent or showed an increase or decrease of at least 25 points in the MADRS score over the week.

Some differences were observed between trials in the proportion of withdrawals. The proportion of patients who withdrew per group was generally higher (19% to 24%) for studies 303, 11984A, 318, 304, 315, 13926A, and Liebowitz et al., than that of other studies.

Table 12: Patient Disposition

	305			303		316			317			CCT-002			
	PBO	VOR 5 mg	VOR 10 mg	PBO	VOR 5 mg	PBO	VOR 10 mg	VOR 20 mg	PBO	VOR 10 mg	VOR 15 mg	PBO	VOR 5 mg	VOR 10 mg	VOR 20 mg
Screened, N	664			849		792			1111			720			
Randomized total N (%)	560 (84)[a]			600 (71)		462 (58)			469 (42)			600 (83)			
Randomized, N	140	140	140	300	300	157	155	150	160	157	152	152	144	150	154
Withdrawal, N (%)	13 (9)	11 (8)	18 (13)	64 (21)	56 (19)	18 (12)	31 (20)	28 (19)	27 (17)	26 (17)	31 (20)	16 (11)	17 (12)	18 (12)	22 (14)
Reasons for withdrawal, N															
Adverse event	2	1	5	11	9	2	9	7	6	8	12	6	2	9	9
Lack of efficacy	8	2	3	6	11	1	3	1	4	2	0	2	2	2	2
Withdrew consent	1	5	7	12	8	5	7	3	2	6	10	3	9	3	4
Lost to follow-up	0	1	1	22	17	7	7	10	7	7	3	1	2	4	2
Protocol violation	1	1	1	11	5	2	2	5	4	3	3	1	1	0	4
Non-adherent	0	1	0	2	3	0	2	0	2	0	1	3	1	0	0
Other	1	0	1	0	3	1	1	2	2	0	2	0	0	0	1
FAS, N[b]	139	139	139	286	292	155	154	148	149	143	142	151	144	148	150
Safety, N[c]	140	140	139	298	299	157	155	150	160	154	151	151	144	148	150
PPS, N[d]	134	134	132	266	269	147	139	136	140	139	132	140	136	135	137

FAS = full analysis set; PBO = placebo; PPS = per-protocol set; VOR = vortioxetine.

[a] Study also included a low-dosage vortioxetine group (1 mg per day or 2.5 mg per day), which was excluded from this report.

[b] All patients who received at least one dose of study medication and had a baseline and one post-baseline outcome measure.

[c] All patients who received at least one dose of study medication.

[d] All FAS patients without major protocol violations.

Source: Clinical Study Report,[11-30] Levada et al. (2019),[55] Liebowitz et al. (2017).[56]

Table 12: Patient Disposition (continued)

	CCT-003			11984A				304			13267A			
	PBO	VOR 5 mg	VOR 10 mg	PBO	VOR 5 mg	VOR 10 mg	DUL 60 mg	PBO	VOR 5 mg	DUL 60 mg	PBO	VOR 15 mg	VOR 20 mg	DUL 60 mg
Screened, N	447			NR				961			731			
Randomized total N (%)	366 (82)			776[a]				611 (64)[a]			608 (83)			
Randomized, N	124	119	123	152	159	153	157	153	153	152	158	152	151	147
Withdrawal, N (%)	11 (9)	7 (6)	10 (8)	25 (17)	35 (22)	34 (23)	42 (27)	33 (22)	31 (20)	42 (28)	25 (16)	34 (23)	26 (17)	16 (11)
Reasons for withdrawal, N														
Adverse event	6	3	4	12	18	15	19	7	12	17	7	10	17	7
Lack of efficacy	1	2	1	5	3	4	6	1	2	0	6	8	2	1
Withdrew consent	3	2	3	8	8	11	8	6	5	6	6	6	2	2
Lost to follow-up	1	0	0	0	2	0	3	8	8	11	1	1	0	2
Protocol violation	0	0	1	0	3	2	4	5	2	5	5	3	2	1
Non-adherent	0	0	1	0	0	2	1	3	0	2	0	1	0	1
Other	0	0	0	0	1	0	1	3	2	1	0	5	3	2
FAS, N[b]	124	119	122	145	155	151	149	149	153	149	158	149	151	146
Safety, N[c]	124	119	122	148	157	151	155	151	153	150	158	151	151	147
PPS, N[d]	118	117	120	122	127	110	116	122	131	126	144	140	136	135

DUL = duloxetine; FAS = full analysis set; PBO = placebo; PPS = per-protocol set; VOR = vortioxetine.

[a] Study also included a low-dose vortioxetine group (1 mg per day or 2.5 mg per day) which was excluded from this report.

[b] All patients who received at least one dose of study medication and had a baseline and one post-baseline outcome measure.

[c] All patients who received at least one dose of study medication.

[d] All FAS patients without major protocol violations.

Source: Clinical Study Report,[11-30] Levada et al. (2019),[55] Liebowitz et al. (2017).[56]

Table 12: Patient Disposition (continued)

	315				12541A			11492A				13926A	
	PBO	VOR 15 mg	VOR 20 mg	DUL 60 mg	PBO	VOR 5 mg	DUL 60 mg	PBO	VOR 5 mg	VOR 10 mg	VEN 225 mg	VOR 10 mg	VEN 150 mg
Screened, N	1141				NR			NR				NR	
Randomized total N (%)	614 (45)				453			429				443	
Randomized, N	161	147	154	152	145	157	151	105	109	101	114	213	230
Withdrawal, N (%)	32 (20)	34 (23)	41 (27)	37 (24)	17 (12)	20 (13)	23 (15)	18 (17)	10 (9)	18 (18)	20 (18)	38 (18)	62 (27)
Reasons for withdrawal, N													
Adverse event	4	14	14	10	6	10	15	4	3	7	16	14	32
Lack of efficacy	9	0	2	1	7	2	0	6	6	3	2	8	3
Withdrew consent	5	5	4	6	1	2	2	4	0	4	1	5	13
Lost to follow-up	8	8	11	15	0	0	2	1	0	1	0	4	2
Protocol violation	4	3	3	2	3	3	2	0	1	2	0	1	5
Non-adherent	1	3	4	1	0	0	0	0	0	0	1	2	4
Other	1	1	3	2	0	3	2	3	0	1	0	4	3
FAS, N[a]	153	145	147	146	145	155	148	105	108	100	112	209	215
Safety, N[b]	159	147	154	150	145	156	151	105	108	100	113	211	226
PPS, N[c]	150	127	135	134	133	139	124	93	104	84	98	180	164

DUL = duloxetine; FAS = full analysis set; NR = not reported; PBO = placebo; PPS = per-protocol set; VEN = venlafaxine; VOR = vortioxetine.

[a] All patients who received at least one dose of study medication and had a baseline and one post-baseline outcome measure.

[b] All patients who received at least one dose of study medication.

[c] All FAS patients without major protocol violations.

Source: Clinical Study Report,[11-30] Levada et al. (2019),[55] Liebowitz et al. (2017).[56]

Table 12: Patient Disposition (continued)

	CCT-004			11985A		318		Liebowitz et al. (2017)		Levada et al. (2019)	
	PBO	VOR 10 mg	VOR 20 mg	PBO	VOR 5 mg to 10 mg	ESC 10 mg to 20 mg	VOR 10 mg to 20 mg	PBO	VOR 10 mg to 20 mg	VOR 10 mg to 20 mg	ESC 10 mg to 20 mg
Screened, N	662			NR		711		53		119	
Entered OL or run-in phase	530 (80)			639[a]		NA		NA		NA	
Randomized total N (%)	493 (68)			400 (63)		447 (63)		42 (79)		66 (55)	
Randomized, N	164	165	164	194	206	222	225	21	21	41	25
Withdrawal, N (%)	15 (10)[b]	13 (8)	12 (7)	90 (46.4)	81 (39.3)	43 (19)	56 (25)	5 (24)	4 (19)	5 (12)	5 (25)
Reasons for withdrawal, N (%)											
Adverse events	4 (3)	6 (4)	7 (4)	5 (2.6)	16 (7.8)	14 (6.3)	20 (8.9)	0	0		
Lack of efficacy	1 (1)	0	0	52 (27.1)	28 (13.7)	0 (0.0)	6 (2.7)	0	0		
Withdrew consent	6 (4)	4 (3)	4 (3)	7 (3.6)	3 (1.5)	7 (3.2)	9 (4.0)	4 (19)	1 (5)	5 (12)	5 (25)
Lost to follow-up	1 (1)	0	0	0 (0.0)	2 (1.0)	13 (5.9)	12 (5.3)	0	3 (14)		
Protocol violation	1 (1)	0	0	11 (5.7)	8 (3.9)	8 (3.6)	4 (1.8)	1 (5)	0		
Non-adherent	1 (1)	1 (1)	1 (1)	3 (1.6)	4 (2.0)	0 (0.0)	1 (0.4)	0	0		
Other	1 (1)[b]	2 (1)	0	10 (5.2)	18 (8.8)	1 (0.5)	4 (1.8)	0	0		
FAS, N[c]	161	165	163	192	204	207	217	20	20		
Safety, N[d]	161	165	163	192	204	221	224	20	20		
PPS, N[e]	158	162	156	167	176	195	192	NA	NA		

ESC = escitalopram; FAS = full analysis set; NA = not applicable; NR = not reported; OL = open-label; PBO = placebo; PPS = per-protocol set; VOR = vortioxetine.

[a] The study involved two phases. Patients were screened into a 12-week OL phase. Patients who completed the open-label phase (n = 492) and experienced remission (MADRS total score ≤ 10) at weeks 10 and 12 were randomized to the double-blind period lasting 24 to 64 weeks.

[b] Includes one patient who withdrew prior to receiving treatment.

[c] All patients who received at least one dose of study medication and had a baseline and one post-baseline outcome measure.

[d] All patients who received at least one dose of study medication.

[e] All FAS patients without major protocol violations.

Source: Clinical Study Report,[11-30] Levada et al. (2019),[55] Liebowitz et al. (2017).[56]

Table 12: Patient Disposition (continued)

	14122A			15906A			15905A			15907A	
	PBO	VOR 10 mg	VOR 20 mg	PBO	VOR 10 mg	PAR 20 mg	VOR 10 mg to 20 mg + SSRI	VOR 10 mg to 20 mg	SSRI	VOR 10 mg to 20 mg	ESC 10 mg to 20 mg
Screened, N	887			199			NR			144	
Randomized total N (%)	602 (68)			152 (76)			151			101 (70)	
Randomized, N	198	197	207	49	48	55	52	50	49	51	50
Withdrawal, N (%)	33 (17)	22 (11)	29 (14)	3 (6)	7 (14)	8 (16)	5 (10)	3 (6)	5 (10)	4 (8)	5 (10)
Reasons for withdrawal, N (%)											
Adverse events	8 (4.1)	7 (3.6)	11 (5.3)	1 (2)	3 (6)	3 (6)	3 (6)	1 (2)	2 (4)	3 (6)	1 (2)
Lack of efficacy	10 (5.1)	2 (1.0)	2 (1.0)	1 (2)	2 (4)	1 (2)	0	0	1 (2)		
Withdrew consent	7 (3.6)	3 (1.5)	5 (2.4)	0	1 (2)	1 (2)	0	0	0	0	1 (2)
Lost to follow-up	3 (1.5)	3 (1.5)	5 (2.4)	0	0	0	0	1 (2)	0		
Protocol violation	0 (0.0)	2 (1.0)	4 (1.9)	0	0	1 (2)	0	0	1 (2)	0	1 (2)
Non-adherent	0 (0.0)	1 (0.5)	0 (0.0)	0	0	1 (2)	1 (2)	0	0		
Other	5 (2.6)	4 (2.1)	2 (1.0)	1 (2)[a]	1 (2)	1 (2)[a]	1 (2)	1 (2)	1 (2)	1 (2)[a]	2 (4)[a]
FAS, N[b]	194	193	204	48	48	52	51	50	49	50	49
Safety, N[c]	196	195	207	48	48	54	52	50	49	50	49
PPS, N[d]	180	182	180	NR	NR	NR	NR	NR	NR	NR	NR

ESC = escitalopram; FAS = full analysis set; NR = not reported; PBO = placebo; PPS = per-protocol set; VOR = vortioxetine.

[a] Includes one patient who withdrew prior to receiving treatment.

[b] All patients who received at least one dose of study medication and had a baseline and one post-baseline outcome measure.

[c] All patients who received at least one dose of study medication.

[d] All FAS patients without major protocol violations.

Source: Clinical Study Report,[11-30] Levada et al. (2019),[55] Liebowitz et al. (2017).[56]

Exposure to Study Treatments

The mean exposure to study treatments was 5.4 to 5.9 weeks in the six-week RCTs (303 and 11492A) and from 6.5 to 7.9 weeks in the eight-week trials (305, 316, 317, CCT-002, CCT-003, CCT-004, 11984A, 304, 13267A, 315, 12541A, 13926A, 14122A, 318, 15905A, 15906A, and 15907A). In general, the mean exposure to treatment was similar between groups within studies except for 13926A, in which the mean exposure was lower for venlafaxine (6.5 weeks) compared to vortioxetine (7.4 weeks). This difference can be explained by the higher withdrawal rate in the venlafaxine group.

In the relapse prevention study (11985A), the mean exposure to treatment during the double-blind period was 30.1 weeks. The primary end point was measured after 24 weeks of treatment; however, 67% of patients in the vortioxetine group and 60% of patients in the placebo group were treated beyond 24 weeks.[16,50] Patients in the vortioxetine group accumulated a total of 116.0 patient-years of exposure and the placebo group accumulated 97.8 patient-years of exposure during the double-blind phase.

No exposure information was reported in the studies by Liebowitz et al.[56] or Levada et al.[55]

Critical Appraisal

Internal Validity

The studies by Liebowitz et al. and Levada et al. had several key limitations, including small sample size, single-centre design, unclear methods to randomize patients and conceal allocation, and inadequate reporting of statistical methods and results. In addition, the study by Levada et al. was open-label and did not analyze patients using an intention-to-treat (ITT) approach. Due to these limitations, no conclusions can be drawn from these studies.

Twenty manufacturer-sponsored, randomized, double-blind trials met the inclusion criteria. Fifteen of the RCTs used acceptable methods to randomize patients and conceal allocation that included use of a central computer or voice response system to allocate patients to treatment groups. However, five studies used sealed envelopes to assign patients to treatment groups and it was unclear if allocation was adequately concealed (Study 11984A, 12541A, 11492A, CCT-004, and 11985A).

Of the 20 trials, only four were designed to compare vortioxetine to an active comparator. Although seven of the placebo-controlled trials included an active comparator, none were powered to detect differences between active agents and vortioxetine, thus any non-statistically significant differences in efficacy outcomes cannot be interpreted as noninferiority.

All studies used identical-looking tablets or capsules to maintain double-blinding. Some unblinding may have occurred among patients previously treated with antidepressants, as these patients may be familiar with the side effect profiles of SSRIs or SNRIs. Nausea was a frequent adverse event reported among those receiving active treatments and may have led to unblinding. Given the subjective nature of the outcomes, unblinding is of concern and may potentially bias the outcome assessments. In the noninferiority study, blinding offers no protection against an investigator biasing the results toward a preconceived belief in equivalence by assigning similar ratings to the treatment responses of all patients.[62] During the double-blind period of the relapse prevention study, the presence of discontinuation symptoms and/or the absence of common adverse events in patients who were randomized

to the placebo group, after having received vortioxetine during the open-label period, may have contributed to an unblinding of the investigator and a biasing of the results in favour of the vortioxetine group.

Fourteen of the included studies assessed change in depression scores as their primary outcome using validated outcome measures (HAM-D, MADRS) with established MCIDs. Time to relapse (survival analysis), sexual functioning (CSFQ-14) and cognitive functioning (composite z score, or DSST) were assessed as primary outcomes in each of the three remaining studies. No MCIDs have been established for the CSFQ-14, the composite z score (DSST and RAVLT) or DSST. It is therefore difficult to interpret a change score on the CSFQ-14, DSST, and RAVLT, and it is unclear how these measures correlate to a patient's day-to-day sexual or cognitive functioning.

Three studies (13926A, 11985A, and 318) did not describe any methods to control for multiplicity. Thirteen trials reported using a hierarchical ordered testing strategy or other procedures to control for inflated type I error due to multiple testing. However, the authors continued conducting statistical tests after outcomes in the hierarchy failed to reach statistical significance. We therefore cannot interpret the statistical significance of outcomes or comparisons that fall after the hierarchy was stopped. Any statistically significant outcomes outside the hierarchy should be interpreted as inconclusive.

It is unclear if the three studies (15906A, 15907A, and 15905A) designed to detect differences between vortioxetine and control groups (placebo, escitalopram, or SSRI monotherapy) in the change from baseline to week 8 in the DSST were adequately powered. Although no references were provided, the power calculations appear to be based on the difference observed between vortioxetine and placebo in Study 14122A. However, two of the studies had active comparators and enrolled patients receiving therapy for the MDD and showing either an incomplete response, or a full or partial response to treatment. All three failed to demonstrate statistically significant differences between vortioxetine and comparator on the primary outcome.

All trials used a modified ITT population (patients who took the study drug and had a baseline and post-baseline outcome measure) for the primary efficacy outcome, not a true ITT analysis. In 11 trials, the SDS scores were reported for 49% to 81% of patients in the FAS; only one study provided an explanation for the missing data. The proportion of withdrawals exceeded 20% in six studies (303, 11984A, 318, 304, 315, and 13926A) and the magnitude of withdrawals could potentially threaten the validity of the results. Of these trials, only 13926A and 318 accounted for withdrawals in their power calculations (assuming 20% and 15% withdrawal rate, respectively). In the noninferiority study, 13926A, statistically significantly more patients on venlafaxine withdrew than vortioxetine (27% versus 18%). Within the studies, the reasons for withdrawal were generally similar between treatment groups except in Study 13926A, in which there were twice as many withdrawals due to adverse events or withdrawal of consent in the venlafaxine group.

The methods to manage missing data varied across the included studies (LOCF or observed cases); however, in most trials, the overall findings were similar regardless of the model used. In the MMRM, missing data were assumed to be missing at random, but some data may be missing not at random (i.e., due to lack of efficacy or adverse events). The Health Canada reviewer stated that the MMRM may overestimate the treatment effects and the true effect may lie between the results of the MMRM and ANCOVA/LOCF models.[6] The LOCF also assumes that there is no change in outcomes at subsequent time points, which may not be a valid assumption.

Study 13926A found vortioxetine was noninferior to venlafaxine by a margin of +2.5 points on the MADRS total score. Considering that pooled data from a number of antidepressants[5] showed a mean difference (MD) of 2 points between active treatments and placebo, the selected noninferiority margin may be considered overly large. Moreover, the estimated MCID is 2 points for the MADRS total score, thus the chosen noninferiority margin exceeds this value. In this study vortioxetine was noninferior to venlafaxine based on the FAS and PPS analysis, although the upper limit of the 95% CI was higher for the PPS analysis (1.99) compared with the FAS (0.63). In a noninferiority study the PPS analysis is generally a more conservative estimate than the FAS analysis because it excludes patients who are non-adherent to treatments or have other protocol violations that tend to dilute the treatment effect and may bias toward the null (i.e., finding the treatment noninferior). Use of LOCF to impute missing data in a noninferiority study may result in bias toward declaring noninferiority between treatments. More patients in the venlafaxine group withdrew early (27%) than in the vortioxetine group (18%). The doses of active treatments used in the trial were clinically similar and within dosing guidelines.

The relapse prevention study (11985A) used a randomized withdrawal design in which patients who achieved remission to open-label vortioxetine were randomized to placebo, or ongoing vortioxetine therapy (double-blind). While the 12-week open-label vortioxetine treatment period and the 24-week double-blind period may be considered acceptable by regulatory bodies, longer durations of stabilization may be preferable.[6] In this study, patients had to meet the criteria for remission (MADRS score ≤ 10) for a minimum of two weeks to enter the withdrawal phase of the trial; in clinical practice, longer periods of stabilization may be recommended before considering changing therapy. Approximately 60% of patients in Study 11985A met remission criteria for at least four weeks and 37% met criteria for six or more weeks.[6] After randomization, there were differential losses to follow-up with 46% of patients in the placebo group and 39% in the vortioxetine group withdrawing from the trial. Approximately one-half (58%) of the withdrawals in the placebo group and one-third (35%) of the withdrawals in the vortioxetine group were due to a lack of efficacy (which overlapped with the primary end point of the study: relapse). Reasons for withdrawal other than a lack of efficacy were higher in the vortioxetine group compared to the placebo group (26% versus 19%). In the survival analysis, it is possible that censored patients who withdrew from the study due to adverse events or other reasons may have experienced a differential risk of relapse compared to those patients who remained in the study.[63] Due to the differential withdrawal due to relapse in the placebo and vortioxetine groups, the analysis of secondary outcomes analyzes using ANCOVA models and either LOCF or observed cases data was considered biased according to the Health Canada Reviewers Report.[6] Moreover, there was no control for multiplicity for the secondary outcomes, creating an inflated risk of type I error, and any statistically significant findings should be interpreted as inconclusive.

External Validity

Although the patients enrolled may be generalizable to a subset of patients seeking treatment in Canada, the generalizability to the broader MDD population has been questioned because of the exclusion of patients with mild depression, treatment-resistant depression, comorbid psychiatric illnesses, substance abuse, or those at risk of suicide.[64-67] Studies that examined the characteristics of individuals seeking care for depression in community-based practices found that the minority of patients would qualify for antidepressant trials.[64-67] The patients enrolled in the vortioxetine trials were predominantly outpatients in their mid 40s, with a higher proportion of females than males, and MADRS

scores in the moderate-to-severe MDD range. All but one trial excluded adults who were 75 years of age or older and eight excluded those who were 65 years or older; the data in older adults are therefore limited. In several trials, the number of patients screened was not reported, or less than half of those screened were eligible for and enrolled in the trials, suggesting there may be differences between the screened and enrolled populations. Few details were available on the patients screened, and there is no information that can be used to assess the similarity between patients enrolled and those seeking care at the study sites. However, the inclusion and exclusion criteria used in the vortioxetine studies were similar to those used in other antidepressant trials, and generalizability may be restricted. Generalizability may be further limited by the exclusion of patients receiving psychotherapy or specific concomitant medications. The excluded medications were drugs to manage psychiatric or neurologic disorders and also cardiovascular conditions, chronic pain, and migraines. Studies 11492A, 316, and 13267A also restricted the use of proton-pump inhibitors, which are commonly prescribed agents.

Limited data were available on the use of vortioxetine in elderly patients. Of the 16 included studies, one exclusively enrolled patients 65 years of age or older (N = 453), eight excluded patients over 65 years of age, and 11 studies excluded patients older than 75.

The trials with an active comparator (duloxetine, venlafaxine, or paroxetine) excluded patients who previously had not responded to that agent, and the generalizability of the observed treatment effects in patients with a history of non-response to certain drugs is unclear.

All trials included Health Canada–approved doses of vortioxetine (5 mg to 20 mg per day). In eight trials, patients who received vortioxetine 5 mg per day may have received a suboptimal dose, as the majority of patients enrolled were younger than 65 years of age. The recommended starting dose in adults less than 65 years old is 10 mg daily.

The daily dose of active comparators (duloxetine 60 mg, venlafaxine XR 150 mg, or 225 mg, escitalopram 10 mg to 20 mg) was consistent with Health Canada recommendations. All but four studies used fixed dosing regimens, which do not allow for dose adjustments based on the patient's response or tolerance to the medication and do not reflect clinical practice.

Nineteen of the studies were short-term trials. While six to eight weeks of therapy may be sufficient to demonstrate a difference versus placebo in terms of depression symptom severity and are consistent with FDA and European Medicines Agency guidelines, this treatment duration is not consistent with the standard of care in Canada[9] and does not provide information on long-term tolerability or persistence with treatment.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. See Appendix 4 for detailed efficacy data and Appendix 5 for the meta-analysis conducted by CADTH.

There was no information available on hospitalizations or emergency room visits, which were outcomes of interest that were listed in the CDR review protocol.

Health-Related Quality of Life

The impact of treatment on HRQoL was reported in five RCTs using the SF-36 questionnaire (305, 303, 11984A, 11492A, and 11985A), the Q-LES-Q in two studies (13267A and 13926A) and the EQ-5D-3L in one study (15906A). These outcomes were outside the statistical testing procedures used to control the risk of type I error related to multiple testing.

Table 13 summarizes data from four short-term studies on the MDs observed between active treatments and placebo in the change from baseline scores for the eight SF-36 domains. In all studies, the subscale scores increased from baseline to the end of treatment for placebo, vortioxetine, duloxetine, and venlafaxine, suggesting improved HRQoL. MDs in the subscale scores ranged from [redacted] for vortioxetine, from [redacted] for duloxetine and from [redacted] for venlafaxine versus placebo. In two studies (305 and 11492A), some of the subscale scores statistically significantly favoured vortioxetine versus placebo, and the differences exceeded 4 points. In patients with depression there are no known MCIDs for the domain scores; but in a general population, a change of 2 to 4 points in each domain of the SF-36 indicates a clinically meaningful improvement as determined by the patient.

Table 13: Treatment Differences Versus Placebo in SF-36 Subscale Mean Change from Baseline Scores (Studies 305, 303, 11984A, and 11492A)

Domain	MD versus placebo in change from baseline scores		
	VOR 5 mg or 10 mg (range)	DUL 60 mg	VEN 225 mg
Physical functioning	[redacted]	[redacted]	[redacted]
Role physical	[redacted]	[redacted]	[redacted]
Bodily pain	[redacted]	[redacted]	[redacted]
General health	[redacted]	[redacted]	[redacted]
Vitality	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]
Role emotional	[redacted]	[redacted]	[redacted]
Mental health	[redacted]	[redacted]	[redacted]

DUL = duloxetine; MD = mean difference ; VEN = venlafaxine extended release; VOR = vortioxetine.

Source: Clinical Study Report.[11,12,14,15]

In the relapse study (11985A), all SF-36 subscale scores increased from baseline (the end of the open-label period) to week 24 for the vortioxetine group, except for the physical functioning domain, which decreased by 0.5 points. For the placebo group, there was a decrease in scores for the majority of domains (range −3.3 to 0.5). Treatment differences versus placebo ranged from −1.0 (physical functioning) to 5.3 (mental health) and were statistically different for the mental health and bodily pain domains.

In studies 13267A and 13926A, the mean baseline Q-LES-Q SF scores were between 33.2 and 34.8 and were similar across treatment groups. The adjusted change from baseline to end of treatment scores were 5.2 (placebo), 8.5 to 9.8 (vortioxetine), 8.6 (venlafaxine 150 mg), and 12.7 (duloxetine) (Appendix 4, Table 25). The differences between placebo and vortioxetine 5 mg or 10 mg, or duloxetine were statistically significant (13267A). No statistically significant difference was found between vortioxetine 10 mg and venlafaxine 150 mg in Study 13926A.

In Study 15906A, the placebo, vortioxetine, and paroxetine groups showed an increase in the EQ-5D-3L index scores and VAS scores from baseline to week 8, but there were no statistically significant differences found between groups. The MD in the change from baseline to week 8 in the EQ-5D-3L index score was 0.02 (95% CI, 0.06 to 0.11) and the mean difference in VAS scores was 4.1 (95% CI, −2.6 to 10.8) for vortioxetine versus placebo (Appendix 4, Table 26).

Disability

The SDS was reported as a secondary outcome in 13 short-term trials (305, 303, 316, 317, CCT-002, CCT-003, CCT-004, 11984A, 304, 13267A, 315, 13926A, and 15905A) (Appendix 4, Table 27) and in the relapse prevention study (11985A) (Appendix 4, Table 28). The SDS is scored from 0 to 30, with higher scores indicating more severe impairment of patients' work, family, and social life. No evidence on the validity or MCID of the SDS was found in the literature. SDS scores were reported for a subset of patients in 11 trials, ranging from 49% to 81% of patients in the FAS (studies 305, 303, 316, 317, CCT-002, 11984A, 304, 13267A, 315, and 13926A). No explanations for the missing data were provided, except in Study 13267A, which based the analysis on the patients who were employed.

At baseline, the mean SDS scores per treatment group were lowest for Study 15906A (12.4 to 13.6), which enrolled patients already on SSRI treatment, and highest for studies 305, 317 and 13267A (range 19.8 to 21.0), among the short-term trials. The adjusted mean change from baseline to the end of treatment ranged from −2.9 to −9.4 for placebo, −4.0 to −10.3 for vortioxetine, and −3.0 to −11.4 for active control groups. The changes from baseline scores were similar across the vortioxetine dosage groups within studies.

The inclusion criteria for 11 placebo-controlled short-term trials were deemed sufficiently similar, making a meta-analysis feasible. Forest plots of the pooled data are presented in Appendix 5, Figure 7 and Figure 8. Compared with placebo, the change from baseline scores were statistically significantly different favouring vortioxetine 10 mg (mean difference [MD] −1.4; 95% CI, −2.0 to −0.8), vortioxetine 20 mg (MD −1.8; 95% CI, −2.8 to −0.9) and duloxetine (MD −3.2; 95% CI, −5.5 to −0.9) (Table 14). The differences between vortioxetine 5 mg and vortioxetine 15 mg and placebo were not statistically significant. The degree of statistical heterogeneity varied, with I^2 values showing high heterogeneity for the comparison of vortioxetine 15 mg and duloxetine versus placebo (67% and 80%). The comparisons between duloxetine and vortioxetine 5 mg, 15 mg, or 20 mg were statistically significantly different favouring duloxetine (5 mg: MD 1.9; 95% CI, 0.6 to 3.3; 15 mg: MD 2.8; 95% CI, 1.0 to 4.5; 20 mg: MD 2.0; 95% CI, 0.2 to 3.9) (Table 14). No statistically significant differences were observed between vortioxetine 10 mg and duloxetine.

In the active-controlled studies, no statistically significant differences were found between vortioxetine 10 mg and venlafaxine XR 150 mg (MD −1.0; 95% CI, −2.6 to 0.5) in Study 13926A, between vortioxetine plus SSRI and SSRI alone (MD −1.2; 95% CI, −3.8 to 1.3), or vortioxetine and SSRI (MD −2.3; 95% CI, −4.9 to 0.3) in Study 15905A (Appendix 4, Table 27).

In the relapse prevention study (11985A), the mean baseline SDS scores (at the end of the open-label vortioxetine treatment period) were 8.9 points in the placebo group and 9.1 points in the vortioxetine group. There was a statistically significant difference in the SDS change from baseline (end of open-label period) to week 24 between the vortioxetine and placebo groups (MD −1.8; 95% CI,

−3.2 to −0.4), although this should be interpreted as inconclusive as there was no control for multiplicity among the secondary outcomes tested (Appendix 4, Table 28).

Table 14: Meta-Analysis of Change from Baseline in Sheehan Disability Scale for Short-Term Trials

Outcome/intervention	Comparison versus placebo			Comparison versus duloxetine		
SDS[a]	N trials	MD (95% CI)[b]	I^2	N trials	MD (95% CI)[b]	I^2
VOR 5 mg	6	−0.67 (-1.43, 0.10)	20	2	**1.91 (0.55 to 3.28)**	0
VOR 10 mg	7	**−1.39 (−2.03 to −0.75)**	0	1	0.10 (−1.98 to 2.18)	0
VOR 15 mg	3	−0.91 (−3.27 to −1.46)	67	2	**2.76 (1.04 to 4.49)**	6
VOR 20 mg	5	**−1.84 (−2.78 to −0.90)**	28	2	**2.04 (0.17 to 3.90)**	23
DUL 60 mg	4	**−3.16 (−5.46 to −0.87)**	80	--	--	--

CI = confidence interval; DUL = duloxetine; MD = mean difference; VOR = vortioxetine.

Note: Comparisons in bold had a 95% CI that excluded the null.

[a] Sheehan Disability Scale ranges from 0 (no disability) to 30 (severe disability). A negative MD indicated a reduction in disability (i.e., improvement) favouring the experimental treatment versus control.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 with data from the Clinical Study Report for studies 305, 303, 316, 317, CCT-002, CCT-003, 11984A, 304, 13267A, 315, and CCT-004.[12-15,18-21,23,26]

Remission

The proportion of patients achieving remission at week 6 or 8 was reported in 16 of the manufacturer-sponsored short-term trials, as well as the sexual functioning study (318) and the longer-term relapse prevention study (11985A). Remission was defined as a MADRS total score of no more than 10 in 16 trials (305, 303, 316, 317, CCT-002, CCT-003, 11984A, 304, 13267A, 315, 11492A, 13926A, 15906A, CCT-004, 318, and 14122A), HAM-D17 total score of no more than 7 in one trial (12541A), or as both MADRS total score of 10 or lower and a HAM-D17 total score of 7 or lower in one trial (11985A) (Appendix 4,Table 29, Table 30, and Table 31).

In the short-term efficacy trials, 8% to 34% of patients who received placebo were in remission at the end of treatment (week 6 or 8), compared to 21% to 49% for those on vortioxetine, 26% to 54% for those on duloxetine, 41% to 55% for those on venlafaxine, and 29% for those who received paroxetine. Pooled data from the 15 placebo-controlled efficacy trials showed that those on vortioxetine 10 mg or 20 mg, duloxetine, paroxetine, or venlafaxine 225 mg were statistically significantly more likely to achieve remission than those on placebo (risk difference [RD] 9%, 11%, 14%, and 29%, respectively) (Table 15). The differences between vortioxetine 5 mg or 15 mg and placebo were not statistically significant. There were no statistically significant differences between any vortioxetine dose group and duloxetine based on pooled data from the five trials. The proportion of patients who achieved remission was similar for vortioxetine 5 mg or 10 mg (43% to 49%) compared with venlafaxine 150 mg (41%) and 225 mg (55%) in studies 11492A and 13926A, and for vortioxetine 10 mg and paroxetine 20 mg groups in Study 15906A (25% versus 29%, respectively) (Appendix 4, Table 29). Forest plots of the pooled remission data are presented in Appendix 5, Figure 9 and Figure 10.

In the relapse prevention study (11985A), 400 patients (63%) of the 693 patients who started 12 weeks of vortioxetine treatment
(5 mg to 10 mg daily) were in remission and eligible for randomization into the double-blind period. After 24 weeks of double-blind treatment with either placebo or vortioxetine, more

patients in the vortioxetine group remained in remission (81%) than in the placebo group (63%), according to the MADRS definition (LOCF). The proportion of patients in remission according to the HAM-D17 definition were lower (72% and 53%) but still favoured vortioxetine versus placebo.

Rates of remission were higher for patients in the vortioxetine and placebo groups in the sexual functioning trial (Study 318) (79% for vortioxetine and 77% for escitalopram at week 8). The proportion of patients in remission in Study 11985A and 318 was higher than in the short-term trials, but the treatment durations were longer in both these studies. In Study 318, all patients were on an SSRI prior to enrolment, and in Study 11958A only those in remission were eligible for inclusion into the double-blind period. The percentage of patients who remained in remission at week 24 of the double-blind period for the vortioxetine 5 mg or 10 mg group compared to placebo was RD 18% (95% CI, 10% to 27%), based on the MADRS score (LOCF), and RD 19% (95% CI, 10% to 28%), according to the HAM-D17 (LOCF analysis) (Appendix 4, Table 31). There was no difference between the vortioxetine and escitalopram groups in the odds of achieving remission at week 8 in the sexual functioning study (318) (OR 1.03; 95% CI, 0.62 to 1.71) (Appendix 4, Table 30). There was no adjustment for multiplicity for these outcomes in either study.

Table 15: Meta-Analysis of Response and Remission Outcomes for Short-Term Trials

Outcome/intervention	Comparison versus placebo			Comparison versus duloxetine		
Remission	**N trials**	**RD (95% CI)[a]**	**I^2**	**N trials**	**RD (95% CI)[a]**	**I^2**
VOR 5 mg	8	6% (−0 to 11)	61	3	−8% (−19 to 4)	69
VOR 10 mg	10	**9% (6 to 12)**	13	1	1% (−10 to 12)	0
VOR 15 mg	3	6% (−4 to 16)	67	2	−9% (−29 to 11)	85
VOR 20 mg	6	**11% (5 to 17)**	62	2	−6% (−25 to 12)	83
DUL 60 mg	5	**14% (1 to 27)**	87		--	
PAR 10 mg	1	**21% (6 to 35)**	0			
VEN 225 mg	1	**29% (16 to 41)**	0		--	
Response	**N trials**	**RD (95% CI)[a]**	**I^2**	**N trials**	**RD (95% CI)[a]**	**I^2**
VOR 5 mg	8	**12% (6 to 18)**	57	3	**−8% (−15 to −1)**	19
VOR 10 mg	10	**14% (9 to 19)**	45	1	1% (−11 to 12)	0
VOR 15 mg	3	11% (−2 to 25)	77	2	**−14% (−22 to −6)**	0
VOR 20 mg	6	**17% (9 to 25)**	73	2	**−12% (−19 to −4)**	0
DUL 60 mg	5	**23% (12 to 34)**	81		--	
PAR 10 mg	1	**32% (15 to 48)**	0		--	
VEN 225 mg	1	**28% (15 to 40)**	0		--	

CI = confidence interval; DUL = duloxetine; PAR = paroxetine; RD = absolute risk difference; VEN = venlafaxine extended release; VOR = vortioxetine.

Note: Comparisons in bold had a 95% CI that excluded the null.

[a] Proportion of patients who met criteria of remission or response at the end of treatment (week 6 or week 8). A positive risk difference favours the active-treatment versus placebo (column 1) or versus duloxetine (column 2).

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 using data from studies 305, 303, 316, 317, CCT-002, CCT-003, 11984A, 304, 13267A, 315, 12541A, 11492A, CCT-004, 15906A, and 14122A.

Response

The proportion of patients achieving a response in depression symptom severity at the end of treatment was reported in 16 of the manufacturer-sponsored short-term trials, as well as the sexual functioning study (318) and the longer-term relapse prevention study (11985A). Response was defined as a 50% or greater reduction in MADRS (316, 317, CCT-002, CCT-003, 11984A, 13267A, 315, 11492A, 13926A, 15906A, CCT-004, and 14122A), HAM-D24 scores (305, 303, 304, and 12541A), or both MADRS and HAM-D17 (11985A) (Appendix 4, Table 29, Table 30, and Table 31).

In the short-term trials, the proportion of patients who responded to therapy at the end of treatment ranged from 15% to 47% in the placebo groups, 34% to 68% in the vortioxetine groups, 51% to 74% in duloxetine, 61% to 72% in the venlafaxine groups, and 46% in the paroxetine group. The proportion responding was similar for the vortioxetine dosage groups within trials.

Data from the 15 placebo-controlled efficacy trials were pooled (Table 15) and showed that patients who received vortioxetine 5 mg, 10 mg, or 20 mg were statistically significantly more likely to respond than those who received placebo (RD 12%, 14%, and 17%, respectively). Patients who received duloxetine (RD 23%), venlafaxine 225 mg/day (RD 28%), or paroxetine 20 mg (RD 32%) were also statistically significantly more likely to respond than placebo. The differences between vortioxetine 15 mg and placebo were not statistically significant. Substantial heterogeneity was detected between trials (I^2, 45% to 81%) (Appendix 5, Figure 11).

Compared with duloxetine, patients who received vortioxetine 5 mg, 15 mg, or 20 mg were statistically significantly less likely to respond to treatment, based on pooled data from the five RCTs (RDs of −8%, −14%, and −12%, respectively) (Table 15). No difference was detected between vortioxetine 10 mg and duloxetine based on data from one trial (Appendix 5, Figure 12). Response rates were similar for vortioxetine 5 mg or 10 mg (67% to 68%) compared with venlafaxine 150 mg (61%) and 225 mg (72%) in studies 11492A and 13926A (Appendix 4, Table 15).

In the longer-term relapse prevention study (11985A), all patients who entered the double-blind period had responded to therapy during the open-label period. During the double-blind period, 85% of patients in the vortioxetine group and 72% of patients in the placebo group remained responders at week 24 according to the MADRS definition (LOCF analysis) with a RD of 13% (95% CI, 5% to 21%). (Appendix 4, Table 29). There was no control for multiplicity for this outcome.

In the study by Liebowitz et al.[56] that enrolled patients with MDD and societal affective disorder, 10 of 20 patients (50%) in the vortioxetine group and six of 20 (30%) in the placebo group met the criteria for response based on the CGI-I for both MDD and social anxiety features (i.e., rated as much improved or very much improved). The difference in the proportion of responders was not statistically significantly different (0.20; 95% CI, −0.10 to 0.50, P = 0.20) (primary outcome).

Depression Symptom Severity – Primary Outcome

The primary outcome in 14 short-term studies was the change from baseline to the end of treatment in depression symptom severity, measured using the MADRS or HAM-D24 scales. With these scales, higher scores reflect more severe symptoms and a negative MD in the change from baseline scores indicates that the intervention reduced symptom severity scores more than the control treatment.

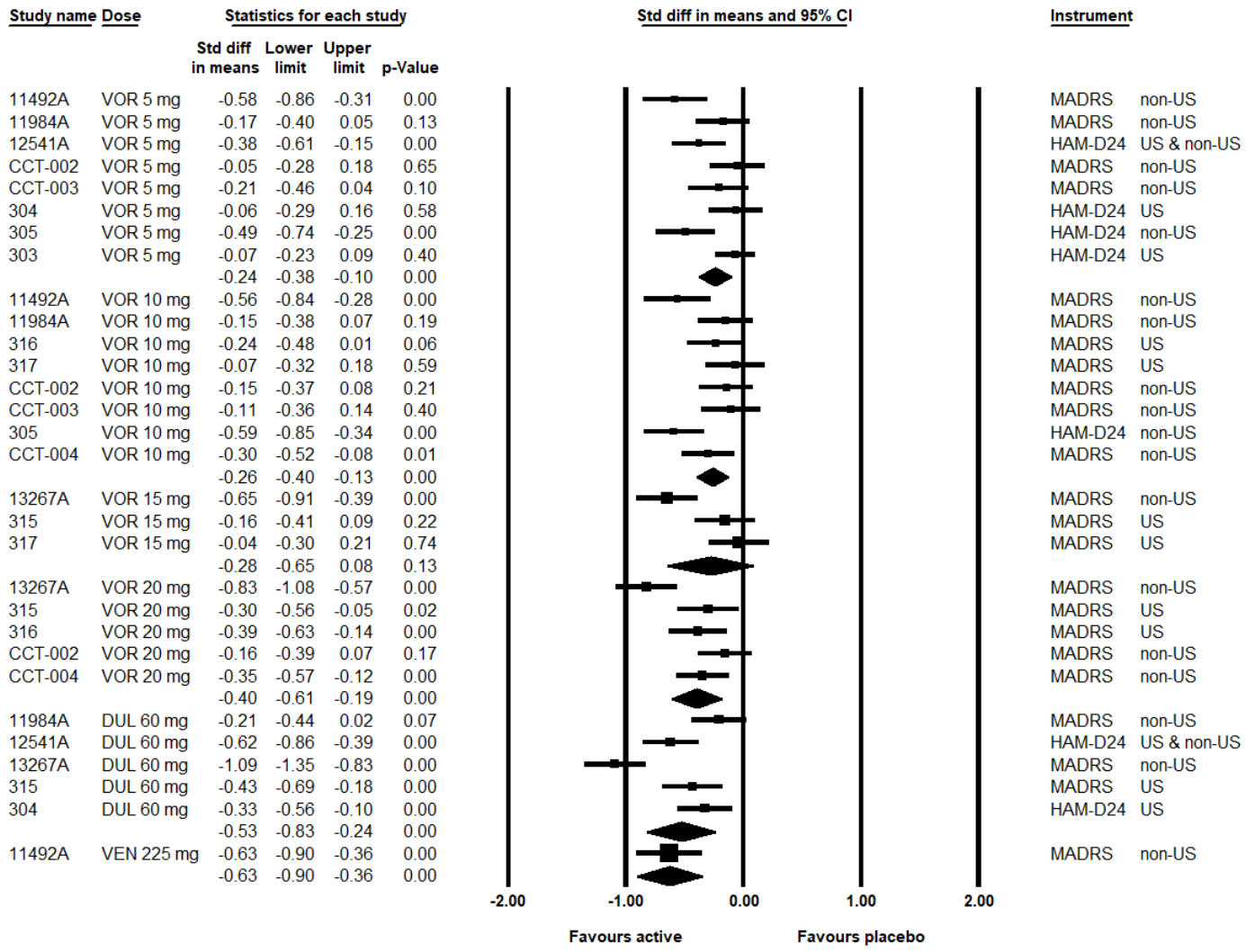
Among the 13 placebo-controlled trials, seven studies (305, 13267A, 12541A, 11492A, 315, 316, and CCT-004) showed statistically significant differences between vortioxetine and placebo for the primary outcome for at least one vortioxetine dosage group tested. Six trials (303, 317, CCT-002, CCT-003, 11984A, and 304) did not detect a statistically significant difference between vortioxetine and placebo in the primary outcome. In two trials (316 and 315), the vortioxetine 20 mg per day, but not the 10 mg or 15 mg dosage, was statistically significantly different than placebo with respect to MADRS or HAM-D24 total scores, and in one study (305), the vortioxetine 10 mg group, but not the 5 mg group, was statistically significant when compared to placebo (Appendix 4, Table 32, Table 35).

None of the US studies (303, 317, and 304) reported a statistically significant difference, or showed statistically significant differences for the highest vortioxetine dose (20 mg) only (316 and 315), whereas in the studies conducted in other countries, five were positive (Study 305 [10 mg dose only], 13267A, 12541A, 11492A, and CCT-004) and three were negative trials (CCT-002, CCT-003, and 11984A).

The primary outcome from the 13 placebo-controlled short-term efficacy trials (305, 303, 316, 317, CCT-002, CCT-003, 11984A, 304, 13267A, 315, 12541A, 11492A, and CCT-004) was pooled and the standardized mean differences (SMDs) are reported in Table 16.

Figure 3 shows the forest plot comparing active treatments to placebo, and Figure 4 compares vortioxetine and duloxetine. The differences between vortioxetine 5 mg, 10 mg, or 15 mg and placebo were small (a range of −0.24 to −0.28) according to the accepted interpretation of SMD, where 0.2 is small, 0.5 is moderate, and 0.8 is considered a large difference.[68] The SMD for vortioxetine 20 mg versus placebo was higher (−0.40). Moderate differences were observed between duloxetine 60 mg or venlafaxine XR 225 mg and placebo (−0.53 and −0.63, respectively). The pooled data for all antidepressant groups were statistically significantly different than placebo, except for vortioxetine 15 mg per day. Substantial heterogeneity was observed with I^2 values ranging from 66% to 86%.

Figure 3: Change from Baseline in Depression Rating Scale (Primary Outcome) — Active-Treatment Versus Placebo (Random-Effects Model)



CI = confidence interval; DUL = duloxetine; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; Std diff = standardized difference; VEN = venlafaxine extended release; VOR = vortioxetine.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 32 and Table 35.

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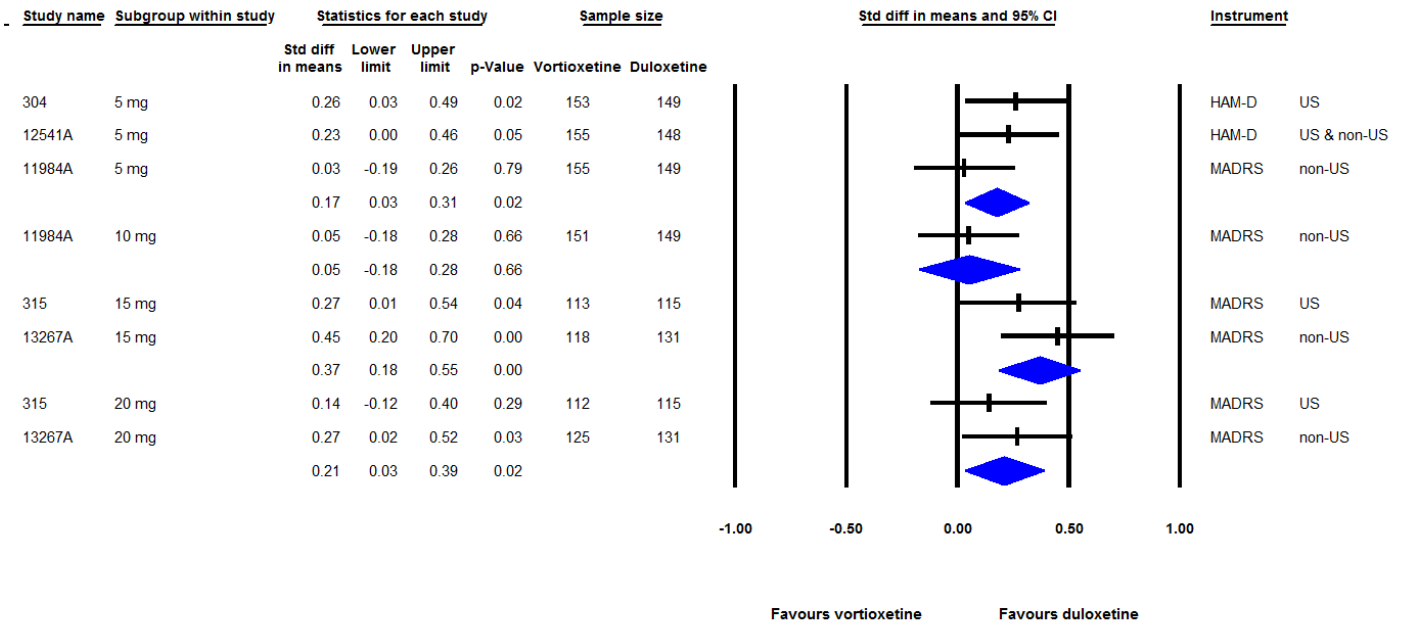
Based on pooled data from the five trials that included duloxetine as an active control (11984A, 304, 13267A, 315, and 12541A), statistically significant differences were found favouring duloxetine over vortioxetine 5 mg, 15 mg, and 20 mg per day (SMDs of 0.17, 0.37, and 0.21, respectively) (Table 16). No statistically significant differences were found between duloxetine and vortioxetine 10 mg per day (1 trial) (Figure 4).

Figure 4: Depression Rating Scale (Primary Outcome) – Vortioxetine Versus Duloxetine (Random-Effects Model)



CI = confidence interval; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Scale; Std diff = standardized difference.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 32 and Table 35.

Table 16: Meta-Analysis of Depression Symptom Scale Data for Short-Term Trials

Outcome/intervention	Comparison versus placebo			Comparison versus duloxetine		
Primary Depression Scale (MADRS or HAM-D24)	**N trials**	**SMD (95% CI)[a]**	**I^2**	**N trials**	**SMD (95% CI)[a]**	**I^2**
VOR 5 mg	8	**−0.24 (−0.38 to −0.10)**	66	3	**0.17 (0.03 to 0.32)**	15
VOR 10 mg	8	**−0.27 (−0.40 to −0.13)**	58	1	0.05 (−0.18 to 0.28)	0
VOR 15 mg	3	−0.28, (−0.65 to 0.08)	84	2	**0.37 (0.18 to 0.55)**	0
VOR 20 mg	5	**−0.40 (−0.61 to −0.19)**	75	2	**0.21 (0.03 to 0.39)**	0
DUL 60 mg	5	**−0.53 (−0.83 to −0.24)**	86		--	
VEN 225 mg	1	**−0.63 (−0.90 to −0.36)**	0		--	
MADRS	**N trials**	**MD (95% CI)[a]**	**I^2**	**N trials**	**MD (95% CI)[a]**	**I^2**
VOR 5 mg	8	**−2.36 (−3.82 to −0.90)**	71	3	**1.89 (0.36 to 3.41)**	31
VOR 10 mg	9	**−2.93 (−4.23 to −1.64)**	60	1	0.50 (−1.73 to 2.73)	0
VOR 15 mg	3	−2.61 (−5.75 to 0.53)	80	2	**3.34 (1.72 to 4.97)**	0
VOR 20 mg	5	**−3.74 (−5.54 to −1.95)**	69	2	**1.91 (0.30 to 3.53)**	0
DUL 60 mg	5	**−5.08 (−7.81 to −2.36)**	87		––	
PAR 10 mg	1	**−7.97 (−11.30 to −4.64)**	0		––	
VEN 225 mg	1	**−6.42 (−9.13 to −3.72)**	0		––	
HAM-D	**N trials**	**SMD (95% CI)[a]**	**I^2**	**N trials**	**SMD (95% CI)[a]**	**I^2**
VOR 5 mg	7	**−0.27 (−0.42 to −0.12)**	68	3	**0.19 (0.06 to 0.32)**	0

Outcome/intervention	Comparison versus placebo			Comparison versus duloxetine		
VOR 10 mg	5	**−0.33 (−0.54 to −0.11)**	74	1	0.08 (−0.15 to 0.31)	0
VOR 20 mg	1	**−0.27 (−0.49 to −0.04)**	0		--	
DUL 60 mg	3	**−0.40 (−0.62 to −0.18)**	63		--	
VEN 225 mg	1	**−0.57 (−0.85 to −0.30)**	0		--	

CI = confidence interval; DUL = duloxetine; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; MD = mean difference; SMD = standardized mean difference; VEN = venlafaxine extended release; VOR = vortioxetine.

Note: Comparisons in bold had 95% CI that excluded the null.

[a] A negative MD or SMD in depression rating scores indicates a reduction in depression symptoms (i.e., improvement) favouring the experimental treatment versus control.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 using data from studies 305, 303, 316, 317, CCT-002, CCT-003, 11984A, 304, 13267A, 315, 12541A, 11492A, CCT-004, and 15906A.

Montgomery–Åsberg Depression Rating Scale

Among the included studies, the change from baseline to end of treatment in the MADRS total score was the primary outcome in
10 studies (316, 317, CCT-002, CCT-003, 11984A, 13267A, 315, 11492A, CCT-004, and 13926A) and a secondary or exploratory outcome in eight trials (305, 303, 304, 12541A, 15906A, 318, 14122A, and 11985A) (Appendix 4, Table 32).

MADRS data from the 14 placebo-controlled trials were pooled (Table 16). The MD in the change from baseline scores for vortioxetine 5 mg, 10 mg, 15 mg, and 20 mg versus placebo were −2.4, −2.9, −2.6, and −3.7, respectively (Appendix 5, Figure 13). The MD for duloxetine, paroxetine, or venlafaxine versus placebo was −5.1, −8.0, and −6.4 respectively. All comparisons were statistically significantly different except for vortioxetine 15 mg versus placebo. Substantial heterogeneity was detected between studies, with the I^2 ranging from 63% to 74%. The point estimates for the pooled MD between active treatments versus placebo groups exceeded the estimated MCID of 2 points for the MADRS.

Data comparing vortioxetine to duloxetine were pooled from the five trials (Appendix 5, Figure 14). The MD in the change from baseline scores was not significantly different for vortioxetine 10 mg versus duloxetine (one trial) but was statistically significantly different favouring duloxetine over vortioxetine 5 mg, 15 mg, and 20 mg (MD 1.9, 3.3, and 1.9, respectively) (Table 16). The MDs between groups exceeded the MCID for the 15 mg vortioxetine dose only. Heterogeneity was low (I^2 0% to 31%); however, only two or three studies compared the 5 mg, 15 mg, and 20 mg doses.

Two trials included venlafaxine as an active comparator (11492A and 13926A). In Study 13926A, vortioxetine 10 mg/day was noninferior to venlafaxine XR 150 mg per day based on the MADRS total score (FAS: MD −1.2; 95% CI, −3.03 to 0.63; PPS: MD, 0.19; 95% CI, −1.61 to 1.99). The upper bounds of the 95% CIs (FAS: 0.63, PPS: 1.99) did not exceed the noninferiority margin of +2.5 points. In the second study (11492A), the mean changes from baseline to end of treatment in MADRS scores were similar for vortioxetine 5 mg (−20.4), 10 mg (−20.2), and venlafaxine XR 225 mg (−20.9).

Studies involving cognitive functioning (14122A), sexual functioning (318) and relapse prevention (11985A) assessed the change from baseline to end of treatment in the MADRS as a secondary outcome (11985A and 14122A) or as an additional outcome (318). In the cognitive functioning study (14122A), there was a statistically significant difference in the mean change from baseline to week 8 in the MADRS total score for vortioxetine 10 mg and

20 mg compared to placebo (MD −4.7; 95% CI, −6.5 to −3.0 and MD −6.7; 95% CI, −8.4 to −5.0, respectively) (Appendix 4, Table 33). In the relapse prevention study (11985A) and the sexual functioning study (318), all patients were receiving treatment prior to randomization and had baseline MADRS total scores ranging from 4.7 to 4.9 in the relapse prevention study and 8.2 to 8.5 in the sexual functioning study. In the relapse prevention study (11985A), there was a statistically significant difference in the change from baseline to week 24 in MADRS total score between the vortioxetine and placebo groups (MD −3.2; 95% CI, −4.9 to −1.5) (Appendix 4, Table 28); no statistically significant difference between vortioxetine and escitalopram in change from baseline to week 8 was found in the sexual functioning study (318) (MD 0.4; 95% CI, −0.9 to 1.7) (Appendix 4, Table 34). As there was no control for multiplicity in these trials, any statistically significant findings should be interpreted as inconclusive.

In Liebowitz et al.,[56] the MD between vortioxetine and placebo in the change from baseline in MADRS scores was 5.5 points (95% CI, 0.3 to 10.7, P = 0.04). In the placebo and vortioxetine groups, eight patients (40%) and 12 patients (60%), respectively, had a reduction of 50% or greater in MADRS score at 12 weeks (absolute difference 20%; 95% CI, −10% to 50%), and four patients (20%) and five patients (25%) met the criteria for remission based on a MADRS score of no more than 7 (absolute difference 5%; 95% CI, −21% to 31%) (all were listed as secondary outcomes).

Levada et al.[55] reported the mean MADRS scores decreased from baseline to week 8 for both the vortioxetine and escitalopram groups, with a −4.0 point MD between groups (standard error [SE] 2.1, P = 0.06). At eight weeks, 83% and 75% met the criteria for response (an improvement of 50% or greater in MADRS score) and 62% and 42% met the criteria for remission (MADRS ≤ 6) in the vortioxetine and escitalopram groups, respectively (no statistical testing reported).

HAM-D24 or HAM-D17

The primary outcome in four trials (305, 303, 304, and 12541A) was the change from baseline to end of treatment in HAM-D24 total scores. Three of the four trials found no statistically significant differences between vortioxetine and placebo (305, 303, and 304) (Appendix 4, Table 35). The fourth (12541A) reported an MD of −3.3 (95% CI, −5.3 to −1.3) for vortioxetine 5 mg versus placebo. The estimated MCID for the HAM-D17 is 2 to 3; no estimate of the MCID for HAM-D24 was identified in the literature, although the HAM-D17 is the foundation for the HAM-D24.

The HAM-D24 was reported as a secondary outcome in two trials (11984A, 11492A) and the HAM-D17 was reported in three short-term studies (CCT-003, CCT-004, and 15905A) and the relapse preventions study (11985A) (Appendix 4, Table 35 and Table 28).

HAM-D24 and HAM-D17 data from the seven placebo-controlled efficacy trials were pooled. The SMD in the change from baseline scores for vortioxetine 5 mg, 10 mg, 20 mg, duloxetine 60 mg, and venlafaxine 225 mg versus placebo were −0.27, −0.33, −0.27, −0.40, and −0.57, respectively (Table 16). All comparisons were statistically significant, although substantial heterogeneity was detected (I^2 63% to 74%) and based on Cohen's criteria,[68] the differences between vortioxetine and placebo would be considered small. Pooled data comparing vortioxetine 5 mg to duloxetine were statistically significantly different favouring duloxetine (SMD 0.19; 95% CI, 0.06 to 0.32) but not statistically significant for vortioxetine 10 mg versus duloxetine. Forest plots of the meta-analysis are included in Appendix 5, Figure 15 and Figure 16). In Study 11492A, the HAM-D24 changes from baseline scores

were similar for vortioxetine 5 mg, 10 mg, and venlafaxine 225 mg (−17.5, −17.6, and −17.3, respectively). No statistical comparisons were conducted between vortioxetine and venlafaxine.

In the relapse prevention study (11985A), all patients in both the placebo and vortioxetine groups were receiving treatment prior to randomization. Baseline HAM-D17 scores were 4.0 in the placebo group and 4.5 in the vortioxetine (5 or 10 mg) group. The mean difference in the change from baseline to week 24 between the vortioxetine and placebo groups was −2.3 (95% CI, −3.5 to −1.1) (no control of multiplicity).

Withdrawals or Discontinuation of Treatment

The number of withdrawals and number of withdrawals due to lack of efficacy from 15 placebo-controlled trials was pooled (Table 17). No statistically significant differences were found between any vortioxetine dosage group versus placebo.

Table 17: Meta-Analysis of Withdrawals for Active-Treatment Versus Placebo (Random-Effects Model)

Outcome/intervention	Comparison versus placebo		
Withdrawals	**N trials**	**RD (95% CI)**	**I^2**
VOR 5 mg	8	−1.1% (−3.7 to 1.5)	0
VOR 10 mg	10	0.8% (−2.0 to 3.6)	17
VOR 15 mg	3	4.5% (−0.6 to 9.6)	0
VOR 20 mg	6	1.8% (−1.6 to 5.2)	18
DUL 60 mg	5	3.5% (−1.7 to 8.6)	44
PAR 10 mg	1	8.4 (−3.1 to 19.9)	0
VEN 225 mg	1	0.4% (−9.6 to 10.4)	0
Withdrawals due to lack of efficacy	**N trials**	**RD (95% CI)**	**I^2**
VOR 5 mg	8	−0.3 (−1.6 to 1.1)	28
VOR 10 mg	10	−0.7 (−1.7 to 0.2)	5
VOR 15 mg	3	−2.4 (−5.9 to 1.0)	63
VOR 20 mg	6	−1.4 (−2.8 to 0.0)	42
DUL 60 mg	5	**−2.4 (−4.5 to −0.3)**	54
PAR 10 mg	1	−0.2 (−5.5 to 5.1)	0
VEN 225 mg	1	−4.0 (−9.0 to 1.1)	0

CI = confidence interval; DUL = duloxetine; PAR = paroxetine; RD = risk difference; VEN = venlafaxine extended release; VOR = vortioxetine.

Note: Comparisons in bold had a 95% CI that excluded the null.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 using data from studies 305, 303, 316, 317, CCT-002, CCT-003, 11984A, 304, 13267A, 315, 12541A, 11492A, CCT-004, 14122A, and 15906A.

Relapse

The primary outcome in one study (11985A) was the time to relapse within the first 24 weeks of the double-blind phase of the study. Following successful treatment (i.e., achieving remission) during the open-label period, patients who were randomized to the placebo group (i.e., discontinued active-treatment) were two times more likely to relapse than patients who were randomized to the vortioxetine group (5 mg or 10 mg) (i.e.,

remained on active-treatment) within the first 24 weeks of the double-blind phase (26.0% versus 13.2%; hazard ratio (HR) 2.01; 95% CI, 1.26 to 3.21, P = 0.0035) (Table 18).

The primary efficacy result was supported with a sensitivity analysis that excluded patients who relapsed within the first seven, 14, and 28 days of the double-blind period and patients who were considered as having relapsed by the investigator (HR 1.87; 95% CI, 1.10 to 3.16).[50] A post hoc sensitivity analysis that classified all patients who withdrew due to adverse events as having relapsed also confirmed the primary efficacy analysis (HR 1.49; 95% CI, 1.01 to 2.10).[50] A subgroup analysis comparing the rate of relapse between the placebo group and the vortioxetine group according to dose received at the end of the open-label phase found that there were only statistically significant differences between the groups for the 10 mg dose (HR 1.94; 95% CI, 1.12, 3.35). There were no statistically significant differences between the placebo group and the vortioxetine groups among patients who were on a 5 mg dose at the end of the open-label period (HR 2.26; 95% CI, 0.89 to 5.74, P = 0.0852) (Table 18, Figure 5).

Table 18: Study 11985A Time to Relapse (Placebo Versus Vortioxetine)

	Primary efficacy analysis[a] (time to relapse 0 to 24 weeks)				Secondary efficacy analysis[b] (time to relapse 0 to 64 weeks)	
	PBO		VOR 5 mg or 10 mg		PBO	VOR 5 mg or 10 mg
N	192		204		192	204
No. of Events (%)	50 (26.0)		27 (13.2)		58 (30.2)	31 (15.2)
Hazard ratio (95% CI)	2.01 (1.26 to 3.21)		Reference		2.09 (1.35 to 3.23)	Reference
P value – Cox model	0.0035				0.0010	
Subgroup analysis[c]	**PBO**		**VOR**			
Dose of VOR at end of OL period	5 mg	10 mg	5 mg	10 mg		
N	66	126	52	152	NR	NR
No. of events (%)	17 (25.8)	33 (26.2)	6 (11.5)	21 (13.8)		
Hazard ratio (95% CI)	2.26 (0.89 to 5.74)	1.94 (1.12 to 3.35)				
P value – Cox model	0.0852	0.0179				

CI = confidence interval; NR = not reported; OL = open-label; PBO = placebo; VOR = vortioxetine

[a] The primary efficacy analysis was based on the full analysis set data from week 0 to week 24 of the double-blind randomized phase. Six patients in the VOR group and 14 in the placebo group were defined as relapsed by the investigator.

[b] The secondary efficacy analysis was based on the full analysis set data from week 0 to week 64 of the double-blind randomized phase. Week 0 represents the end of the start of the double-blind phase.

[c] Based on the proportion of patients receiving 5 mg or 10 mg doses at the end of the open-label phase.

Source: Clinical Study Report.[16]

Figure 5: Study 11985A Survival Curve (Time to Relapse Within 24 Weeks)

Figure redacted as per sponsor's request

AA21004 = vortioxetine; DB = double-blind; FAS = full analysis set; PBO = placebo.

Source: Clinical Study Report.[16]

Cognitive Function

The primary outcome in Study 14122A was the change in the composite z score (comprised of the DSST, RAVLT acquisition, and RAVLT delayed recall) from baseline to week 8. There was no evidence found in the literature for the validity, MCID, or accepted standard for interpreting the change score of this measure. Patients in the vortioxetine 10 mg and 20 mg group experienced a statistically significantly greater change from baseline in composite z score compared to the placebo group (vortioxetine 10 mg versus placebo: MD 0.36; 95% CI, 0.22 to 0.50; and vortioxetine 20 mg versus placebo: MD 0.33; 95% CI, 0.19 to 0.47) (Table 19).

Table 19: Study 14122A Composite Z Score at 8 Weeks (Vortioxetine Versus Placebo)

	Total N	Baseline	Week 8	Treatment group difference versus control		
		Mean (SE)	Mean change from baseline (SE)	N	Mean difference (95% CI)	P value
Composite z score for DSST and RAVLT[a]						
Placebo	194	−0.007 (0.061)	−0.235 (0.053)	178	Reference	
VOR 10 mg	193	−0.009 (0.057)	0.128 (0.052)	180	0.36 (0.22, 0.50)	P < 0.0001
VOR 20 mg	204	0.015 (0.059)	0.095 (0.051)	187	0.33 (0.19, 0.47)	P < 0.0001

CI = confidence interval; DSST = Digit Symbol Substitution Test; RAVLT = Rey Auditory Verbal Learning Test; SE = standard error; VOR = vortioxetine.

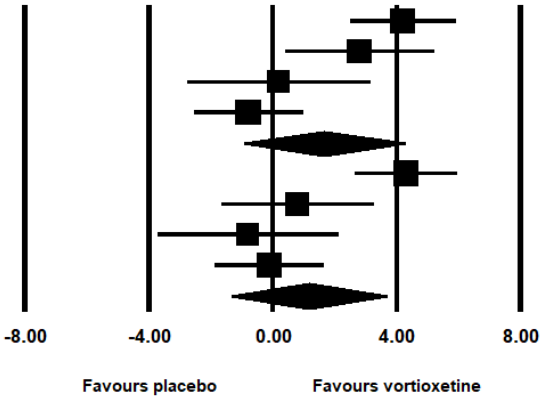
[a] Based on the full analysis set, using the mixed-effect model for repeated measures controlling for grouped site, baseline composite z score, and interaction terms (baseline composite z score by visit; treatment by visit).

Source: Clinical Study Report.[22]

The change from baseline to week 8 on the DSST was reported in six studies (14122A, 12541A, 15905A, 15906A, 15907A, and CCT-004) (Appendix 4, Table 36 and Table 37). The DSST is scored from 0 to 133, with higher scores indicating better cognitive functioning. No MCID has been reported in the literature. Across these trials there was substantial heterogeneity in the DSST findings. Study 14122A showed statistically significant treatment effects favouring vortioxetine over placebo (MD 4.2; 95% CI, 2.5 to 5.9 for vortioxetine 10 mg and MD 4.3; 95% CI, 2.6 to 5.9 for vortioxetine 20 mg) (Appendix 4, Table 36). In contrast, studies 15906A, 15905A, and 15907A found no statistically significant differences in the change from DSST (the primary outcome) compared with placebo, SSRI, or escitalopram. Data from four RCTs were pooled and found no statistically significant differences between vortioxetine 10 mg or vortioxetine 20 mg and placebo in the change from baseline to week 8 in the DSST (I^2 was 82% for both comparisons) (Figure 6). The meta-analysis that excluded Study CCT-004, which had higher mean DSST scores at baseline compared with the other studies, also showed high heterogeneity (I^2 63% and 82%) (Appendix 5, Figure 18).

Figure 6: Change from Baseline in DSST — Vortioxetine Versus Placebo (Random-Effects Model)

Study name	Dose	Difference in means	Lower limit	Upper limit	p-Value
11492A	VOR 10 mg	4.20	2.51	5.89	0.00
12541A	VOR 10 mg	2.80	0.41	5.19	0.02
15906A	VOR 10 mg	0.20	-2.76	3.16	0.89
CCT-004	VOR 10 mg	-0.79	-2.54	0.96	0.38
		1.65	-0.94	4.23	0.21
14122A	VOR 20 mg	4.30	2.66	5.94	0.00
12541A	VOR 20 mg	0.80	-1.64	3.24	0.52
15906A	VOR 20 mg	-0.80	-3.71	2.11	0.59
CCT-004	VOR 20 mg	-0.11	-1.85	1.63	0.90
		1.16	-1.35	3.67	0.36



CI = confidence interval; VOR = vortioxetine.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 using data from (Appendix 4, Table 36 and Table 37).

The RAVLT (acquisition and delayed recall) were assessed as secondary end points in two studies (14122A and 12541A). RAVLT (acquisition) is scored from 0 to 45 and the RAVLT (delayed recall) is scored from 0 to 15, with higher scores indicating greater cognitive functioning. There was no evidence found in the literature on the validity or MCID for the RAVLT in patients with MDD. The vortioxetine and placebo groups in Study 14122A (Appendix 4 Table 36) showed no statistically significant differences. In Study 12541A patients in the vortioxetine 5 mg group achieved statistically significant improvements in RAVLT (acquisition) (MD 1.1; 95% CI, 0.2 to 2.1) and RAVLT (delayed recall) (MD 0.5; 95% CI, 0.02 to 0.9) from baseline to week 8 compared to placebo. Patients in the duloxetine 60 mg group also exhibited statistically significant improvements in RAVLT (acquisition) (MD 1.4; 95% CI, 0.4 to 2.4) and RAVLT (delayed recall) (MD 0.6; 95% CI, 0.02 to 1.1) from baseline to week 8 compared to placebo (Appendix 4, Table 36).

A path analysis was undertaken as a secondary assessment of the direct effects of vortioxetine on composite z scores at week 8 that were independent of the effects mediated through changes in MADRS total scores. The completeness of this model in capturing all possible indirect effect pathways is unknown. Of the total direct and indirect effects captured in the model, there was a statistically significantly greater direct effect of vortioxetine 10 mg and 20 mg on composite z score at week 8 compared to placebo (vortioxetine 10 mg direct effect 64%; 95% CI, 47 to 82; vortioxetine 20 mg direct effect 48%; 95% CI, 23 to 73) (Appendix 4, Table 38).

The study by Levada et al.[55] reported MDs for vortioxetine versus escitalopram in the change from baseline to week 8 in DSST (MD 7.7 points; SE 4.2, P = 0.72), RAVLT immediate recall (MD 6.4 points; SE 2.4, P = 0.01), RAVLT proactive interference (MD 0.2 points; SE 0.5, P = 0.7), RAVLT retroactive interference (MD 1.6 points; SE 0.6, P = 0.007), RAVLT delayed recall (MD 1.1; SE 0.5, P = 0.03) and RAVLT delayed recognition scores (MD 0.06; SE 0.1, P = 0.5). There was no control of type I error due to multiple testing.

Three trials analyzed the change from baseline in the UPSA-B, which measures performance accuracy on everyday tasks: managing finances (e.g., counting correct change, writing a check to pay a bill) and communication with others (e.g., calling an emergency telephone number, rescheduling a medical appointment). Raw scores of the two subscales were converted to scaled scores from 0 to 100, where higher scores indicate better functional capacity. No statistically significant differences were detected between vortioxetine (10 mg or 20 mg) and placebo, SSRI, or escitalopram (Appendix 4, Table 39).

Harms

Only those harms identified in the review protocol are reported below. See Appendix 4, Table 40 to Table 55, for detailed harms data.

Adverse Events

Among the 21 short-term studies, the incidence of treatment-emergent adverse events ranged from 38% to 70% in the placebo groups, 25% to 81% in the vortioxetine groups, 69% to 85% for duloxetine, 70% to 76% for venlafaxine, 25% to 62% for escitalopram, 43% for paroxetine, and 33% for the SSRI group in Study 15915A (Appendix 4, Table 40). In the relapse prevention study (11985A), the incidence of treatment-emergent adverse events was 64% for the placebo group and 62% for the vortioxetine group during the double-blind phase (up to 64 weeks).

Thirteen placebo-controlled short-term efficacy trials (305, 303, 316, 317, CCT-002, CCT-003, CCT-004, 11984A, 304, 13267A, 315, 12541A, 11492A) and two cognitive function trials (14122A, 15906A) used similar inclusion and exclusion criteria and thus the adverse event data were suitable for meta-analysis (Table 20). Except for paroxetine, the frequency of adverse events was higher in those receiving active treatments versus placebo. Pooled data from 10 trials found an absolute RD for adverse events of 7.0% (95% CI, 3.5% to 10.5%) for vortioxetine 10 mg versus placebo. For vortioxetine 20 mg versus placebo, the RD was 10.5% (95% CI, 6.3% to 14.7%), based on data from six trials. No substantial statistical heterogeneity was detected as I^2 values ranged from 0% to 12%.

Table 20: Pooled Harms Outcomes for Short-Term Trials[a]

Outcome/intervention	Comparison versus placebo		
AE	**N trials**	**RD (95% CI)**	**I^2**
VOR 5 mg	8	**5.2% (1.5 to 9.0)**	0
VOR 10 mg	10	**7.0% (3.5 to 10.5)**	12
VOR 15 mg	3	**6.0% (0.1 to 11.9)**	0
VOR 20 mg	6	**10.5% (6.3 to 14.7)**	0
DUL 60 mg	5	**15.2% (10.7 to 19.7)**	7
PAR 10 mg	1	5.0% (−13.9 to 24.1)	0
VEN 225 mg	1	**15.0% (3.0 to 27.4)**	0
SAE	**N trials**	**RD (95% CI)**	**I^2**
VOR 5 mg	8	0.0% (−0.8 to 0.9)	0
VOR 10 mg	10	0.1% (−0.7 to 0.8)	0
VOR 15 mg	3	0.1% (−0.9 to 1.0)	0
VOR 20 mg	6	0.3% (−0.4 to 1.0)	0

Outcome/intervention	Comparison versus placebo		
DUL 60 mg	5	−0.0% (−1.1 to 1.0)	12
PAR 10 mg	1	1.6% (−4.8 to 8.1)	0
VEN 225 mg	1	0.9% (-1.6 to 3.4)	0
WDAE	**N trials**	**RD (95% CI)**	**I^2**
VOR 5 mg	8	−0.0% (−1.5 to 1.1)	0
VOR 10 mg	10	**1.5% (0.1 to 3.0)**	0
VOR 15 mg	3	**4.0% (0.9 to 7.0)**	0
VOR 20 mg	6	**2.7% (0.9 to 4.5)**	4
DUL 60 mg	5	**3.6% (1.1 to 6.1)**	0
PAR 10 mg	1	3.5% (−3.9 to 10.8)	0
VEN 225 mg	1	**10.3% (3.0 to 17.7)**	0

AE = adverse event; CI = confidence interval; DUL = duloxetine; PAR = paroxetine; RD = risk difference;
SAE = serious adverse event; VEN = venlafaxine extended release; VOR = vortioxetine; WDAE = withdrawal due to adverse event.

[a] Includes data from studies 305, 303, 316, 317, CCT-002, CCT-003, CCT-004, 11984A, 304, 13267A, 315, 12541A, 11492A, 14122A, and 15906A.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2, random-effects model.

Nausea was reported in 1% to 11% of patients on placebo, 13% to 38% of those on vortioxetine, 31% to 42% on duloxetine, 24% to 34% on venlafaxine, 5% to 10% on escitalopram, 17% on paroxetine, and 2% on SSRIs in the short-term studies (Appendix 4, Table 40). The FDA identified three adverse events (nausea, vomiting, and constipation) that had a higher incidence in the vortioxetine groups than in placebo (Table 20). Based on pooled data from short-term trials, the relative risk of vomiting was 2.9 (95% CI, 1.9 to 4.5), 2.7 for nausea (95% CI, 2.3 to 3.2) and 1.4 for constipation (95% CI, 1.0 to 1.9) for vortioxetine versus placebo.[57]

Table 21: FDA Pooled Treatment-Emergent Adverse Events With Incidence of At Least 5% in Any Vortioxetine Group in the Short-term Studies[a]

Preferred Term	Number of Subjects (%)						
	Placebo N=1621	Lu AA21004 (mg)					Duloxetine N=753
		5 N=1013	10 N=699	15 N=449	20 N=455	Total (a) N=3060	
Subjects with TEAEs	1002 (61.8)	672 (66.3)	465 (66.5)	316 (70.4)	331 (72.7)	2029 (66.3)	583 (77.4)
Nausea	149 (9)	216 (21)	180 (26)	144 (32)	144 (32)	745 (24)	268 (36)
Vomiting	22 (1)	29 (3)	33 (5)	29 (7)	26 (6)	124 (4)	31 (4)
Constipation	53 (3)	35 (4)	35 (5)	26 (6)	28 (6)	135 (4)	74 (10)

Compiled from ISS Table 2.1.1.3.1, Table 2.U page 114/410
(a) Lu AA21004 Total also includes 1 and 2.5 mg doses.

Lu AA21004 = vortioxetine; TEAE = treatment-emergent adverse events.

[a] Includes adverse events experienced by ≥ 5% of patients in any vortioxetine group and at least twice the incidence in the placebo group among short-term studies (11492A, 11984A, 305, 13267A, 315, 316, 303, 304, 317, and 12541).

Source: FDA Medical Review.[57]

In the longer-duration 64-week relapse prevention study (11985A), 64% and 62% of patients experienced an adverse event in the placebo and vortioxetine groups, respectively. Nausea was reported in 3% of placebo patients and 9% of vortioxetine patients (Appendix 4, Table 40). Only patients who completed 12 weeks of therapy with vortioxetine and were

in remission were eligible for enrolment, and any patients who were unable to tolerate vortioxetine during the run-in phase were excluded from this trial.

Serious Adverse Events

The incidence of serious adverse events was low among the 21 short-term trials, ranging from 0% to 3% for placebo, 0% to 2% for vortioxetine, 0% to 2% for duloxetine, 1% to 4% for venlafaxine, 0% to 0.5% for escitalopram, 4% for paroxetine, and 0% for the SSRI group. No differences were found between any of the active treatments and placebo for the risk of serious adverse events based on pooled data from the short-term placebo-controlled trials (Table 20).

The incidence of serious adverse events for the longer-duration (up to 64 weeks) relapse prevention study (11985A) was 2% in the placebo group and 3% in the vortioxetine group during the double-blind phase (Appendix 4, Table 40).

Withdrawals Due to Adverse Events

Among the 21 short-term trials, the proportion of patients who withdrew due to adverse events ranged from 1% to 8% in the placebo groups, 1% to 14% for vortioxetine, 5% to 12% for duloxetine, 14% for venlafaxine, 2% to 6% for escitalopram, 6% for paroxetine and 4% for the SSRI group (Appendix 4, Table 40). Based on pooled data from the short-term placebo-controlled trials (Table 20), withdrawals due to adverse events occurred more frequently among those receiving higher doses of vortioxetine (15 mg or 20 mg), duloxetine, or venlafaxine, compared with placebo (Appendix 5, Figure 17).

In the relapse prevention study (11958A), 54 of the 639 patients who entered the open-label vortioxetine treatment period stopped therapy due to adverse events. After randomization, 7% of patients on vortioxetine withdrew due to adverse events compared to 1% of those on placebo over the double-blind period (up to 64 weeks) (Appendix 4, Table 40).

Mortality

In the short-term trials, one patient who received vortioxetine 5 mg per day died due to gallbladder cancer. No other deaths were reported (Appendix 4 Table 40).

Notable Harms

Suicide Ideation or Behaviour

Health Canada presented pooled data on suicide-related events [redacted]

Suicidality was not systematically collected during the longer-term relapse prevention study (11985A). During the open-label period, one patient attempted suicide and was withdrawn from the study, one patient had suicide ideation, and one patient was withdrawn due to a MADRS score greater than 5 on question 10, which is related to suicidal thoughts. No suicidal ideation or events were reported during the double-blind period, although one patient had an intentional overdose in the post-dose follow-up period.

Sexual Dysfunction

The primary outcome in Study 318 was the mean change from baseline to week 8 on the CSFQ-14. The mean CSFQ-14 scores in each group increased from baseline to week 8, and the MDs were statistically significant favouring the vortioxetine group versus escitalopram (least squares MD 2.2; 95% CI, 0.5 to 4.0, P = 0.013) (Table 22). The analysis was based on data from 73% and 78% of patients randomized to vortioxetine and escitalopram, respectively. Sensitivity analyses that used LOCF and pattern mixture models to account for missing data showed results similar to those of the primary analysis. No evidence of an MCID for the CSFQ-14 was found in the literature; however, a threshold of no more than 41 for males and 47 for females was found to be indicative of sexual dysfunction (Appendix 5).

There were no statistically significant differences in the odds of achieving normal sexual functioning (> 41 for males and > 47 for females) or in the odds of responding to therapy (change ≥ 3 points on the CSFQ-14) at week 8 for vortioxetine versus escitalopram (Appendix 4, Table 45 and Table 46).

Table 22: Study 318 Change from Baseline in CSFQ-14 Total Score at Week 8[a]

CSFQ-14 total score	ESC 10 mg or 20 mg N = 222	VOR 10 mg or 20 mg N = 225
Baseline		
N	207	217
LS mean (SE)[a]	36.0 (0.4)	36.1 (0.4)
Week 8		
N	173	165
Mean (SD)	42.9 (9.2)	45.7 (9.5)
Change from baseline, LS mean (SE)[b]	6.6 (0.6)	8.8 (0.6)
LS mean difference versus ESC (95% CI)[c]	2.2 (0.48 to 4.02)	
P value	0.013	

CI = confidence interval; CSFQ-14 = Changes in Sexual Functioning Questionnaire Short-Form; ESC = escitalopram; LS = least squares; SD = standard deviation; SE = standard error; VOR = vortioxetine

[a] Analysis was based on the full analysis set and analysis of variance controlling for treatment and pooled centre.

[b] Analysis was based on the full analysis set and mixed-effect model for repeated measures controlling for site, week, treatment, baseline score by week, and week by treatment.

[c] A positive number favours vortioxetine.

Source: Clinical Study Report.[24]

Treatment-emergent sexual dysfunction based on the ASEX instrument was reported in six short-term studies (11984A, 304, 13267A, 315, 316, and 317). Among the subgroup of patients with no sexual dysfunction at baseline, 28% to 50% in the placebo groups and 20% to 66% in the vortioxetine groups developed a sexual dysfunction (Appendix 4,

Table 47). Treatment-emergent sexual dysfunctions were reported in 75 of 152 patients (49%) who received duloxetine in studies 11984A (9 of 15, 60%), 304 (23 of 49, 49%), 13267A (18 of 41, 44%), and 315 (25 of 47, 53%). Based on pooled data from Health Canada, vortioxetine 10 mg to 20 mg was associated with [redacted].[6] In general, sexual dysfunction was reported more frequently among women than men (Appendix 4, Table 48).

The incidence of sexual dysfunction was low based on spontaneously reported adverse events and is likely under-reported. Based on Health Canada pooled data of 12 short-term trials, [redacted] (Appendix 4, Table 49). The incidence of sexual dysfunction for the 24-week relapse prevention study (11985A) was 2% in the vortioxetine group and 1% in the placebo group during the double-blind phase (Appendix 4, Table 50). In four other studies, sexual dysfunction adverse events were reported in less than 1% of patients who received vortioxetine monotherapy, 4% of those on vortioxetine plus SSRI, and 0% to 4% of those on an SSRI (Appendix 4, Table 50).

All patients enrolled in Study 318 were experiencing treatment-emergent sexual dysfunction at baseline. Treatment-emergent adverse events related to sexual dysfunction were reported spontaneously during the double-blind period by 4% of patients in the escitalopram group and no patients in the vortioxetine group (Appendix 4, Table 50).

Serotonin Syndrome

In Study 11985A, one patient had a serious adverse event of serotonin syndrome during the open-label vortioxetine run-in period. Two other serious adverse events related to serotonin syndrome were reported in Study 11984A, including one patient in the placebo group and one in the duloxetine group. No other serotonergic syndrome adverse events were reported in the other 20 RCTs.

Weight Gain

Based on pooled data from Health Canada, no substantial differences in body weight were observed for vortioxetine compared to placebo among the six- to eight-week studies (305, 303, 316, 11984A, 304, 13267A, 315, 12541A, and 11492A). [redacted].[6]

Additional data on changes in weight from seven trials were summarized in Appendix 4 Table 51. The relapse study (11985A) reported a higher proportion of patients with increases in body weight (6.5% for vortioxetine; 5.8% for placebo) compared to the shorter-term trials; however, no substantial differences were observed between the vortioxetine and placebo groups. Among the other short-term studies, 1% of patients on placebo, 1% to 4% of patients in the vortioxetine groups, and 0% to 4.5% who received an active control reported weight gain of at least 7%. The mean change from baseline in weight ranged from −0.5 kg (SD 1.8) for venlafaxine to 0.9 kg (SD 2.7) for vortioxetine (Appendix 4, Table 51).

Withdrawal Symptoms

The DESS checklist, which was reported in five studies (316, CCT-002, 13267A, 315, and CCT-003), includes 43 items that query for signs and symptoms that may be related to treatment discontinuation.[6] A new or worsened adverse event scores 1 point and the total score is the sum of all positive responses.[6]

The mean DESS scores were similar in the placebo and vortioxetine groups, one or two weeks after discontinuation of therapy (Appendix 4,Table 52 and Table 53). Pooled data from Health Canada showed [redacted]

[redacted].[6] Discontinuation-related adverse events reported in individual trials are summarized in Appendix 4, Table 55).

The relapse prevention study (11985A) included two discontinuation periods of two weeks each. The first discontinuation period was after the 12-week open-label period, and the second was after the 24-week double-blind period. In both discontinuation periods, there was a higher number of adverse events during the first week compared to the second (Appendix 4, Table 53). During the first discontinuation period, nervous system disorders (most commonly headache) were reported in 7% and 9%, gastrointestinal disorders (most commonly nausea) were reported in 4% and 7%, and infections and infestations (most commonly gastroenteritis) were reported in 5% and 4% of patients in placebo and vortioxetine groups, respectively. During the second discontinuation period, the most common adverse events by system organ class were nervous system disorders (3% and 6%), gastrointestinal disorders (2% and 6%) and psychiatric disorders (7% and 6%) in the placebo and vortioxetine groups, respectively.

In the sexual functioning study (318) there was a one-week taper-down period during which 6% and 2% of patients in the escitalopram and vortioxetine groups, respectively, reporting discontinuation-related adverse events (Appendix 4, Table 53). The most frequent adverse event (reported by at least two patients) was irritability. Other adverse events included dizziness, headache, anxiety, and depression.

Discussion

Summary of Available Evidence

A total of 22 RCTs met the inclusion criteria for the systematic review. The trials evaluated the efficacy and safety of vortioxetine
(5 mg to 20 mg daily) in adults with MDD over six to 12 weeks of therapy (21 short-term trials) or up to 64 weeks (one relapse prevention study). The trials were designed to test the difference between vortioxetine and placebo (17 RCTs), venlafaxine (one noninferiority study), or escitalopram (three studies). One other trial was designed to compare vortioxetine as add-on therapy to SSRI or vortioxetine as monotherapy, with SSRI monotherapy. Seven placebo-controlled trials also included an active-reference group (duloxetine, venlafaxine, or paroxetine).

Fourteen short-term efficacy trials assessed the impact of vortioxetine on depression symptom severity, measured as the change from baseline to week 6 or 8 for either the MADRS or HAM-D24. Four short-term trials examined cognitive function as the primary outcome, which was assessed using the DSST or a composite of the DSST and the RAVLT. The other studies evaluated sexual function (Study 318), CGI-I (Liebowitz et al.) and one study (Levada et al.) did not specify the primary outcome. One trial used a withdrawal design (Study 11985A), in which patients who had achieved remission of their MDD with 12 weeks of vortioxetine therapy were randomized to placebo or continuation of vortioxetine; time to relapse over 24 weeks was the primary outcome. The number of patients enrolled per study ranged from 40 to 766, with a median of 457.5 patients per study.

Key limitations included the short duration of most trials (up to eight weeks), possible unblinding that may bias subjective outcomes, and the magnitude of withdrawals or differential losses to follow-up (10 studies). Data comparing vortioxetine with other antidepressants were limited. Similar to other antidepressant clinical trials, the generalizability of the findings may be limited by the patient selection criteria used in the trials, which may not be representative of patients seeking care for depression in community-based practice.

Interpretation of Results

Efficacy

Although HRQoL and disability were identified as key efficacy outcomes of interest to patients, none of the included studies were designed or powered to evaluate these outcomes. Eight trials included HRQoL as a secondary or exploratory outcome, and the findings were inconsistent between trials. Placebo and active-treatment groups generally showed improvement in HRQoL scores, although statistically significant differences between vortioxetine and placebo were observed only in some studies, with other trials showing no differences between groups. The inconsistency may be related to the short duration of treatment, as six to eight weeks of therapy may be insufficient to show meaningful changes in HRQoL. Thirteen trials reported data for the SDS, and most found no statistically significant difference between vortioxetine and controls groups. Meta-analysis of disability data showed statistically significant differences between vortioxetine 10 mg and 20 mg versus placebo with a MD of −1.4 and −1.8 points, respectively, out of a total of 30 points on the SDS. However, the clinical importance of these findings is unclear

given the uncertain validity of the SDS and the lack of an MCID. Not all trials implemented procedures to control for inflated type I error among secondary outcomes and, although many studies used hierarchical testing procedures, P values were reported for all analyses, even if testing procedures were reported to be stopped. For HRQoL and SDS, statistically significant results should be interpreted with caution as there is an increased risk of a false-positive statistical test due to the lack of adjustment for multiple testing.

With regard to depression symptom severity, six of the 13 short-term placebo-controlled trials did not find statistically significant differences between vortioxetine and placebo in the primary outcome of depression symptom severity (change from baseline to end of treatment in MADRS or HAM-D24 scores), four studies showed statistically significant differences between vortioxetine and placebo, and in three trials statistically significant differences were observed for the highest dosage of vortioxetine tested (20 mg or 10 mg per day), but not the lower vortioxetine dosages included in those studies. Pooled data on the change from baseline in the MADRS or HAM-D24 total score showed vortioxetine (5 mg, 10 mg, and 20 mg) were statistically significantly different than placebo. The differences favouring vortioxetine were generally small (pooled primary outcome SMDs of −0.24 to −0.40) but exceeded the MCID of 2 for the MADRS score (MD −2.4 to −3.7), with substantial between-study heterogeneity (I^2 > 50%). Regional differences in efficacy were noted by Health Canada, but no clear explanation for these differences was identified.[6] Meta-analysis of US studies found statistically significant differences for the 20 mg dose only, while pooled data from non-US trials showed statistically significant differences for vortioxetine 5 mg, 10 mg, 15 mg, and 20 mg.[6] Substantial heterogeneity remained among the non-US studies, with I^2 values between 62% and 85%,[6] and other factors besides region contributing to the observed between-study variability. Although the CADTH meta-analysis of all short-term efficacy trials showed statistically significant differences for most vortioxetine doses compared with placebo, the generally small differences observed, and the variable treatment effects across studies, make the clinical significance of the differences unclear. As well, the variability in treatment effects and heterogeneity across studies reduces confidence in the findings. The meta-analysis of secondary outcomes, response, and remission showed results similar to those of the primary outcome, with some vortioxetine doses showing statistically significant differences versus placebo, but with substantial between-study heterogeneity.

Seven of the short-term efficacy studies included an active control group, although only one trial, 13926A, was powered to compare active treatments (venlafaxine versus vortioxetine) for changes in depressive symptom severity. Compared with placebo, the SMD in the change from baseline in MADRS or HAM-D scores was −0.53 and −0.63 for duloxetine and venlafaxine, respectively; whereas the pooled data for vortioxetine versus placebo showed an SMD from −0.24 to −0.40. When data were pooled from the duloxetine-controlled studies, statistically significant differences were observed favouring duloxetine over vortioxetine 5 mg, 15 mg, and 20 mg for the primary outcome (change from baseline in MADRS or HAM-D). Study 13926A found vortioxetine to be noninferior to venlafaxine as the upper bounds of the 95% CIs did not exceed the noninferiority margin of +2.5 points on the MADRS scale. This margin may be overly large, considering that the MCID of the MADRS was estimated at 2 points, and pooled data from a number of antidepressant trials[5] showed a MD of 2 points between active treatments and placebo. In Study 13926A, the results of the PPS were less favourable compared to the FAS, and the upper limit of the 95% CI for the PPS analysis was 1.99 (FAS: 0.63).This trial was also limited by the extent of withdrawals, which were also imbalanced between groups, and the use of LOCF to impute missing outcome data. Among the trials with an active-reference group, the

possibility of selection bias was raised due to the exclusion of patients with a history of lack of response to the active-reference drug. It was postulated that exclusion of these patients may have inflated the differences between active-reference drugs (e.g., duloxetine) versus placebo. However, there was no clear consensus from regulatory agencies with regard to the potential for selection bias in these trials.[6,69-71] Health Canada acknowledges the possibility of selection bias but states the impact on the findings is unclear and cannot be estimated.[6] While the available head-to-head data are suggestive of a smaller treatment effect for vortioxetine relative to venlafaxine and duloxetine, definitive conclusions cannot be made.[6] The CADTH pooled analysis suggests that vortioxetine may be less effective than duloxetine in reducing depression symptom severity, but the observed differences were small and of unclear clinical significance. Because there are no data on the proportion of patients with prior exposure to duloxetine or venlafaxine, it is not possible to estimate the magnitude of any potential bias, and the possibility of bias should be considered when interpreting the meta-analysis.

Input from patient groups suggested the need for an effective treatment option that improves cognition and day-to-day functioning and has limited adverse effects, particularly with respect to sexual dysfunction and metabolism. Although the effect of vortioxetine on cognitive function tests was measured in six studies, the findings were heterogeneous and the impact of vortioxetine on cognition was unclear. The key outcomes tested were the DSST and a composite z score of the change in DSST and RAVLT. The DSST is a timed task requiring patients to match geometric symbols to corresponding numbers as designated by an answer key. It is unclear how a change in DSST scores relates to how patients function at home or at work. While the composite z score of the DSST and RAVLT covers a broader range of cognitive functions, the validity and clinical importance of a change in scores on this composite measure is not known. Study 14122A reported statistically significant improvement in the composite z score of the DSST and RAVLT in patients receiving vortioxetine compared to patients receiving placebo. However, three other studies found no statistically significant differences between vortioxetine and control groups in the change from baseline in DSST (the primary outcome in these studies). A meta-analysis of the change from baseline in DSST scores showed high heterogeneity between trials, with I^2 values of 82%. Three trials measured the change from baseline in UPSA-B, a performance-based assessment that includes financial (e.g., writing a cheque) and communication skills (e.g., changing a medical appointment). While the UPSA-B assesses everyday living skills, the clinical expert consulted for this review stated that such skills are better aligned with impairments observed in people with serious mental illness (such as schizophrenia) rather than outpatients with depression. Moreover, no statistically significant difference was found between vortioxetine and control groups on the UPSA-B in studies 15905A, 15906A, and 15907A.

Among patients who responded to treatment with vortioxetine during a 12-week open-label period in the relapse prevention study (11985A), those who were randomized to vortioxetine were statistically significantly less likely to experience a relapse compared to those who received placebo over the course of a 24-week double-blind period. Although there was a risk of patient and investigator unblinding after randomization (due to withdrawal symptoms of rebound depression symptoms), the findings were similar among sensitivity analyses that excluded early relapses and used different definitions of relapse.

In addition to the evidence provided by the pivotal and other RCTs included in the systematic review, there is evidence from six extension studies (Appendix 7), five non-randomized studies (Appendix 8), and five indirect treatment comparisons (ITCs) (Appendix

9). While the extension data and non-randomized studies provide some evidence on longer-term use of vortioxetine, or report outcomes (such as hospitalizations) not assessed in clinical trials, the utility of these studies were limited by potential selection bias, lack of control groups, or lack of blinding. One published ITC (Cipriani et al.) and one manufacturer-submitted analysis provided evidence used to inform the pharmacoeconomic analysis.[7,8] Cipriani et al.[8] based their analysis on 522 double-blind, short-term RCTs that evaluated treatment response and acceptability of 21 antidepressant drugs. In this analysis, all approved dosages of antidepressants were pooled, whereas in the manufacturer-submitted analysis, dosage data from Cipriani et al. was divided and analyzed separately as high- and low-dosage groups, based on the WHO's defined daily dose. Vortioxetine was found to be more efficacious than placebo in achieving a response defined as at least 50% reduction in the total score on a standardized observer-rating scale for depression (OR 1.66; 95% credibility interval, 1.45 to 1.92) and as acceptable as placebo (OR 1.01, 95% credible interval, 0.86 to 1.19), based on the proportion of patients who withdrew from the study for any reason. Based on a primary analysis that included placebo and active-controlled trials, the response rate and acceptability of vortioxetine was similar to other antidepressants. Data from the manufacturer-submitted analysis by dose showed similar results. These ITCs support a general finding that most drugs used for the acute treatment of MDD have similar efficacy and all are more efficacious than placebo. Three other ITCs are summarized in Appendix 9; however, these did not provide additional information regarding the overall or comparative efficacy of vortioxetine.[72-74]

Determining the benefits of an intervention in antidepressant RCTs can be difficult, in part because a large proportion of RCTs do not demonstrate a statistically significant difference between the intervention and comparator. The proportion of antidepressant RCT "failure" has been reported to be as high as 50%, and has been associated with a number of factors including the lack of statistical power, issues related to the complex and variable presentation of MDD, and limitations of the composite scales used to measure treatment effects.[75,76] The instruments used to test for efficacy rely on detailed recall by patients who may be cognitively impaired.[75] Moreover, expectancy may confound patient recall and has been shown to inflate both placebo and active-treatment response.[75] Although increasing placebo response rates have been listed as a reason for antidepressant trial failure, meta-analyses have shown that placebo response rates have remained stable since the 1990s in a range of 35% to 40%.[77,78] In clinical trials, all patients receive frequent interactions with and monitoring by clinical experts, potentially relieving depressive symptoms for both placebo and active-treatment groups.[75] Baseline disease severity may also have an impact on drug-placebo differences.[5] As well, relatively restrictive eligibility criteria (used to ensure more homogeneous study populations in a heterogenous condition) make it difficult to generalize trial results to patients with MDD seen in clinical practice, as confirmed by the clinical expert involved in the review. These limitations were observed with the RCTs for vortioxetine and affect the interpretability of the findings, as discussed. However, they appear to be in common with RCTs of other antidepressants available in Canada. While this does not ease interpretation of the findings for vortioxetine, it provides context for interpreting the comparative efficacy of vortioxetine against placebo and other antidepressants.

Harms

The overall frequency of adverse events was higher among those receiving vortioxetine compared with placebo; nausea was the most common adverse event in the vortioxetine groups. Withdrawals due to adverse events were also reported more frequently among those on the higher doses of vortioxetine (15 mg and 20 mg) compared with placebo. The incidence of serious adverse events, including suicidal behaviour and serotonin syndrome, was low and similar between groups, although the studies were not powered to detect differences in rare adverse events. Moreover, the duration of most studies was limited to six to eight weeks. Data from open-label extension studies did not reveal any new safety signals, but these trials lacked control groups and thus cannot provide information of comparative safety.

Treatment-emergent sexual dysfunction was reported more frequently among those receiving vortioxetine 10 mg to 20 mg per day, compared with placebo or vortioxetine 5 mg, based on data from the ASEX instrument. Self-reported sexual dysfunction was low and likely under-reported. Vortioxetine was found to statistically significantly improve treatment-related sexual dysfunction based on the change from baseline to week 8 in the CSFQ-14 scores, compared with escitalopram, among patients with SSRI-related sexual dysfunction at baseline. Both groups showed improvement in their CSFQ-14 scores and although the between-groups differences favoured vortioxetine, the clinical significance of the change score is unknown. It is unclear how changes on the CSFQ-14 scores correlate to changes in day-to-day patient functioning. Moreover, no statistically significant differences were detected between treatments in the odds of achieving normal sexual functioning based on the established thresholds on the CSFQ-14 for normal sexual functioning.

No substantial increases in body weight were observed in the short-term studies, and in the longer-term relapse prevention trial, the proportion of patients with clinically important weight gain was similar between vortioxetine and placebo. Abrupt cessation of vortioxetine was associated with an increased incidence of adverse events including headache, sudden outbursts of anger, mood swings, increased dreaming or nightmares, muscle tension or stiffness, dizziness, confusion or trouble concentrating, insomnia, and runny nose. The product monograph recommends a gradual reduction in dose rather than abrupt cessation of therapy.[4]

The ITC by Cipriani et al.[8] found no difference in the odds of stopping therapy for vortioxetine versus other antidepressants or placebo. However, patients who received vortioxetine were more likely to stop treatment due to adverse events compared with placebo (OR 1.64; 95% CI, 1.25 to 2.14).[8]

Patients report that the adverse effects of antidepressants can be difficult to manage, and they affect patients' ability to remain on therapy. As the NMA did not examine specific adverse events, no conclusions can be drawn on the relative incidence of adverse events such as nausea, sexual dysfunction, or suicidal ideation and behaviour. Additional longer-term safety data are needed to determine the comparative safety of vortioxetine.

Potential Place in Therapy[b]

The first-line agents recommended for the treatment of MDD include several SSRIs, a few SNRIs, bupropion, mirtazapine, and vortioxetine.[9] Medications with different mechanisms of action show different treatment effects and safety profiles. According to the clinical expert, approximately 30% of patients experience a remission of an MDE with the first selected antidepressant medication.[10] This means that most people following a single trial of an antidepressant medication will either be nonresponsive, or partly responsive with remaining symptoms. Vortioxetine is a potentially useful treatment with a core SSRI action and a variety of additional serotonergic receptor effects. It can be prescribed in inpatient, outpatient, community, specialty clinic, and family-practice clinic settings. Vortioxetine is likely to be used as a first-line antidepressant agent. It is unclear whether satisfactory data are available for the use of vortioxetine as a second- or third-line agent.

Clinically meaningful outcomes when assessing treatment effects of an antidepressant include reduction in the number, frequency, and severity of depression symptoms, improvement in quality of life, and return to baseline functioning in a variety of domains (e.g., work, school, interpersonal, and recreational). In the maintenance phase, prevention of relapse or recurrence of depressive episodes is the key outcome. Ideally, during acute outpatient treatment, treatment response will be assessed frequently (e.g., every one to two weeks), and periodically during maintenance treatment. There is a general alignment between clinical practice and clinical trials in the way response to treatment is determined, in that both practice and trials rely on questions to determine how much change has occurred in key depression symptoms. However, in clinical practice, symptomatic change is usually evaluated somewhat informally without reliance on standardized rating scales, and the use of standardized scales has not been consistently adopted for mental health outcome assessments.

Treatment with vortioxetine may be discontinued due to adverse events or lack of effectiveness, or when the pre-scheduled recommended maintenance treatment interval is complete.

Conclusions

Twenty short-term double-blind RCTs, one short-term open-label RCT, and one double-blind randomized withdrawal study provided evidence on the efficacy and safety of vortioxetine 5 mg to 20 mg daily compared with placebo, venlafaxine, or escitalopram.

Overall, vortioxetine showed statistically significant differences over placebo in reducing depression symptom severity after six to eight weeks of therapy. However, treatment effects varied substantially across trials, with approximately half of the short-term efficacy trials reporting no statistically significant differences between vortioxetine and placebo for the primary outcome (MADRS or HAM-D depression symptom severity scores). Vortioxetine was noninferior to venlafaxine in one trial for the change from baseline to week 8 in the MADRS score, but pairwise meta-analysis suggests vortioxetine may be less effective than duloxetine in reducing depression symptom severity in the short-term. However, the differences between duloxetine and vortioxetine were small and the clinical significance was unclear.

[b] This information is based on information provided in draft form by the clinical expert consulted by CADTH reviewers for the purpose of this review.

Vortioxetine may be more effective in preventing relapse than placebo based on data from one trial. No conclusions can be drawn on the impact of vortioxetine on HRQoL, disability, cognitive function, or in reducing SSRI-related sexual dysfunction due to methodological issues or questions regarding the clinical relevance of the outcome measures utilized.

Serious adverse events, including suicidal behaviour, were reported infrequently in all treatment groups, although the studies were not powered to detect differences in rare adverse events, and treatment duration was eight weeks or less for most RCTs. Withdrawals due to adverse events occurred more frequently in the higher-dose vortioxetine groups compared to the placebo groups. No new safety signals were identified in the longer-term open-label extension studies.

Indirect evidence suggests that the drugs used for the acute treatment of MDD, including vortioxetine, other second-generation antidepressants, tricyclic antidepressants, and trazodone, have similar efficacy and acceptability (in terms of treatment response and withdrawal frequency) compared with each other, and all are more effective than placebo.

The available evidence was limited by the short duration of trials (six to eight weeks), possible unblinding that may have biased subjective outcomes, and concerns with the generalizability of the findings. Direct evidence comparing vortioxetine with other antidepressants available in Canada was limited.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Five patient groups, the Mood Disorders Society of Canada (MDSC), the national and Alberta offices of the Canadian Mental Health Association (CMHA), the Stigma-Free Society (SFS), and the Hope + Me-Mood Disorders Association of Ontario (MDAO), provided patient input for this summary. The MDSC is a non-governmental organization that was formally launched and incorporated in 2001. Its objective is give people suffering from mood disorders a strong, cohesive voice at the national level to improve access to treatment, inform research and shape program development and government policies with the goal of improving their quality of life (https://mdsc.ca). CMHA is a nationwide not-for-profit registered charity founded in 1918 (https://cmha.ca). Supported by its volunteers and staff across Canada, CMHA facilitates access to the resources people require to maintain and improve mental health and community integration, builds resilience, and supports recovery from mental illness across Canada. CMHA Alberta focuses on recovery and support for Albertans affected by mental illness (https://alberta.cmha.ca). CMHA National and CMHA Alberta submitted aggregate patient input for this review. The SFS has been a registered Canadian charity since 2010. It has designed programs providing education about stigmas (with a focus on mental health) and peer support for those facing mental health challenges, for the purpose of creating awareness of the various stigmas that exist in the world, developing an understanding of the challenges faced by many people, and encouraging all people to foster acceptance of themselves and others (https://stigmafreesociety.com). The MDAO is a community-based mental health services provider with a history of more than 35 years. It supports Ontarians who experience mood disorders, early psychosis, and multiple mental health or addictions issues and their caregivers through peer support (most of the peer support facilitators are highly trained volunteers who have personal knowledge about mental illness), as well as professional counselling in the Toronto area (https://www.mooddisorders.ca).

The MDSC and the MDAO reported that they had no outside help collecting and analyzing data or completing the submission. The MDSC received financial payments from Janssen Inc., Pfizer Canada, and Lundbeck Canada Inc. (manufacture of Trintellix), all in excess of $50,000, over the past two years; however, the MDSC indicated that its millions of dollars in funding come primarily from non-pharmaceutical companies, and its positions were not influenced by the funding sources. The MDAO received financial payments from Lundbeck Canada Inc. (< $5,000), Canadian Biomarker Integration Network in Depression ($5,001 to $10,000), and Janssen Pharmaceutical Companies of Johnson & Johnson ($5,001 to $23,500) over the past two years. Global Public Affairs (a privately held strategic communications and government advocacy consultancy organization) and Janssen Scientific Affairs (one of CMHA National's funders) provided contact information for the psychiatrists, general practitioners, and patients during the preparation of the submission by CMHA National. CMHA Alberta declared receiving help collecting and analyzing data (by individuals and EXEP Consulting Inc.) in the preparation of this submission. However, none of them received help completing the submission from outside their patient groups. Over the past two years, CMHA National received financial payments from Lundbeck Canada Inc. (> $50,000), and CMHA Alberta also declared a financial payment from Janssen Pharmaceutical Companies of Johnson & Johnson ($10,001 to $50,000). The SFS received help from outside its patient group to collect data (online survey setup by WestPAR

Consultancy Inc.) used in its submission; however, the survey results and information were processed by SFS staff exclusively. It declared financial payments from Lundbeck Canada Inc. and Otsuka Pharmaceuticals ($5,001 to $10,000 each) over the past two years.

Each organization provided the source(s) of information contained in their submissions. The MDSC gathered perspectives via direct discussions with patients diagnosed with major depressive disorder (MDD) through focus groups, meetings, and online discussions. Family members and/or caregivers also provided input to MDSC. In addition, a national online survey was conducted in March 2018 to identify priority issues and improvements or changes to the Canadian mental health care system that need to be addressed in relation to treatment-resistant depression. In total, 119 respondents completed this survey. Among them, 51% reported experiencing more than 10 bouts of depression. CMHA National gathered patient perspectives by conducting semi-structured phone interviews and online surveys. Two patients with depression or MDD were identified: one in Canada (a female patient with experience of Trintellix) and one in the US (a male patient without experience of Trintellix). CMHA Alberta conducted a survey (16 individuals completed and five partially completed the survey) and follow-up focus groups with nine Albertan adults with depression and experience with antidepressant medications on the topic of depression that was unresolved after the use of two or more antidepressant agents. The SFS used an online survey for data collection, from April 18 to May 21, 2019. Twenty respondents who were all Canadian and residing in Victoria and metropolitan Vancouver provided input to its submission, and one respondent had experience with Trintellix. Respondents included 16 people with major depressive disorder and two caregivers. The MDAO collected personal experiences using a survey for patients receiving Trintellix across Ontario, from April 12 to 30, 2019. Five people (two males and three females ranging in age from 27 to 64 years) responded to the survey. They also conducted individual interviews with two patients (both females aged 35 to 42) in the Toronto area. All the respondents were patients.

2. Condition-Related Information

Patient groups emphasized that MDD is a chronic, complex, and disabling disease. It negatively affects a person's life in different ways. Specifically, survey respondents indicated that MDD affected sleep (trouble falling or staying asleep, or sleeping too much), appetite (poor appetite or overeating), mood, relationships, exercise, work, and the ability to do the activities they used to enjoy, as well as the tasks of daily life such as getting out of bed, getting ready, preparing meals, or tidying the house. Respondents also reported feeling apathetic, tired, and down or hopeless, along with little interest or pleasure in doing things, difficulty concentrating, and a sense of "darkness" and negativeness about themselves. "Negative coping" strategies such as self-harm and alcohol or drug abuse were reported. Respondents' depression was also accompanied by suicidal thoughts, particularly when their depressive symptoms were compounded with life- and/or work-related stress. Their relationships with family, friends, colleagues, and society were negatively affected as well, with some reporting experiencing stigma and social isolation due to their mental illness. Many reported the need to hide their condition from employers and a fear of adverse impacts from disclosing their illness. In addition, patients with MDD may not be able to provide self-care and care for their family. The financial burden can be profound, as many patients are unable to work and must rely on disability payments or savings, and may have limited access to government support and resources or face high out-of-pocket treatment costs.

Some examples of quotes from patients are provided below.

- *"I can remember back in my drinking days specific instances of being so depressed and kind of retreat to the bed for a couple of days and not want to go out or do anything. Very overwhelming."*
- *"Sometimes I feel embarrassed to tell my job I need to go to the hospital or that I was in the hospital. It's also hard talking to my school if I miss a day due to mental health."*
- *"I don't want to be around me, so how can I expect that of others."*

3. Current Therapy-Related Information

Various antidepressant drugs are available. The MDSC survey suggested that 69% of the respondents have been treating their MDD for more than 11 years, while 49% of them did not respond well to the treatment. Wellbutrin, Effexor/Effexor Extended-Release, Celexa, Prozac, Zoloft, Cipralex, and Paxil were commonly prescribed antidepressants. The two patients in the CMHA National submission had taken multiple antidepressants, sometimes trying several medications simultaneously. One patient said that he experienced benefits after initiating pharmacotherapy for his depressive symptoms, but he had to discontinue the prescribed treatment due to substantial side effects, which in turn negatively impacted his experience with depression. CMHA Alberta echoed that patients in its group had tried multiple medications, and most of them reported severe side effects, including memory loss, worsening of symptoms, or complications of in other conditions that they had. Consequently, medication-related side effects had an impact on patient's overall quality of life and willingness and ability to seek new treatments. For some individuals, the medications had no impact. Results of the SFS submission showed that approximately 65% of the respondents were treated with more than two antidepressant medications. One patient stated, "*[I have tried] Celexa, Effexor, trazadone, Wellbutrin, Abilify. Discontinued because they did not significantly impact my depression.*"

The most challenging issue that the patient groups identified was related to the financial impact. In the CMHA Alberta survey, 86.7% of the respondents reported experiencing financial difficulties since the diagnosing of MDD.

There were no patients from the MDSC and CMHA Alberta who had experience with using Trintellix to treat MDD. One patient from CMHA National who had experience with Trintellix for six months reported:

> *"Since starting Trintellix my life has turned around and my symptoms are infinitely better ... I call it the miracle drug … My moods are easier to control – when I would get upset or in a bad mood it would often last for hours or days. Now I am able to shake it off fairly quickly... The benefits have made my life so much better and have improved my relationships."*

Another patient from the SFS had been prescribed Trintellix for three months through samples from an emergency psychiatric hospital. The patient had a very negative experience with Trintellix, reporting no benefit but excessive nausea and vomiting for the entire three months on the medication. All patients from the MDAO group had experience with Trintellix, and they obtained the drug through private-payer insurance. Two patients indicated they experienced nausea. For one patient, nausea occurred during the first week of treatment and lasted for two weeks. The other patient experienced mild nausea and vomiting for three weeks, and the symptoms were considered dose-related. Nausea and vomiting diminished after adjustment of the treatment. One patient stated that Trintellix helped with their sadness and indecisiveness. MDAO commented that due to the complexity of MDD (affecting patients' emotion, cognition, and physical health), having

greater choice of antidepressants would help patients find an antidepressant that works better for them.

4. Expectations About the Drug Being Reviewed

CMHA National hopes to ensure the drug review process, specifically for mental health drugs, involves explicit communication and transparency with mental health patient organizations. CMHA Alberta indicated that treatment and wellness maintenance is highly individualized; therefore, patients would be willing to continue to try new medications in the hopes of finding one that works. In addition, affordable, equitable, and timely access to the full spectrum of psychological support is critical for individuals when medication alone does not resolve depression. The MDSC pointed out that access to treatment of MDD should not be limited to those only with private drug plan coverage, and accessing the best medications to treat metal illness should be fully equitable for all those who suffer. The MDAO also stated that many patients with severe MDD are unable to work, leaving them without private insurance, which is a severe inequity in the health care system. When a broader range of medications addressing the three facets of health (emotional, cognitive, and physical) is not available to those who rely on the public system, the chances of successful treatment are considerably slimmer.

There are limited treatment options available in the public system. CMHA Alberta suggests that expanding the publicly funded treatment options would reduce out-of-pocket expenses and improve patient support.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–) Embase (1974–) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 30, 2019
Alerts:	Bi-weekly search updates until September 18, 2019
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	Vortioxetine/
2	(Trintellix* or Brintellix* or vortioxetine* or LuAA21004 or Lu AA21004 or 3O2K1S3WQV or TKS641KOAY).ti,ab,ot,kf,hw,rn,nm.
3	or/1-2
4	3 use medall
5	*vortioxetine/
6	(Trintellix* or Brintellix* or vortioxetine* or LuAA21004 or Lu AA21004).ti,ab,kw,dq.
7	or/5-6
8	7 use oemezd

MULTI-DATABASE STRATEGY	
9	8 not (conference review or conference abstract).pt.
10	4 or 9
11	remove duplicates from 10

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Trintellix, vortioxetine, Brintellix, LuAA21004 or Lu AA21004
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Trintellix, vortioxetine, Brintellix, LuAA21004, or Lu AA21004

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	May 24-May 27, 2019
Keywords:	Trintellix (vortioxetine), Brintellix, LuAA21004, Lu AA21004, major depressive disorder
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Internet Search

Appendix 3: Excluded Studies

Table 23: Excluded Studies

Reference	Reason for exclusion
Christensen MC, Loft H, McIntyre RS. Vortioxetine improves symptomatic and functional outcomes in major depressive disorder: a novel dual outcome measure in depressive disorders. J Affect Disord. 2018;227:787-794. Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y, Keefe RS. 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):2025-2037.	Phase II study
Jacobsen PL, Nomikos GG, Zhong W, Cutler AJ, Affinito J, Clayton A. Clinical implications of directly switching antidepressants in well-treated depressed patients with treatment-emergent sexual dysfunction: a comparison between vortioxetine and escitalopram. Cns Spectrums. 2019:1-14.	Subgroup data not relevant to review
Mahableshwarkar AR, Jacobsen PL, Serenko M, Chen Y. A randomized, double-blind, fixed-dose study comparing the efficacy and tolerability of vortioxetine 2.5 and 10 mg in acute treatment of adults with generalized anxiety disorder. Hum Psychopharmacol. 2014;29(1):64-72.	Population
Montgomery SA, Nielsen RZ, Poulsen LH, Haggstrom L. 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. 2014;29(5):470-482.	Comparator
Wang J, Liu XF, Feng C, Bao Q, Fu HR. RETRACTED ARTICLE: Efficacy and safety of vortioxetine for the treatment of major depressive disorder: a randomised double-blind placebo-controlled study. Int J Psychiatry Clin Pract. 2017:1-6.	Retracted
Florea I, Danchenko N, Brignone M, Loft H, Rive B, Abetz-Webb L. The effect of vortioxetine on health-related quality of life in patients with major depressive disorder. Clin Ther. 2015;37(10):2309-2323.e2306. Alam MY, Jacobsen PL, Chen Y, Serenko M, Mahableshwarkar AR. Safety, tolerability, and efficacy of vortioxetine (Lu AA21004) in major depressive disorder: results of an open-label, flexible-dose, 52-week extension study. Int Clin Psychopharmacol. 2014;29(1):36-44. Chokka P, Bougie J, Proulx J, Tvistholm AH, Ettrup A. Long-term functioning outcomes are predicted by cognitive symptoms in working patients with major depressive disorder treated with vortioxetine: results from the AtWoRC study. Cns Spectrums. 2019:1-12. Baldwin DS, Hansen T, Florea I. Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. Curr Med Res Opin. 2012;28(10):1717-1724. Baldwin DS, Chrones L, Florea I, et al. The safety and tolerability of vortioxetine: analysis of data from randomized placebo-controlled trials and open-label extension studies. J Psychopharmacol. 2016;30(3):242-252. Vieta E, Loft H, Florea I. Effectiveness of long-term vortioxetine treatment of patients with major depressive disorder. Eur Neuropsychopharmacol. 2017;27(9):877-884. Jacobsen PL, Harper L, Chrones L, Chan S, Mahableshwarkar AR. Safety and tolerability of vortioxetine (15 and 20 mg) in patients with major depressive disorder: results of an open-label, flexible-dose, 52-week extension study. Int Clin Psychopharmacol. 2015;30(5):255-264. Chokka P, Bougie J, Rampakakis E, Proulx J. Assessment in work productivity and the relationship with cognitive symptoms (AtWoRC): primary analysis from a Canadian open-label study of vortioxetine in patients with major depressive disorder (MDD). Cns Spectrums. 2019;24(3):338-347.	Study design

Reference	Reason for exclusion
Cao B, Park C, Subramaniapillai M, et al. The efficacy of vortioxetine on anhedonia in patients with major depressive disorder. Front Psychiatr. 2019;10:17. NACTRC Real World Evidence. Research Report: health care resource utilization among patients with depression before and after initiating Trintellix™. 2019 Apr 4. Data analytic report for phase I (feasibility assessment): Lundbeck research project. 2018 May 31.	
McCue M, Parikh S, Mucha L, Lawrence D. Progress toward personalized goal attainment and functional recovery after a switch to vortioxetine in adults with major depressive disorder: interim study results. J Manag Care Spec Pharm. 2018;Oct; 24(10A):s48.	Study design, abstract

Appendix 4: Detailed Study Design and Outcome Data

Study Design

Table 24: Randomization and Allocation Concealment Methods

Study	Randomization and allocation concealment methods
303	Randomized 1:1 via IVRS
304	Randomized 1:1:1:1 via IVRS
305	Randomized 1:1:1:1 via IVRS
315	Randomized 1:1:1:1 via IVRS stratified by patients' baseline sexual functioning status (normal or abnormal, decided by baseline ASEX scores), and site.
316	Randomized 1:1:1 via IVRS stratified by patients' baseline sexual functioning status (normal or abnormal, decided by baseline ASEX scores), and site
317	Randomized 1:1:1 via IVRS stratified by patients' baseline sexual functioning status (normal or abnormal, decided by baseline ASEX scores), and site
CCT-002	Randomized 1:1 via IVRS or IWRS
CCT-003	Randomized 1:1:1 via IWRS
CCT-004	Unclear randomization and allocation concealment methods Patients assigned sequential ID number at site; randomization sequence kept in secure location
11984A	Computer generated randomization code (block size 5) stratified by site Sealed consecutively numbered envelopes held by site investigator or pharmacist.
13267A	Computer generated randomization code (block size not specified) stratified by site. Randomized 1:1:1:1 via IVRS or IWRS
12541A	Computer generated randomization code (block size 6) stratified by site Sealed envelopes with randomization code kept by investigator or pharmacist at each site
11492A	Computer generated randomization code (block size 4) stratified by site Sealed envelopes with randomization code kept by investigator or pharmacist at each site
13926A noninferiority	Computer generated randomization code (block size 4) Randomized 1:1 via IVRS
318	Randomized 1:1 via IVRS, stratified by site
14122A	Computer generated randomization code (block size 4) stratified by site. Randomized 1:1 via IVRS or IWRS
15905A	Randomized 1:1:1 via IVRS or IWRS, stratified by site, block size 6
15906A	Randomized 1:1:1 via IVRS or IWRS, stratified by site, block size 6
15907A	Randomized 1:1 via IVRS or IWRS, stratified by site, block size 4
11985A	Computer generated randomization list, block size 4, stratified by site Sealed envelopes with randomization code kept by investigator or pharmacist at each site
Liebowitz et al. (2017)	Methods were not reported
Levada et al. (2019)	Methods were not reported

ASEX = Arizona Sexual Experiences Scale; ID = identification; IVRS = interactive voice response system; IWRS = interactive web response system.

Source: Clinical Study Report,[11-30] Levada et al. (2019),[55] Liebowitz et al. (2017).[56]

Efficacy Outcomes

Table 25: Quality of Life Enjoyment and Satisfaction Questionnaire – Short-Form

Study	Treatment	Baseline			Adjusted change from baseline to end of treatment			Adjusted difference from placebo	
		N	Mean	SD	N	Mean	SE	Mean (95% CI)	P value
13267A[a]	PBO	153	34.1	7.0	139	5.2	[redacted]	[redacted]	
	VOR 15 mg	143	33.2	7.0	127	8.5	[redacted]	[redacted]	[redacted]
	VOR 20 mg	144	33.8	7.3	134	9.8	[redacted]	[redacted]	[redacted]
	DUL 60 mg	139	34.8	6.3	128	12.7	[redacted]	[redacted]	[redacted]
Study	**Treatment**	**Baseline**			**Adjusted change from baseline to end of treatment**			**Adjusted difference from venlafaxine**	
		N	**Mean**	**SD**	**N**	**Mean**	**SE**	**Mean (95% CI)**	**P value**
13926A[a]	VOR 10 mg	209	34.4	6.7	189	8.5	0.61	[redacted]	[redacted]
	VEN 150 mg	215	34.4	7.0	197	8.6	0.59	[redacted]	

CI = confidence interval; DUL = duloxetine; NS = not statistically significant; PBO = placebo; ref = reference group; SD = standard deviation; SE = standard error; VEN = venlafaxine extended release; VOR = vortioxetine.

[a] Full analysis set, analysis of variance, last observation carried forward.

[b] Outside the statistical testing procedure.

Source: Clinical Study Report.[21,25]

Table 26: EuroQol 5-Dimensions 3-Levels Questionnaire

Study	Treatment	Baseline			Adjusted change from baseline to week 8			Adjusted difference from placebo	
		N	Mean	SD	N	Mean	SE	Mean difference (95% CI)	P value
EQ-5D-3L index[a]									
15906A	PBO	48	[redacted]	NR	47	[redacted]	[redacted]	[redacted]	
	VOR 10 mg	48	[redacted]	NR	46	[redacted]	[redacted]	[redacted]	[redacted]
	PAR 20 mg	52	[redacted]	NR	49	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-3L VAS[a]									
15906A[a]	PBO	48	[redacted]	NR	47	[redacted]	[redacted]	[redacted]	
	VOR 10 mg	48	[redacted]	NR	46	[redacted]	[redacted]	[redacted]	[redacted]
	PAR 20 mg	52	[redacted]	NR	49	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; NS = not statistically significant; PAR = paroxetine; PBO = placebo; ref = reference group; SD = standard deviation; SE = standard error; VAS = visual analogue scale; VOR = vortioxetine.

[a] Full analysis set, mixed-effect model for repeated measurements.

[b] Outside the statistical testing hierarchy.

Source: Clinical Study Report.[29]

Table 27: Sheehan Disability Scale in Short-Term Efficacy Trials

Study	Intervention	Baseline			Adjusted change from baseline to end of treatment			Adjusted mean difference from placebo or active control			
		N	Mean	SD	N	Mean	SE	Mean	SE	(95% CI)	P value
305	PBO	104	20.1	SE 0.62	94	−6.54	0.716				
	VOR 5 mg	106	19.8	SE 0.62	97	−7.65	0.713	−1.11	1.00	(−3.07 to 0.84)	NS[a]
	VOR 10 mg	99	21.0	SE 0.63	83	−8.08	0.756	−1.54	1.03	(−3.56 to 0.48)	NS[a]
303	PBO	217	17.7	SE 0.45	217	−6.61	0.548				
	VOR 5 mg	220	18.3	SE 0.46	220	−6.69	0.557	−0.09	0.75	(−1.57 to 1.39)	NS[a]
316	PBO	91	19.4	SE 0.63	86	−5.86	0.771				
	VOR 10 mg	101	19.0	SE 0.60	89	−7.25	0.747	−1.39	1.04	(−3.44 to 0.66)	NS[a]
	VOR 20 mg	91	20.4	SE 0.63	77	−8.26	0.794	−2.40	1.07	(−4.50 to −0.30)	NS[a]
317	PBO	89	20.5	SE 0.55	77	−9.38	0.877				
	VOR 10 mg	78	20.3	SE 0.62	74	−10.3	0.959	−0.92	1.25	(−3.38 to 1.55)	NS[a]
	VOR 15 mg	74	20.7	SE 0.62	62	−8.69	0.99	0.69	1.32	(−1.91 to 3.30)	NS[a]
CCT-002	PBO	132	18.2	5.28	126	−6.20	0.602				
	VOR 5 mg	116	17.9	6.27	109	−6.38	0.647	−0.19	0.88	(−1.93 to 1.55)	0.83[b]
	VOR 10 mg	119	18.5	5.42	114	−7.97	0.633	−1.78	0.87	(−3.49 to −0.06)	0.04[b]
	VOR 20 mg	121	18.2	5.70	118	−7.26	0.622	−1.06	0.87	(−2.76 to 0.64)	0.22[b]
CCT-003	PBO	124	15.4	5.45	122	−2.91	0.504				
	VOR 5 mg	119	15.5	6.12	119	−5.01	0.510	−2.11	0.72	(−3.52 to −0.70)	0.0035[b]
	VOR 10 mg	123	15.2	5.97	121	−4.02	0.506	−1.11	0.71	(−2.52 to 0.29)	0.12[b]
CCT-004	PBO	164	13.9	6.2	153	−2.85	0.45				
	VOR 10 mg	165	14.0	6.0	163	−4.20	0.43	−1.34	0.62	(−2.56 to −0.12)	0.031[b]
	VOR 20 mg	164	14.8	5.5	158	−4.43	0.44	−1.57	0.63	(−2.81 to −0.34)	0.013[b]
11984A	PBO	122	19.9	5.8	116	−6.11	0.72				
	VOR 5 mg	127	19.6	6.2	119	−6.52	0.73	−0.41	0.98	(−2.35 to 1.52)	NS[a]
	VOR 10 mg	124	19.6	6.5	115	−7.81	0.74	−1.70	0.99	(−3.64 to 0.25)	NS[a]
	DUL 60 mg	115	19.2	5.9	108	−7.91	0.76	−1.80	1.01	(−3.79 to 0.19)	NS[a]

Study	Intervention	Baseline			Adjusted change from baseline to end of treatment			Adjusted mean difference from placebo or active control			
		N	Mean	SD	N	Mean	SE	Mean	SE	(95% CI)	P value
304	PBO	130	19.1	SE 0.56	130	−6.83	0.64				
	VOR 5 mg	123	18.6	SE 0.56	123	−6.59	0.64	0.23	0.87	(−1.48 to 1.95)	NS[a]
	DUL 60 mg	114	18.0	SE 0.59	114	−8.91	0.67	−2.09	0.90	(−3.85 to −0.32)	NS[a]
13267A	PBO	115	19.8	6.0	81	−4.46	0.82				
	VOR 15 mg	97	20.6	5.3	65	−7.70	0.89	−3.24	1.16	(−5.5 to −1.0)	0.0054
	VOR 20 mg	107	20.7	4.8	80	−8.38	0.85	−3.92	1.11	(−6.1 to −1.7)	0.0005
	DUL 60 mg	99	20.5	4.4	79	−11.39	0.85	−6.93	1.13	(−9.2 to −4.7)	< 0.0001
315	PBO	102	19.2	SE 0.63	85	−7.68	0.776				
	VOR 15 mg	87	18.7	SE 0.67	77	−7.73	0.821	−0.05	1.111	(−2.24 to 2.13)	NS[a]
	VOR 20 mg	95	18.2	SE 0.65	77	−8.55	0.81	−0.88	1.103	(−3.05 to 1.29)	NS[a]
	DUL 60 mg	86	18.9	SE 0.67	73	−9.66	0.834	−1.99	1.123	(−4.19 to 0.22)	NS[a]
13926A	VOR 10 mg	196	18.9	6.4	171	−7.59	0.61	−1.03	0.79	(−2.58 to 0.53)	0.20[b]
	VEN 150 mg	195	19.2	6.2	173	−6.56	0.60				
15905A	VOR 10 mg to 20 mg + SSRI	42	13.3	7.4	38	−4.20	0.98	−1.21	1.28	(−3.75 to 1.33)	0.35 [b]
	VOR 10 mg to 20 mg +PBO	37	12.4	5.3	36	−5.26	1.00	−2.27	1.31	(−4.87 to 0.33)	0.09 [b]
	SSRI + PBO	41	13.6	7.0	37	−2.99	0.97				

CI = confidence interval; DUL = duloxetine; NS = not statistically significant; PBO = placebo; SD = standard deviation; SE = standard error; SSRI = selective serotonin reuptake inhibitor; VEN = venlafaxine extended release; VOR = vortioxetine.

[a] Statistical hierarchy failed at this or a previous level.

[b] Secondary or tertiary outcome that was outside of the hierarchical testing procedure or other methods used to control for type I error.

Source: Clinical Study Report.[12-15,18-21,23,25,26,30]

Table 28: Study 11985A Mean Change from Baseline to Week 24 (MADRS, HAM-D, and SDS)[a,b,c]

	PBO		5 mg or 10 mg VOR		Mean difference VOR versus PBO	
	Baseline mean (SD)[a]	LS mean change (SE)	Baseline mean (SD)[a]	LS mean change (SE)	Mean difference (95% CI)[b]	P value
MADRS Total Score						
OC Analysis	4.7 (3.2) (n = 192)	1.5 (0.6) (n = 132)	4.9 (3.0) (n = 204)	−0.6 (0.5) (n = 151)	−2.1 (−3.4 to −0.8)	0.0020[c]
LOCF Analysis	4.7 (3.2) (n = 192)	5.6 (0.7) (n = 192)	4.9 (3.0) (n = 204)	2.4 (0.7) (n = 203)	−3.2 (−4.9 to −1.5)	0.0003[c]
HAM-D17 Total Score						
OC Analysis	4.0 (3.2) (n = 192)	1.6 (0.5) (n = 136)	4.5 (3.3) (n = 204)	0.3 (0.4) (n = 158)	−1.3 (−2.4 to −0.2)	0.0171[c]
LOCF Analysis	4.0 (3.2) (n = 192)	4.1 (0.5) (n = 192)	4.5 (3.3) (n = 204)	1.8 (0.5) (n = 203)	−2.3 (−3.5 to −1.1)	0.0003[c]
SDS Total Score						
OC Analysis	8.4 (7.4) (n = 163)	0.1 (0.6) (n = 118)	9.0 (7.1) (n = 181)	−0.5 (0.6) (n = 135)	−0.7 (−2.1 to 0.8)	0.3642[c]
LOCF Analysis	8.9 (7.6) (n = 176)	2.1 (0.6) (n = 171)	9.1 (7.2) (n = 192)	0.3 (0.6) (n = 184)	−1.8 (−3.2 to −0.4)	0.0148[c]

CI = confidence interval; HAM-D17 = 17-item Hamilton Depression Rating Scale; LOCF = last observation carried forward; MADRS = Montgomery–Åsberg Depression Scale; OC = observed cases; PBO = placebo; SD = standard deviation; SDS = Sheehan Disability Scale; SE = standard error; VOR = vortioxetine.

[a] Baseline of the double-blind period (i.e., at randomization). Prior to randomization, all patients received open-label vortioxetine for 12 weeks and those in remission were eligible for the double-blind period.

[b] Analysis was based on the full analysis set, observed cases, and LOCF, and an analysis of covariance model controlling for site and baseline score.

[c] No control for multiple statistical testing.

Source: Clinical Study Report.[16]

Table 29: Response and Remission in Short-Term Efficacy Trials

Study	Intervention	Response			Remission		
		n	N	%	n	N	%
305[ab]	PBO	32	139	23	23	139	17
	VOR 5 mg	63	139	45	40	139	29
	VOR 10 mg	69	139	50	37	139	27
303[ab]	PBO	132	286	46	92	286	32
	VOR 5 mg	135	292	46	85	292	29
316[bc]	PBO	44	155	28	22	155	14
	VOR 10 mg	52	154	34	33	154	21
	VOR 20 mg	58	148	39	33	148	22
317[bc]	PBO	49	149	33	33	149	22
	VOR 10 mg	54	143	38	38	143	27
	VOR 15 mg	53	142	37	34	142	24
CCT-002[bc]	PBO	59	150	39	40	150	27
	VOR 5 mg	70	142	49	35	142	25
	VOR 10 mg	80	147	54	43	147	29
	VOR 20 mg	76	149	51	46	149	31

Study	Intervention	Response			Remission		
		n	N	%	n	N	%
CCT-003[bc]	PBO	49	123	40	27	123	22
	VOR 5 mg	61	119	51	35	119	29
	VOR 10 mg	56	122	46	35	122	29
11984A[bc]	PBO	68	145	47	49	145	34
	VOR 5 mg	87	155	56	56	155	36
	VOR 10 mg	87	151	58	54	151	36
	DUL 60 mg	85	149	57	52	149	35
304[ab]	PBO	48	149	32	33	119	28
	VOR 5 mg	58	153	38	32	120	27
	DUL 60 mg	76	149	51	51	110	46
13267A[bc]	PBO	51	158	32	30	158	19
	VOR 15 mg	85	149	57	52	149	35
	VOR 20 mg	93	151	62	58	151	38
	DUL 60 mg	108	146	74	79	146	54
315[bc]	PBO	60	153	39	41	153	27
	VOR 15 mg	64	145	44	39	145	27
	VOR 20 mg	65	147	44	43	147	29
	DUL 60 mg	80	146	55	38	146	26
12541A[ade]	PBO	51	145	35	28	145	19
	VOR 5 mg	82	155	53	45	155	29
	DUL 60 mg	93	148	63	52	148	35
11492A[bc]	PBO	47	105	45	28	105	27
	VOR 5 mg	72	108	67	53	108	49
	VOR 10 mg	68	100	68	49	100	49
	VEN 225 mg	81	112	72	62	112	55
13926A[bc]	VOR 10 mg	139	209	67	90	209	43
	VEN 150 mg	132	215	61	89	215	41
15906A[bcf]	PBO	7	48	15	4	48	8
	VOR 10 mg	18	48	38	12	48	25
	PAR 20 mg	24	52	46	15	52	29
CCT-004[bc]	PBO	59	161	37	34	161	21
	VOR 10 mg	79	165	48	53	165	32
	VOR 20 mg	82	162	51	50	162	31
14122A[bc]	PBO	57	194	29	33	194	17
	VOR 10 mg	92	193	48	57	193	30
	VOR 20 mg	120	204	59	78	204	38

DUL = duloxetine; PBO = placebo; VEN = venlafaxine extended release; VOR = vortioxetine.

[a] Response defined as ≥ 50% decrease HAM-D24.
[b] Remission defined as MADRS score ≤ 10.

[c] Response defined as ≥ 50% decrease MADRS.

[d] Remission defined as HAM-D17 score ≤ 7.

[e] Number of patients with response or remission (n) calculated from the sample size and % response or remission reported in the Clinical Study Report.

[f] Patients with missing data imputed as non-responders.

Source: Clinical Study Report.[11-15,17-23,25-27,29]

Table 30: Study 318 Remission at Week 8 (MADRS)

	ESC N = 222		VOR N = 225		VOR versus PBO
	N	Remitters n, %	N	Remitters n, %	OR (95% CI); P value
MADRS Remission[ab]					
OC Analysis	174	139 (79.9)	165	135 (81.8)	1.01 (0.56 to 1.82); 0.984
LOCF Analysis	203	157 (77.3)	211	166 (78.7)	1.03 (0.62 to 1.71); 0.902

CI = confidence interval; ESC = escitalopram; MADRS = Montgomery–Åsberg Depression Scale; OC = observed cases; LOCF = last observation carried forward; OR = odds ratio; VOR = vortioxetine.

[a] Remission defined as MADRS total score ≤ 10.

[b] Analysis was based on the full analysis set, logistic regression with explanatory variables for treatment and baseline MADRS total score. OC and LOCF.

Source: Clinical Study Report.[24]

Table 31: Study 11985A Patients Remaining as Responders and Remitters at Week 24 (MADRS and HAM-D17)[a,b]

	PBO		5 mg or 10 mg VOR		RD VOR versus PBO		
	N	Responders/ remitters N, %	N	Responders/ remitters N, %	RD (95% CI)	P value (chi-square test)	P value (Fisher's exact test)
MADRS Response[c]							
OC Analysis	132	[redacted]	151	[redacted]	[redacted]	[redacted]	[redacted]
LOCF Analysis	192	[redacted]	203	[redacted]	[redacted]	[redacted]	[redacted]
HAM-D17 Response[c]							
OC Analysis	136	[redacted]	158	[redacted]	[redacted]	[redacted]	[redacted]
LOCF Analysis	192	[redacted]	203	[redacted]	[redacted]	[redacted]	[redacted]
MADRS Remission[d]							
OC Analysis	132	[redacted]	151	[redacted]	[redacted]	[redacted]	[redacted]
LOCF Analysis	192	[redacted]	203	[redacted]	[redacted]	[redacted]	[redacted]
HAM-D17 Remission[e]							
OC Analysis	136	[redacted]	159	[redacted]	[redacted]	[redacted]	[redacted]
LOCF Analysis	192	[redacted]	204	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; HAM-D17 = 17-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Scale; OC = observed cases; LOCF = last observation carried forward; PBO = placebo; RD = risk difference; VOR = vortioxetine.

[a] Analysis was based on the full analysis set, OC, and LOCF.

[b] 100% of patients responded to treatment and were in remission at baseline (i.e., the end of the open-label period). The percentage of responders and remitters represent the number of patients who remained as remitters or responders at week 24 of the double-blind period.

[c] Defined as ≥ 50% reduction in total score.

[d] Defined as MADRS total score ≤ 10.

[e] Defined as HAM-D17 score ≤ 7.

Source: Clinical Study Report.[16]

Table 32: MADRS Total Score in Short-Term Trials

Study	Intervention	Baseline			Adjusted change from baseline to end of treatment			Adjusted mean difference from placebo or active control			
		N	Mean	SD	N	Mean	SE	Mean	SE	(95% CI)	P value
305	PBO	139	30.7	SE 0.26	128	−10.9	0.71				
	VOR 5 mg	139	30.6	SE 0.26	129	−15.1	0.71	−4.18	1.00	(−6.14 to −2.22)	< 0.001[a]
	VOR 10 mg	139	31.6	SE 0.26	122	−15.7	0.73	−4.75	1.01	(−6.74 to −2.76)	< 0.001[a]
303	PBO	286	33.8	SE 0.20	284	−15.5	0.71				
	VOR 5 mg	292	34.0	SE 0.20	292	−15.8	0.70	−0.32	0.95	(−2.19 to 1.55)	0.74[a]
316	PBO	155	32.2	SE 0.34	139	−10.8	0.81				
	VOR 10 mg	154	32.3	SE 0.34	124	−13.0	0.83	−2.19	1.15	(−4.45 to 0.08)	0.058
	VOR 20 mg	148	32.6	SE 0.35	122	−14.4	0.85	−3.64	1.16	(−5.92 to -1.35)	0.002
317	PBO	149	33.4	SE 0.36	126	−12.9	1.04				
	VOR 10 mg	143	34.1	SE 0.37	123	−13.7	1.06	−0.79	1.49	(−3.71 to 2.14)	0.60
	VOR 15 mg	142	33.6	SE 0.37	113	−13.4	1.09	−0.49	1.50	(−3.44 to 2.46)	0.75
CCT-002	PBO	150	31.6	3.6	150	−14.0	0.78				
	VOR 5 mg	144	31.6	3.7	142	−14.6	0.81	−0.61	1.12	(−3.26 to 2.04)	0.91
	VOR 10 mg	147	31.8	4.0	147	−15.7	0.79	−1.69	1.11	(−4.31 to 0.94)	0.30
	VOR 20 mg	149	31.7	3.7	149	−15.8	0.79	−1.82	1.11	(−4.44 to 0.79)	0.24
CCT-003	PBO	124	32.5	4.5	123	−13.8	0.87				
	VOR 5 mg	119	32.2	4.8	119	−15.8	0.89	−2.03	1.24	(−4.47 to 0.41)	0.10
	VOR 10 mg	123	32.5	4.9	122	−14.9	0.87	−1.04	1.23	(−3.46 to 1.39)	0.40
11984A	PBO	145	31.7	4.3	145	−14.8	0.82				
	VOR 5 mg	155	32.7	4.8	155	−16.5	0.80	−1.70	1.13	(−3.92 to 0.51)	0.13
	VOR 10 mg	151	31.8	3.9	151	−16.3	0.80	−1.50	1.13	(−3.73 to 0.72)	0.18
	DUL 60 mg	149	31.4	4.2	149	−16.8	0.81	−2.04	1.14	(−4.27 to 0.20)	0.07
304	PBO	149	29.6	SE 0.37	149	−11.2	0.82				
	VOR 5 mg	153	29.9	SE 0.36	153	−11.3	0.80	−0.08	1.12	(−2.28 to 2.12)	0.94[a]
	DUL 60 mg	149	29.4	SE 0.37	149	−14.1	0.81	−2.87	1.13	(−5.10 to −0.65)	0.01[a]

Study	Intervention	Baseline			Adjusted change from baseline to end of treatment			Adjusted mean difference from placebo or active control			
		N	Mean	SD	N	Mean	SE	Mean	SE	(95% CI)	P value
13267A	PBO	158	31.5	3.6	130	−11.7	0.76				
	VOR 15 mg	149	31.8	3.4	118	−17.2	0.79	−5.53	1.09	(−7.66 to −3.40)	< 0.0001
	VOR 20 mg	151	31.2	3.4	125	−18.8	0.78	−7.09	1.08	(−9.21 to −4.97)	< 0.0001
	DUL 60 mg	146	31.2	3.5	131	−21.2	0.77	−9.45	1.07	(−11.55 to −7.35)	< 0.0001
315	PBO	153	31.5	4.2	129	−12.8	0.83				
	VOR 15 mg	145	31.9	4.1	113	−14.3	0.89	−1.5	1.21	(−3.86 to 0.91)	0.22
	VOR 20 mg	147	32.0	4.4	112	−15.6	0.88	−2.8	1.21	(−5.12 to −0.38)	0.023
	DUL 60 mg	146	32.8	4.3	115	−16.9	0.88	−4.1	1.21	(−6.46 to −1.69)	< 0.001
12541A	PBO	145	30.3	3.2	145	−11.2	0.77				
	VOR 5 mg	155	30.7	3.6	155	−15.5	0.75	−4.29	1.03	(−6.32 to −2.26)	< 0.0001[a]
	DUL 60 mg	148	30.4	3.1	148	−18.0	0.76	−6.83	1.05	(−8.89 to −4.78)	< 0.0001[a]
11492A	PBO	105	33.9	2.7	105	−14.5	1.03				
	VOR 5 mg	108	34.1	2.6	108	−20.4	1.01	−5.90	1.39	(−8.64 to −3.17)	< 0.0001
	VOR 10 mg	100	34.0	2.8	100	−20.2	1.04	−5.70	1.42	(−8.49 to −2.91)	< 0.0001
	VEN 225 mg	112	34.2	3.1	112	−20.9	0.99	−6.42	1.38	(−9.13 to −3.72)	< 0.0001
13926A	VOR 10 mg	209	32.3	4.6	209	−19.4	0.70	−1.20	0.93	(−3.03 to 0.63)	0.20
FAS	VEN 150 mg	215	32.3	4.5	215	−18.2	0.68				
PPS	VOR 10 mg	180	32.4	NR	180	−20.3	0.66	0.19	0.91	(−1.61 to 1.99)	0.84[a]
	VEN 150 mg	164	32.6	NR	164	−20.4	0.70				
15906A[a]	PBO	48	31.8	NR	46	−8.0	1.21				
	VOR 10 mg	48	30.6	NR	42	−15.2	1.27	−7.15	1.77	(−10.65 to −3.65)	< 0.0001[a]
	PAR 20 mg	52	31.3	NR	46	−16.0	1.19	−7.97	1.70	(−11.32 to −4.61)	< 0.0001[a]
Levada	VOR 10 mg to 20 mg	36	28.6	6.2	36	−22.6	1.3	−4.0	2.1	NR	0.06[b]
	ESC 10 mg to 20 mg	20	27.8	10.2	20	−17.9	1.7				
CCT-004	PBO	164	30.5	3.9	NR	−12.4	0.71				
	VOR 10 mg	165	30.8	3.7	NR	−15.0	0.70	−2.66	1.00	−4.63 to −0.70	0.008

Study	Intervention	Baseline			Adjusted change from baseline to end of treatment			Adjusted mean difference from placebo or active control			
		N	Mean	SD	N	Mean	SE	Mean	SE	(95% CI)	P value
	VOR 20 mg	164	30.6	3.6	NR	−15.5	0.71	−3.07	1.00	−5.05 to −1.10	0.0023

CI = confidence interval; DUL = duloxetine; ESC = escitalopram; FAS = full analysis set; MADRS = Montgomery–Åsberg Depression Rating Scale; NR = not reported; PBO = placebo; PAR = paroxetine; SD = standard deviation; SE = standard error; VEN = venlafaxine extended release; VOR = vortioxetine.

[a] MADRS was a secondary outcome and was outside the hierarchical testing procedures; therefore, there was no control of multiplicity.

[b] Levada et al. (2019) did not control for multiplicity for any outcome.

Source: Clinical Study Report,[11-15,17-21,23,25-27,29] Levada et al (2019).[55]

Table 33: Study 14122A Difference in Mean Change from Baseline for MADRS Total Score at Week 8 (Vortioxetine Versus Placebo)

	Baseline mean (SE),[a] N	Mean change from baseline (SE),[b] N	Mean difference VOR versus PBO (95% CI)	P value[c]
MADRS Total Score				
PBO	31.3 (0.3), N = 194	−10.9 (0.6), N = 165		
VOR 10 mg	31.6 (0.3), N = 193	−15.6 (0.6), N = 174	−4.7 (−6.5 to −3.0)	< 0.0001
VOR 20 mg	31.7 (0.3), N = 204	−17.6 (0.6), N = 181	−6.7 (−8.4 to −5.0)	< 0.0001

CI = confidence interval; MADRS = Montgomery–Åsberg Depression Rating Scale; PBO = placebo; SE = standard error; VOR = vortioxetine.

[a] Based on the full analysis set using observed cases.

[b] Based on the full analysis set using the mixed-effect model for repeated measures, controlling for grouped site, baseline composite z score, and interaction terms (baseline composite z score by visit; treatment by visit).

[c] No control for multiple statistical testing.

Source: Clinical Study Report.[22]

Table 34: Study 318 Change from Baseline in MADRS

	ESC N = 222		VOR N = 225		VOR versus ESC	
	N	LS mean change (SE)	N	LS mean change (SE)	LS mean difference (95% CI)	P value
MADRS Total Score[a,b]						
Week 2	203	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	188	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	176	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	174	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ESC = escitalopram; LS = least squares; MADRS = Montgomery–Åsberg Depression Rating Scale; SE = standard error; VOR = vortioxetine.

[a] Baseline MADRS scores: ESC 8.5 (SE 0.38) and VOR 8.2 (SE 0.37).

[b] Analysis was based on the full analysis set, observed cases, and mixed-effect model for repeated measurements controlling for site, week, treatment, baseline by week, and week by treatment.

Source: Clinical Study Report.[24]

Table 35: HAM-D Total Score in Short-Term Trials

Study	Intervention	Baseline			Change from baseline to end of treatment			Mean difference from placebo			
		N	Mean	SD	N	Mean	SE	Mean	SE	(95% CI)	P value
HAM-D24											
305	PBO	139	32.1	SE 0.38	128	−11.3	0.74				
	VOR 5 mg	139	31.6	SE 0.37	129	−15.4	0.74	−4.12	1.04	(−6.17 to −2.08)	NS[a]
	VOR 10 mg	139	32.6	SE 0.38	122	−16.2	0.76	−4.93	1.05	(−6.99 to −2.86)	< 0.001
303	PBO	286	31.7	SE 0.30	286	−13.9	0.66				
	VOR 5 mg	292	32.3	SE 0.29	292	−14.6	0.65	−0.74	0.89	(−2.48 to 1.01)	0.41
11984A	PBO	145	29.8	5.12	145	−13.3	0.82				
	VOR 5 mg	155	31.4	5.84	155	−15.0	0.80	−1.79	1.13	(−4.01 to 0.42)	0.11[b]
	VOR 10 mg	151	30.4	5.42	151	−14.9	0.80	−1.63	1.13	(−3.85 to 0.59)	0.15[b]
	DUL 60 mg	149	29.9	5.75	149	−15.7	0.81	−2.47	1.13	(−4.70 to −0.24)	0.03[b]
304	PBO	149	29.1	SE 0.44	149	−10.5	0.76				
	VOR 5 mg	153	29.6	SE 0.43	153	−11.1	0.74	−0.58	1.04	(−2.61 to 1.46)	0.58
	DUL 60 mg	149	28.8	SE 0.43	149	−13.5	0.75	−2.96	1.05	(−5.02 to −0.91)	0.005
12541A	PBO	145	29.4	5.1	145	−10.3	0.76				
	VOR 5 mg	155	29.2	5.0	155	−13.7	0.74	−3.32	1.01	(−5.31 to −1.34)	0.0011
	DUL 60 mg	148	28.5	4.9	14	−15.8	0.75	−5.48	1.03	(−7.50 to −3.46)	< 0.0001
11492A	PBO	105	29.7	4.96	105	−12.2	0.90				
	VOR 5 mg	108	29.9	5.44	108	−17.5	0.89	−5.28	1.22	(−7.69 to −2.88)	< 0.0001[b]
	VOR 10 mg	100	29.3	5.59	100	−17.6	0.92	−5.33	1.25	(−7.79 to −2.88)	< 0.0001[b]
	VEN 225 mg	111	29.4	5.00	111	−17.3	0.88	−5.09	1.21	(−7.48 to −2.70)	< 0.0001[b]
HAM-D17											
CCT-003	PBO	124	21.5	4.48	122	−8.40	0.58				
	VOR 5 mg	119	20.9	4.12	119	−9.56	0.59	−1.15	0.82	(−2.78 to 0.47)	0.16[b]
	VOR 10 mg	123	21.2	4.43	121	−8.54	0.58	−0.14	0.82	(−1.75 to 1.48)	0.87[b]
CCT-004	PBO	164	22.0	3.2	153	−8.4	0.54				

Study	Intervention	Baseline			Change from baseline to end of treatment			Mean difference from placebo			
		N	Mean	SD	N	Mean	SE	Mean	SE	(95% CI)	P value
	VOR 10 mg	165	22.1	3.1	163	−10.2	0.52	−1.81	0.75	(−3.29 to −0.33)	0.017[b]
	VOR 20 mg	164	22.2	3.1	158	−10.2	0.53	−1.79	0.76	(−3.28 to −0.30)	0.019[b]
15905A	VOR 10 mg to 20 mg + SSRI	51	5.6	NR	47	−1.8	0.47	−0.83	0.66	(−2.14 to 0.49)	0.22[b]
	VOR 10 mg to 20 mg + PBO	50	6.1	NR	47	−1.2	0.48	−0.21	0.67	(−1.53 to 1.12)	0.76[b]
	SSRI + PBO	49	5.6	NR	44	−1.0	0.48				

CI = confidence interval; DUL = duloxetine; HAM-D17 = 17-item Hamilton Depression Rating Scale; HAM-D24 = 24-item Hamilton Depression Rating Scale; NR = not reported; NS = not statistically significant; PBO = placebo; SD = standard deviation; SE = standard error; SSRI = selective serotonin reuptake inhibitor; VOR = vortioxetine.

[a] Statistical testing stopped due to failure in an earlier outcome in the hierarchical testing procedure.

[b] Outside the statistical testing hierarchy or other procedures to adjust for multiplicity.

Source: Clinical Study Report.[11-15,17,26,27,30]

Table 36: Study 14122A and 12541A Difference in Mean Change from Baseline for Cognitive Outcomes at Week 8 (Vortioxetine Versus Placebo)

Study	Treatment group	N	Baseline mean (SE)[a]	Mean change from baseline (SE),[b] N	Mean difference VOR versus PBO (95% CI)	P value
DSST number of correct symbols[a]						
14122A	PBO	194	42.4 (1.0)	4.8 (0.6), N = 179		
	VOR 10 mg	193	42.0 (0.9)	9.0 (0.6), N = 180	4.2 (2.5 to 5.9)	< 0.0001
	VOR 20 mg	204	41.6 (0.9)	9.1 (0.6), N = 187	4.3 (2.6 to 5.9)	< 0.0001
RAVLT acquisition[a]						
14122A	PBO	194	22.1 (0.4)	3.1 (0.3), N = 179		
	VOR 10 mg	193	22.3 (0.4)	4.1 (0.3), N = 180	1.0 (0.1 to 1.9)	0.0287
	VOR 20 mg	204	22.6 (0.4)	3.7 (0.3), N = 187	0.6 (−0.3 to 1.5)	NS[b]
RAVLT delayed recall[a]						
14122A	PBO	194	5.7 (0.2)	0.9 (0.2), N = 178		
	VOR 10 mg	193	5.8 (0.2)	1.6 (0.2), N = 180	0.7 (0.2 to 1.2)	NS[b]
	VOR 20 mg	204	6.1 (0.2)	1.6 (0.2), N = 187	0.7 (0.2 to 1.1)	NS[b]
DSST number of correct symbols						
12541A	PBO	145	44.0 (1.4)	1.5 (0.9)		
	VOR 5 mg	154	44.7 (1.4)	4.3 (0.9)	2.8 (0.4 to 5.2)	0.02[c]
	DUL 60 mg	148	46.0 (1.4)	2.3 (0.9)	0.8 (-1.7 to 3.2)	0.53[c]
RAVLT acquisition						
12541A	PBO	145	21.7 (0.5)	2.3 (0.4)		
	VOR 5	155	22.3 (0.5)	3.5 (0.4)	1.1 (0.2, 2.1)	0.02[c]
	DUL 60 mg	148	22.0 (0.5)	3.7 (0.4)	1.4 (0.4 to 2.4)	0.005[c]
RAVLT delayed recall						
12541A	PBO	145	6.2 (0.2)	0.9 (0.2)		

Study	Treatment group	N	Baseline mean (SE)[a]	Mean change from baseline (SE),[b] N	Mean difference VOR versus PBO (95% CI)	P value
	VOR 5	155	6.5 (0.2)	1.4 (0.2)	0.5 (0.02 to 0.9)	0.04 [c]
	DUL 60 mg	148	6.6 (0.2)	1.6 (0.2)	0.6 (0.2 to 1.1)	0.007 [c]

CI = confidence interval; DSST = Digit Symbol Substitution Test; DUL = duloxetine; NS = not statistically significant; PBO = placebo; RAVLT = Rey Auditory Verbal Learning Test; SE = standard error; VOR = vortioxetine.

[a] Based on the full analysis set, using the mixed-effect model for repeated measures (observed cases) controlling for grouped site, baseline composite z score, and interaction terms (baseline composite z score by visit; treatment by visit).

[b] P values not reported; pre-specified hierarchy failed to reach significance at higher level.

[c] Based on the full analysis set, observed cases and analysis of covariance. Secondary outcome outside of the hierarchical testing procedure used to control for inflated type I error.

Source: Clinical Study Report.[17,22]

Table 37: Difference in Mean Change from Baseline for DSST at Week 8 (Studies 15905A, 15906A, 15907A, and CCT-004)

Study	Treatment group	N	Baseline mean (SD),[a] N	Adjusted change from baseline to week 8		Mean difference VOR versus control (95% CI)	P value
				N	Mean (SE)[b]		
15905A[a]	VOR 10 mg or 20 mg + SSRI	51	47.9 (NR)	48	7.9 (1.1)	−0.05 (−3.2 to 3.1)	0.98
	VOR 10 mg or 20 mg	50	46.8 (NR)	48	8.1 (1.2)	0.16 (−3.0 to 3.3)	0.92[b]
	SSRI	49	47.1 (NR)	47	7.9 (1.2)	ref	
15906A[a]	PBO	48	46.2 (NR)	47	7.4 (1.1)		
	VOR 10 mg	48	46.1 (NR)	46	7.6 (1.1)	0.2 (−2.8 to 3.2)	0.88
	PAR 20 mg	52	45.6 (NR)	48	6.6 (1.1)	−0.8 (−3.7 to 2.2)	0.61[c]
15907A[a]	VOR 10 mg or 20 mg	50	42.0 (NR)	48	8.5 (1.2)	2.0 (−1.3 to 5.3)	0.23
	ESC 10 mg or 20 mg	49	38.5 (NR)	45	6.5 (1.2)	ref	
CCT-004[d]	PBO	164	60.2 (13.9)	161	4.9 (0.63)	ref	
	VOR 10 mg	165	56.8 (15.2)	163	4.1 (0.63)	−0.79 (−2.54 to 0.97)	0.38[c]
	VOR 20 mg	164	58.0 (13.7)	162	4.8 (0.63)	−0.11 (−1.86 to 1.64)	0.90[c]

CI = confidence interval; ESC = escitalopram; NR = not reported; PAR = paroxetine; PBO = placebo; ref = reference; SD = standard deviation; SE = standard error; SSRI = selective serotonin reupdate inhibitor; VOR = vortioxetine.

[a] Based on the full analysis set, using the mixed-effect model for repeated measures (observed cases) controlling for grouped site, baseline score, and interaction terms (baseline score by visit; treatment by visit).

[b] Statistical testing failed on a prior outcome in the statistical hierarchy.

[c] Outside the statistical testing hierarchy or other methods to control for multiplicity.

[d] Based on analysis of covariance; last observation carried forward for the full analysis set.

Source: Clinical Study Report.[27-30]

Table 38: Study 14221A – Direct Effect of Vortioxetine on Cognitive Outcomes (Composite Z Score) at Week 8[a]

	Direct effect (VOR effect on composite z score at week 8 controlling for change in MADRS total score)	Indirect effect (VOR effect on composite z score at week 8 mediated through change in MADRS total score)	Direct effect % (95% CI)
PBO	[redacted]	[redacted]	[redacted]
VOR 10 mg	[redacted]	[redacted]	[redacted]
VOR 20 mg	[redacted]	[redacted]	[redacted]

CI = confidence interval; MADRS = Montgomery–Åsberg Depression Rating Scale; PBO = placebo; SE = standard error; VOR = vortioxetine.

[a] Based on the full analysis set using last observation carried forward.

[b] P value based on the direct effect compared to placebo.

Source: Clinical Study Report.[22]

Table 39: Difference in Mean Change from Baseline for UPSA-B at Week 8 (Studies 15905A, 15906A, and 15907A)

Study	Treatment group	N	Baseline mean (SD)	Adjusted change from baseline to week 8		Mean difference VOR versus control (95% CI)	P value
				N	Mean (SE)		
15905A[a]	VOR 10 mg or 20 mg + SSRI	48	81.2 (NR)	48	5.2 (1.0)	1.0 (−1.8 to 3.7)	0.49[b]
	VOR 10 mg or 20 mg	48	81.8 (NR)	48	6.0 (1.1)	1.7 (−1.0 to 4.5)	0.22[b]
	SSRI	47	80.7 (NR)	47	4.3 (1.0)	ref	
15906A[a]	PBO	47	79.7 (NR)	47	5.3 (1.1)	ref	
	VOR 10 mg	46	78.6 (NR)	46	5.8 (1.1)	0.4 (−2.7 to 3.5)	0.79[b]
	PAR 20 mg	50	80.6 (NR)	50	6.0 (1.1)	0.62 (−2.4 to 3.7)	0.69[c]
15907A[a]	VOR 10 mg or 20 mg	49	77.8 (NR)	49	10.8 (1.0)	1.3 (−1.5 to 4.2)	0.35[b]
	ESC 10 mg or 20 mg	48	78.0 (NR)	48	9.5 (1.1)	ref	

CI = confidence interval; ESC = escitalopram; NR = not reported; PAR = paroxetine; PBO = placebo; ref = reference; SE = standard error; UPSA-B = University of San Diego Performance-Based Skills Assessment – Brief; VOR = vortioxetine.

[a] Based on the full analysis set, using analysis of covariance, last observation carried forward controlling for grouped site, baseline score.

[b] Statistical testing failed on a prior outcome in the statistical hierarchy.

[c] Outside the statistical testing hierarchy.

Source: Clinical Study Report.[28-30]

Harms Outcomes

Table 40: Harms

Study, duration	305 (8 weeks)			303 (6 weeks)		316 (8 weeks)			317 (8 weeks)			CCT-002 (8 weeks)			
Treatment	PBO	VOR 5 mg	VOR 10 mg	PBO	VOR 5 mg	PBO	VOR 10 mg	VOR 20 mg	PBO	VOR 10 mg	VOR 15 mg	PBO	VOR 5 mg	VOR 10 mg	VOR 20 mg
N	**140**	**140**	**139**	**298**	**299**	**157**	**155**	**150**	**160**	**154**	**151**	**151**	**144**	**148**	**150**
Mean exposure duration, weeks	7.7	7.7	7.4	5.4	5.6	7.5	7.3	7.3	7.2	7.4	7.1	7.5	7.5	7.5	7.4
Patients with ≥ 1 AEs, N (%)	60 (43)	79 (56)	58 (42)	192 (64)	209 (70)	98 (62)	114 (74)	103 (69)	114 (71)	119 (77)	118 (78)	97 (64)	96 (67)	93 (63)	106 (71)
SAEs															
Patients with ≥ 1 SAE, N (%)	2 (1)	1 (1)	2 (1)	4 (1)	7 (2)	0	2 (1)	0	1 (1)	1 (1)	0	1 (1)	2 (1)	2 (1)	3 (2)
WDAEs[a]															
WDAEs, N (%)	2 (1)	1 (1)	5 (4)	9 (3)	9 (3)	2 (1)	8 (5)	7 (5)	7 (4)	8 (5)	12 (8)	6 (4)	2 (1)	8 (5)	8 (5)
Deaths															
Number of deaths, N (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Common Harms															
Nausea, N (%)	6 (4)	22 (16)	18 (13)	28 (9)	57 (19)	8 (5)	42 (27)	44 (29)	17 (11)	47 (31)	51 (34)	11 (7)	26 (18)	27 (18)	37 (25)

Table 44: Harms (continued)

Study, duration	CCT-003 (8 weeks)			11984A (8 weeks)				304 (8 weeks)			13267A (8 weeks)			
Treatment	PBO	VOR 5 mg	VOR 10 mg	PBO	VOR 5 mg	VOR 10 mg	DUL 60 mg	PBO	VOR 5 mg	DUL 60 mg	PBO	VOR 15 mg	VOR 20 mg	DUL 60 mg
N	**124**	**119**	**122**	**148**	**157**	**151**	**155**	**151**	**153**	**150**	**158**	**151**	**151**	**147**
Mean exposure duration, weeks	7.5	7.7	7.7	7.1	6.9	6.9	6.7	7.2	7.2	6.8	7.3	7.2	7.2	7.7
Patients with ≥ 1 AE, N (%)	78 (63)	80 (67)	93 (76)	92 (62)	101 (64)	99 (66)	110 (71)	96 (64)	108 (71)	128 (85)	81 (51)	90 (60)	103 (68)	102 (69)
SAEs														
Patients with ≥ 1 SAE, N (%)	1 (1)	1 (1)	1 (1)	3 (2)	3 (2)	2 (1)	2 (1)	2 (1)	3 (2)	2 (1)	0	0	2 (1)	3 (2)
WDAEs[a]														

Study, duration	CCT-003 (8 weeks)			11984A (8 weeks)				304 (8 weeks)				13267A (8 weeks)		
Treatment	PBO	VOR 5 mg	VOR 10 mg	PBO	VOR 5 mg	VOR 10 mg	DUL 60 mg	PBO	VOR 5 mg	DUL 60 mg	PBO	VOR 15 mg	VOR 20 mg	DUL 60 mg
WDAEs, N (%)	4 (3)	4 (3)	4 (3)	12 (8)	17 (11)	14 (9)	19 (12)	8 (5)	13 (9)	16 (11)	7 (4)	10 (7)	17 (11)	7 (5)
Deaths														
Number of deaths, N (%)	0	0	0	0	1 (< 1)	0	0	0	0	0	0	0	0	0
Common Harms														
Nausea, N (%)	9 (7)	20 (17)	35 (29)	13 (9)	26 (17)	33 (22)	52 (34)	16 (11)	44 (29)	63 (42)	16 (10)	40 (27)	48 (32)	45 (31)

Table 44: Harms (continued)

Study, duration	315 (8 weeks)				12541A (8 weeks)			11492A (6 weeks)				13926A (8 weeks)	
AEs	PBO	VOR 15 mg	VOR 20 mg	DUL 60 mg	PBO	VOR 5 mg	DUL 60 mg	PBO	VOR 5 mg	VOR 10 mg	VEN 225 mg	VOR 10 mg	VEN 150 mg
N	**159**	**147**	**154**	**150**	**145**	**156**	**151**	**105**	**108**	**100**	**113**	**211**	**226**
Mean exposure duration, weeks	7.2	6.9	6.8	7.0	7.6	7.4	7.1	5.6	5.9	5.4	5.4	7.4	6.5
Patients with ≥ 1 AE, N (%)	112 (70)	108 (74)	125 (81)	122 (81)	93 (64)	100 (64)	121 (80)	64 (61)	75 (69)	75 (75)	86 (76)	128 (61)	157 (70)
SAEs													
Patients with ≥ 1 SAE, N(%)	0	2 (1)	0	0	4 (3)	1 (1)	1 (1)	0	0	2 (2)	1 (1)	2 (1)	8 (4)
WDAEs[a]													
WDAEs, N (%)	5 (3)	14 (10)	14 (9)	11 (7)	6 (4)	10 (6)	15 (10)	4 (4)	3 (3)	7 (7)	16 (14)	14 (7)	32 (14)
Deaths													
Number of deaths, N (%)	0	0	0	0	0	0	0	0	0	0	0	0	0
Common Harms													
Nausea, N (%)	18 (11)	52 (35)	51 (33)	55 (37)	12 (8)	34 (22)	50 (33)	10 (10)	32 (30)	38 (38)	38 (34)	51 (24)	53 (24)

Table 44: Harms (continued)

Study, duration	CCT-004 (8 weeks)			14122A (8 weeks)			11985A (0 to 64 weeks)		318 (8 weeks)	
Treatment	**PBO**	**VOR 10 mg**	**VOR 20 mg**	**PBO**	**VOR 10 mg**	**VOR 20 mg**	**PBO**	**VOR 5 mg or 10 mg**	**ESC 10 mg or 20 mg**	**VOR 10 mg or 20 mg**
N	**161**	**165**	**163**	**196**	**195**	**207**	**192**	**204**	**221**	**224**
Mean exposure duration, weeks (SD)	7.6 (1.4)	7.7 (1.3)	7.6 (1.5)	7.3 (1.7)	7.6 (1.6)	7.3 (1.7)	27.0 (15.1)	30.1 (16.3)	7.2 (2.1)	7.0 (2.2)
Patients with ≥ 1 AEs, N (%)	75 (47)	83 (50)	89 (55)	76 (38.8)	95 (48.7)	109 (52.7)	122 (63.5)	127 (62.3)	137 (62.0)	146 (65.2)
SAEs										
Patients with ≥ 1 SAE, N (%)	1 (1)	1 (1)	3 (2)	2 (1.0)	0 (0.0)	2 (1.0)	4 (2.1)	7 (3.4)	1 (0.5)	3 (1.3)
WDAEs[a]										
WDAEs, N (%)	4 (3)	6 (4)	6 (4)	8 (4.1)	7 (3.6)	10 (4.8)	2 (1.0)	14 (6.9)	14 (6.3)	24 (9.4)
Deaths										
Number of deaths, N (%)	0	0	0	0	0	0	0	0[b]	0	0
Common Harms										
Nausea	1 (1)	21 (13)	25 (15)	8 (4.1)	32 (16.4)	43 (20.8)	6 (3.1)	18 (8.8)	12 (5.4)	56 (25.0)

Table 44: Harms (continued)

Study, duration	15906A (8 weeks)			15905A (8 weeks)			15907A (8 weeks)		Levada et al. (2019) (8 weeks)		Liebowitz et al. (2017) (12 weeks)	
Treatment	**PBO**	**VOR 10 mg**	**PAR 10 mg**	**VOR 10 mg or 20 mg +SSRI**	**VOR 10 mg or 20 mg**	**SSRI**	**VOR 10 mg or 20 mg**	**ESC 10 mg or 20 mg**	**VOR 10 mg or 20 mg**	**ESC 10 mg or 20 mg**	**PBO**	**VOR 10 mg or 20 mg**
N	**48**	**48**	**54**	**52**	**50**	**49**	**50**	**49**	**36**	**20**	**20**	**20**
Mean exposure duration, weeks (SD)	7.9 (0.7)	7.3 (2.0)	7.4 (1.9)	7.6 (1.4)	7.7 (1.0)	7.6 (1.4)	7.7 (1.3)	7.4 (2.0)	NR	NR	NR	NR
Patients with ≥ 1 AEs, N (%)	18 (38)	28 (58)	23 (43)	36 (69)	35 (70)	16 (33)	21 (42)	19 (39)	9 (25)	5 (25)	NR	NR

Study, duration	15906A (8 weeks)			15905A (8 weeks)			15907A (8 weeks)		Levada et al. (2019) (8 weeks)		Liebowitz et al. (2017) (12 weeks)	
Treatment	**PBO**	**VOR 10 mg**	**PAR 10 mg**	**VOR 10 mg or 20 mg +SSRI**	**VOR 10 mg or 20 mg**	**SSRI**	**VOR 10 mg or 20 mg**	**ESC 10 mg or 20 mg**	**VOR 10 mg or 20 mg**	**ESC 10 mg or 20 mg**	**PBO**	**VOR 10 mg or 20 mg**
SAEs												
Patients with ≥ 1 SAE, N (%)	1 (2)	0	2 (4)	0	0	0	0	0	0	0	0	0
WDAEs[a]												
WDAEs, N (%)	1 (2)	3 (6)	3 (6)	3 (6)	1 (2)	2 (4)	3 (6)	1 (2)	NR	NR	1 (5)	1 (5)
Deaths												
Number of deaths, N (%)	0	0	0	0	0	0	0	0	0	0	0	0
Common Harms												
Nausea, N (%)	1 (2)	18 (38)	9 (17)	16 (31)	11 (22)	1 (2)	13 (26)	5 (10)	9 (25)	2 (10)	1 (5)	7 (35)

AE = adverse event; DB = double-blind; DUL = duloxetine; ESC = escitalopram; PBO = placebo; SAE = serious adverse event; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor; VEN = venlafaxine extended release; VOR = vortioxetine; WDAE = withdrawal due to adverse event.

[a] WDAE refers to treatment-emergent adverse events leading to permanent discontinuation of study drug.

[b] One patient who was treated for 26 days during the open-label phase was withdrawn from the study due to experiencing fatigue, back pain. Patient died of cancer 255 days after event onset.

Source: Clinical Study Report,[11-30,55,56] Levada et al. (2019),[55] Liebowitz et al. (2017).[56]

Table 41: Health Canada Pooled Data on Suicide-Related Events Based on MedDRA Query

Redacted as per sponsor's request.

DUL = duloxetine; MedDRA = Medical Dictionary for Regulatory Activities; MDD = major depressive disorder; TEAE = treatment-emergent adverse event; VEN = venlafaxine extended release; VOR = vortioxetine;

[a] Suicidal ideation and behaviour based on a MedDRA standardized query of suicide or self-injury (pooled data from short-term phase IIb and III MDD randomized controlled trials; 11492A, 11984A, 305, 13267A, 315, 316, 303, 304, 317, 12541A, CCT-002, and 14122A).

Source: Health Canada Protocol Safety and Efficacy Assessment Template – Safety p. 192.[6]

Table 42: Suicide-Related Events Based on MedDRA Query – Studies CCT-003, 13926A, and 11985A

Study/suicide-related event	PBO	VOR 5 mg	VOR 10 mg	VEN 150 mg
CCT-003 (8 weeks)	**N = 124**	**N = 119**	**N = 122**	**--**
Suicidal ideation, n (%)	[redacted]	[redacted]	[redacted]	
Self-injurious behaviour, n (%)	[redacted]	[redacted]	[redacted]	
Suicidal behaviour, n (%)	[redacted]	[redacted]	[redacted]	
13926A (8 weeks)	**--**	**--**	**N = 211**	**N = 226**
Suicidal ideation, n (%)			[redacted]	[redacted]
Intentional overdose, n (%)			[redacted]	[redacted]
Suicidal attempt, n (%)			[redacted]	[redacted]
11985A (DB period; up to 64 weeks)[a]	**N = 192**	**N = 204**		**--**
Suicidal ideation or behaviour, n (%)	[redacted]	[redacted]		

DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; VEN = venlafaxine extended release; VOR = vortioxetine.

[a] Based on a post hoc search of spontaneously reported events using investigator terms.

[b] One patient was withdrawn from the study during the safety follow-up period due to alcohol poisoning and intentional overdose (defined by the investigator as a possibly suicide-related adverse event).

Source: Clinical Study Report.[16,25,26]

Table 43: Health Canada Pooled Data on Suicidal Ideation and Behaviour Based on the C-SSRS Score

Redacted as per sponsor's request.

AA21004 = vortioxetine; C-SSRS = Columbia Suicide Severity Rating Scale; DUL = duloxetine; PBO = placebo.

Note: Includes C-SSRS data from studies 303, 304, 305, 13267A, 315, 316, 317, 14122A, and CCT-002.

Source: Health Canada Protocol Safety and Efficacy Assessment Template – Safety p. 192.[6]

Table 44: Suicide-Related Events During Treatment Period Based on C-SSRS – Studies 318, 12541A, 15905A, 15906A, 15907A, and CCT-004

Study, treatment group	N	No suicidal ideation or behaviour, n (%)	Any suicidal ideation (Q 1-5), n (%)	Preparatory action toward imminent suicidal behaviour (Q 6–8), n (%)	Non-fatal suicide attempt (Q9), n (%)	Death due to suicide (Q 10), n (%)
318						
VOR 10 mg to 20 mg	221	NR	0[a]	0	0	0
ESC 10 mg to 20mg	224	NR	0 [a]	1 (0.4)	0	0
12541A						
PBO	114	103 (90)	[redacted]	[redacted]	[redacted]	[redacted]
VOR 5 mg	121	107 (88)	[redacted]	[redacted]	[redacted]	[redacted]
VOR 10 mg	114	106 (93)	[redacted]	[redacted]	[redacted]	[redacted]
15905A						
VOR + SSRI	52	52 (100)	0	0	0	0
VOR	50	50 (100)	0	0	0	0
SSRI	49	49 (100)	0	0	0	0
15906A						
PBO	48	44 (92)	[redacted]	[redacted]	[redacted]	[redacted]
VOR 10 mg	48	46 (96)	[redacted]	[redacted]	[redacted]	[redacted]
PAR 20 mg	54	52 (96)	[redacted]	[redacted]	[redacted]	[redacted]
15907A						
VOR 10 mg to 20 mg	50	48 (96)	[redacted]	[redacted]	[redacted]	[redacted]
ESC 10 mg to 20 mg	49	48 (98)	[redacted]	[redacted]	[redacted]	[redacted]
CCT-004						
PBO	161	128 (80)	[redacted]	[redacted]	[redacted]	[redacted]
VOR 10 mg	165	145 (88)	[redacted]	[redacted]	[redacted]	[redacted]
VOR 20 mg	162	137 (85)	[redacted]	[redacted]	[redacted]	[redacted]

ESC = escitalopram; PAR = paroxetine; PBO = placebo; Q = question; SSRI = selective serotonin reuptake inhibitor; VOR = vortioxetine.

[a] Detailed data from the C-SSRS were not reported; however, these data appear to exclude passive suicidal ideation thoughts (Q 1 – wish to be dead).

Source: Clinical Study Report.[17,24,27-30]

Table 45: Study 318 Odds of Normal Sexual Functioning Based on the CSFQ-14

	ESC N = 222		VOR N = 225		VOR versus ESC	
Time point	N	Number with normal sexual functioning (%)	N	Number with normal sexual functioning (%)	OR 95% CI,	P value
Odds of normal sexual functioning (CSFQ-14)[ab]						
Baseline	205	0 (0)	213	0 (0)		
Week 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	206	91 (44)	217	113 (52)	1.37 (0.93, 2.03)	0.11

CI = confidence interval; CSFQ-14 = Changes in Sexual Functioning Questionnaire Short-Form; ESC = escitalopram; OR = odds ratio; VOR = vortioxetine.

[a] Normal = CSFQ-14 total score > 41 for females and > 47 for males.

[b] Analysis was based on the full analysis set, logistic regression with explanatory variables for treatment and baseline CSFQ-14 total score, last observation carried forward. No adjustment for multiplicity.

Source: Clinical Study Report.[24]

Table 46: Study 318 Number of Sexual Functioning Responders Based on the CSFQ-14

	ESC N = 222		VOR N = 225		VOR versus ESC	
Time point	N	Number of responders (%)	N	Number of responders (%)	OR (95% CI)	P value
CSFQ-14 responders[ab]						
Week 1	206	85 (41.3)	213	95 (44.6)	1.14 (0.78, 1.69)	0.495
Week 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	207	137 (66.2)	217	162 (74.7)	1.50 (0.99, 2.29)	0.057

CI = confidence interval; CSFQ-14 = Changes in Sexual Functioning Questionnaire Short-Form; ESC = escitalopram; OR = odds ratio; VOR = vortioxetine.

[a] Response was defined as an increase ≥ 3 points from baseline in the CSFQ-14 total score.

[b] Analysis was based on the full analysis set, logistic regression with explanatory variables for treatment and baseline CSFQ-14 total score, last observation carried forward; no adjustment for multiplicity.

Source: Clinical Study Report.[24]

Table 47: Treatment-Emergent Sexual Dysfunction (Based on ASEX)[a]

Redacted as per sponsor's request.

ASEX = Arizona Sexual Experiences Scale.

[a] In Study 11984A, ASEX was added as a protocol amendment and was reported for approximately half of the study participants.

Source: Health Canada Protocol Safety and Efficacy Assessment Template – Safety.[6]

Table 48: Treatment-Emergent Sexual Dysfunction by Sex (Based on ASEX)[a]

Redacted as per sponsor's request.

AA21004 = vortioxetine; ASEX = Arizona Sexual Experiences Scale; DUL = duloxetine; PBO = placebo; TESD = treatment-emergent sexual dysfunction.

[a] Includes data during the six- to eight-week treatment period from six major depressive disorder studies (11984A, 304, 13267A, 315, 316, and 317) and from one study in patients with generalized anxiety disorder (308).

Source: Health Canada Protocol Safety and Efficacy Assessment Template – Safety.[6]

Table 49: Health Canada Pooled Data on Sexual Dysfunction Adverse Events Based on Spontaneous Reports

Redacted as per sponsor's request.

DUL = duloxetine; VEN = venlafaxine extended release; VOR = vortioxetine.

Studies 11492A, 11984A, 305, 13267A, 315, 316, 303, 304, 317, 12541A, CCT-002, 14122A

Source: Health Canada PSEAT – Safety.[6]

Table 50: Sexual Dysfunction Adverse Events – Studies 11985A, 318, 13926A, 15906A, and 15906A

Study, duration	11985A		318		13926A		15906A			15905A		
	DB (0 to 64 weeks)		DB (8 weeks)		DB (8 weeks)		DB (8 weeks)			DB (8 weeks)		
Treatment	PBO	VOR 5 mg or 10 mg	ESC 10 mg or 20 mg	VOR 10 mg or 20 mg	VOR 10 mg	VEN 150 mg	PBO	VOR 10 mg	PAR 20 mg	VOR + SSRI	VOR	SSRI
Sexual dysfunction	2 (1.0)	3 (1.5)	9 (4.1)	0 (0.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DB = double-blind; ESC = escitalopram; NR = not reported; PAR = paroxetine; PBO = placebo; SSRI = selective serotonin reuptake inhibitor; VEN = venlafaxine extended release; VOR = vortioxetine.

Source: Clinical Study Report.[16,24,25,29,30]

Table 51: Weight Change – Studies 11985A, 318, 317, 13926A, 15905A, CCT-004, and CCT-003

Study, duration	Intervention	Weight increased ≥ 7%	Change from baseline in BMI, mean (SD)
11985A	PBO	[redacted]	[redacted]
(0 to 64 weeks)	VOR 5 mg or 10 mg	[redacted]	[redacted]
318	VOR 10 mg or 20 mg	[redacted]	[redacted]
(8 weeks)	ESC	[redacted]	[redacted]
317	PBO	[redacted]	[redacted]
(8 weeks)	VOR 10 mg	[redacted]	[redacted]
	VOR 15 mg	[redacted]	[redacted]
13926A	VOR 10 mg	[redacted]	[redacted]
(8 weeks)	VEN 150 mg	[redacted]	[redacted]
15905A	VOR + SSRI	[redacted]	[redacted]
(8 weeks)	VOR	[redacted]	[redacted]
	SSRI	[redacted]	[redacted]

Study, duration	Intervention	Weight increased ≥ 7%	Change from baseline in BMI, mean (SD)
CCT-004	PBO	[redacted]	[redacted]
(8 weeks)	VOR 10 mg	[redacted]	[redacted]
	VOR 20 mg	[redacted]	[redacted]
CCT-003	PBO	[redacted]	[redacted]
(8 weeks)	VOR 5 mg	[redacted]	[redacted]
	VOR 10 mg	[redacted]	[redacted]

BMI = body mass index; ESC = escitalopram; NR = not reported; PBO = placebo; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor; VEN = venlafaxine extended release; VOR = vortioxetine.

[a] Weight increase is based on a comparison to week 0 of the double-blind period.

Source:[16,20,24-27,30]

Table 52: Health Canada Pooled DESS Total Scores for Studies 13267A, 315, and 316

Redacted as per sponsor's request.

AA21004 = vortioxetine; DESS = Discontinuation-Emergent Signs and Symptoms; DUL = duloxetine; Max = maximum; Min = minimum; PBO = placebo; SD = standard deviation.

Source: Health Canada Protocol Safety and Efficacy Assessment Template – Safety.[6]

Table 53: Discontinuation-Related Adverse Events – Studies 11985A and 318

Study, duration	11985A		318	
	DB (0-64 weeks)		DB (8 weeks)	
Treatment	**PBO**	**VOR 5 mg or 10 mg**	**ESC 10 mg or 20 mg**	**VOR 10 mg or 20 mg**
Discontinuation-related AE	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; DB = double-blind; ESC = escitalopram; P1 = discontinuation period 1 (following the open-label period); P2 = discontinuation period 2 (following the double-blind period); PBO = placebo; VOR = vortioxetine

Source: Clinical Study Report.[16,24]

Table 54: Discontinuation-Emergent Signs and Symptoms Total Score for Studies CCT-002 and CCT-003

Study/visits/statistics	Treatment			
CCT-002	**PBO**	**VOR 5 mg**	**VOR 10 mg**	**VOR 20 mg**
Week 9				
N	128	122	127	125
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 10				
N	125	122	128	126
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
CCT-003	**PBO**	**VOR 5 mg**	**VOR 10 mg**	**--**
Week 9				
N	72	69	70	
Mean (SD)	[redacted]	[redacted]	[redacted]	
Week 10				

Study/visits/statistics	Treatment			
N	69	70	68	
Mean (SD)	[redacted]	[redacted]	[redacted]	

PBO = placebo; SD = standard deviation; VOR = vortioxetine.

Source: Health Canada Protocol Safety and Efficacy Assessment Template – Safetyl,[6] Clinical Study Report CCT-003.[26]

Table 55: Treatment-Emergent Adverse Events with Incidence of 2% or Greater During the Discontinuation Period[a]

Study	VOR	DUL	VEN
11492A	[redacted]		[redacted]
303	[redacted]		
13267A	[redacted]	[redacted]	
315	[redacted]	[redacted]	
316	[redacted]		
CCT-002	[redacted]		
11985A	[redacted]		

DUL = duloxetine; SAE = serious adverse events; VEN = venlafaxine extended release; VOR = vortioxetine.

[a] AE with incidence ≥ 2% and at least twice as high as placebo in the 1 to 2 weeks following discontinuation of the study medication. Based on spontaneously reported adverse event.

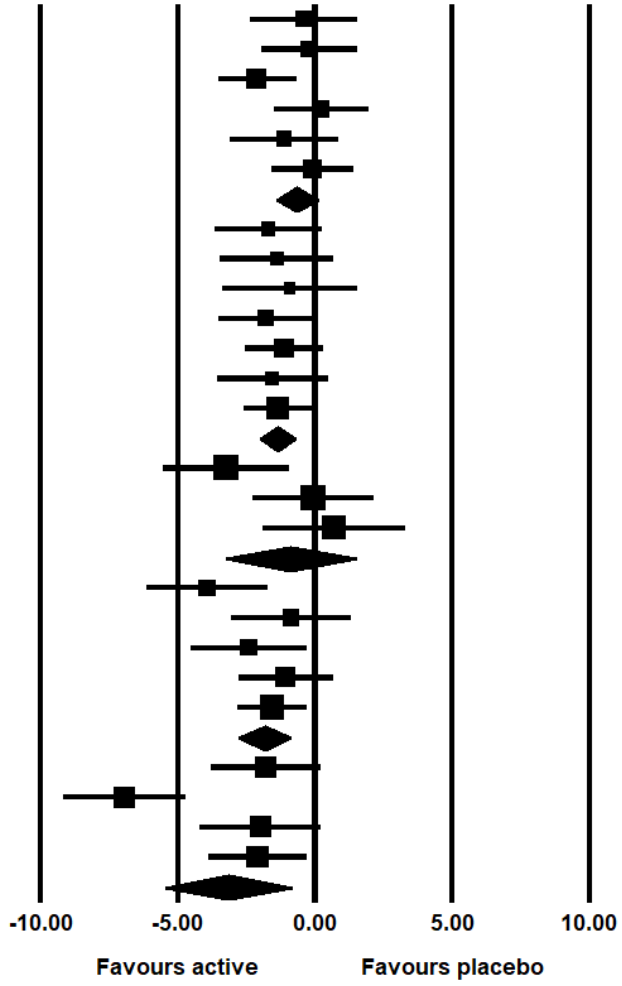
Source: Health Canada Protocol Safety and Efficacy Assessment Template – Safety.[6]

Appendix 5: Meta-Analysis

Efficacy Outcomes

Figure 7: Sheehan Disability Scale – Active Versus Placebo (Random-Effects Model)

Study name	Dose	Difference in means	Lower limit	Upper limit	p-Value
11984A	VOR 5 mg	-0.41	-2.33	1.51	0.68
CCT-002	VOR 5 mg	-0.19	-1.92	1.54	0.83
CCT-003	VOR 5 mg	-2.11	-3.52	-0.70	0.00
304	VOR 5 mg	0.23	-1.48	1.94	0.79
305	VOR 5 mg	-1.11	-3.07	0.85	0.27
303	VOR 5 mg	-0.09	-1.57	1.39	0.90
		-0.67	-1.43	0.09	0.09
11984A	VOR 10 mg	-1.70	-3.64	0.24	0.09
316	VOR 10 mg	-1.39	-3.43	0.65	0.18
317	VOR 10 mg	-0.92	-3.37	1.53	0.46
CCT-002	VOR 10 mg	-1.78	-3.49	-0.07	0.04
CCT-003	VOR 10 mg	-1.11	-2.51	0.29	0.12
305	VOR 10 mg	-1.54	-3.56	0.48	0.13
CCT-004	VOR 10 mg	-1.34	-2.56	-0.12	0.03
		-1.39	-2.03	-0.75	0.00
13267A	VOR 15 mg	-3.24	-5.51	-0.97	0.01
315	VOR 15 mg	-0.05	-2.23	2.13	0.96
317	VOR 15 mg	0.69	-1.90	3.28	0.60
		-0.90	-3.26	1.45	0.45
13267A	VOR 20 mg	-3.92	-6.10	-1.74	0.00
315	VOR 20 mg	-0.88	-3.04	1.28	0.42
316	VOR 20 mg	-2.40	-4.49	-0.31	0.02
CCT-002	VOR 20 mg	-1.06	-2.76	0.64	0.22
CCT-004	VOR 20 mg	-1.57	-2.80	-0.34	0.01
		-1.84	-2.78	-0.89	0.00
11984A	DUL 60 mg	-1.80	-3.78	0.18	0.07
13267A	DUL 60 mg	-6.93	-9.14	-4.72	0.00
315	DUL 60 mg	-1.99	-4.19	0.21	0.08
304	DUL 60 mg	-2.09	-3.85	-0.33	0.02
		-3.16	-5.46	-0.87	0.01

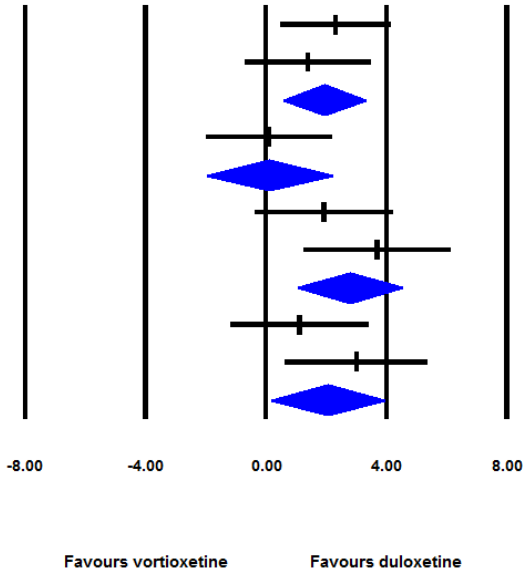


CI = confidence interval; DUL = duloxetine; VOR = vortioxetine.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 27.

Figure 8: Sheehan Disability Scale – Vortioxetine Versus Duloxetine (Random-Effects Model)

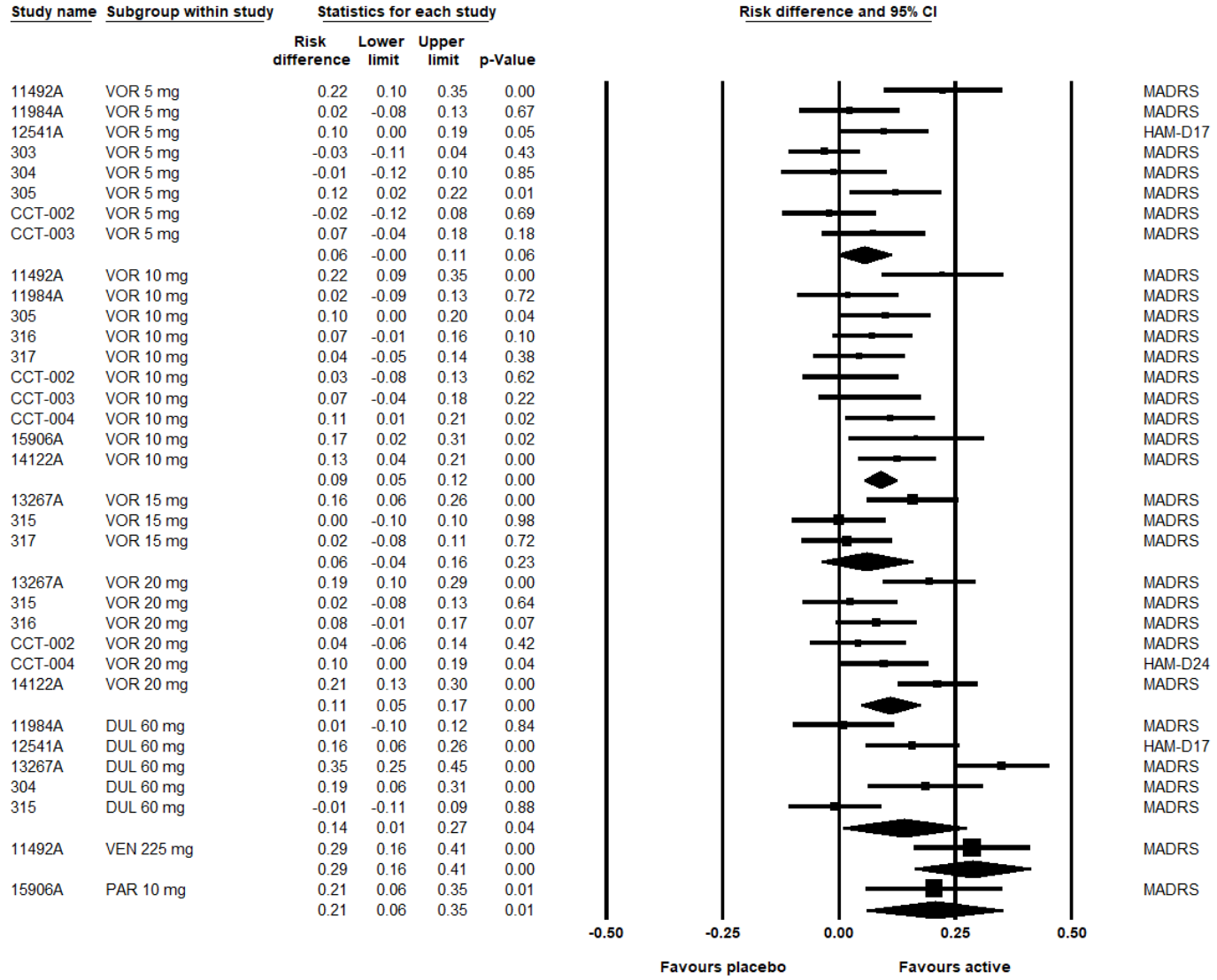
Study name	Subgroup within study	Difference in means	Lower limit	Upper limit	p-Value	Vortioxetine	Duloxetine
304	5 mg	2.32	0.50	4.14	0.01	123	114
11984A	5 mg	1.39	-0.68	3.46	0.19	119	108
		1.91	0.55	3.28	0.01		
11984A	10 mg	0.10	-1.98	2.18	0.92	115	108
		0.10	-1.98	2.18	0.92		
315	15 mg	1.93	-0.36	4.22	0.10	77	73
13267A	15 mg	3.69	1.27	6.11	0.00	65	79
		2.76	1.04	4.49	0.00		
315	20 mg	1.11	-1.17	3.39	0.34	77	73
13267A	20 mg	3.01	0.65	5.37	0.01	80	79
		2.04	0.17	3.90	0.03		



CI = confidence interval.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 27.

Figure 9: Remission – Active-Treatment Versus Placebo (Random-Effects Model)

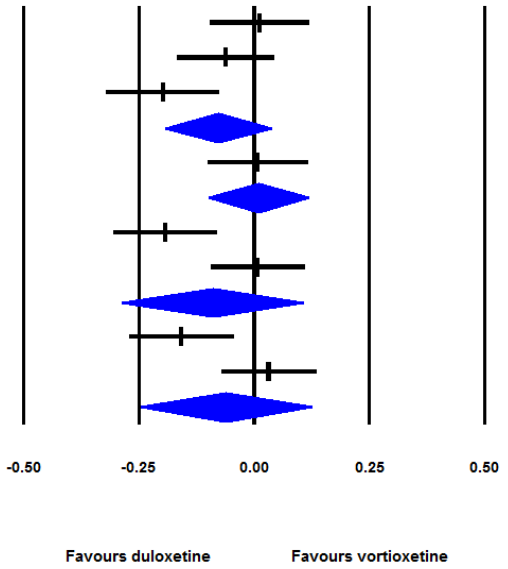


CI = confidence interval; DUL = duloxetine; HAM-D17 = 17-item Hamilton Depression Rating Scale; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; PAR = paroxetine VEN = venlafaxine extended release; VOR = vortioxetine.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 29.

Figure 10: Remission – Vortioxetine Versus Duloxetine (Random-Effects Model)

Study name	Subgroup within study	Remission / Total		Statistics for each study				Risk difference and 95% CI
		Vortioxetine	Duloxetine	Risk difference	Lower limit	Upper limit	p-Value	
11984A	VOR 5 mg	56 / 155	52 / 149	0.01	-0.10	0.12	0.82	MADRS
12541A	VOR 5 mg	45 / 155	52 / 148	-0.06	-0.17	0.04	0.25	HAM-D17
304	VOR 5 mg	32 / 120	51 / 110	-0.20	-0.32	-0.07	0.00	MADRS
				-0.08	-0.19	0.04	0.18	
11984A	VOR 10 mg	54 / 151	52 / 149	0.01	-0.10	0.12	0.88	MADRS
				0.01	-0.10	0.12	0.88	
13267A	VOR 15 mg	52 / 149	79 / 146	-0.19	-0.30	-0.08	0.00	MADRS
315	VOR 15 mg	39 / 145	38 / 146	0.01	-0.09	0.11	0.87	MADRS
				-0.09	-0.29	0.11	0.37	
13267A	VOR 20 mg	58 / 151	79 / 146	-0.16	-0.27	-0.04	0.01	MADRS
315	VOR 20 mg	43 / 147	38 / 146	0.03	-0.07	0.13	0.54	MADRS
				-0.06	-0.25	0.12	0.52	

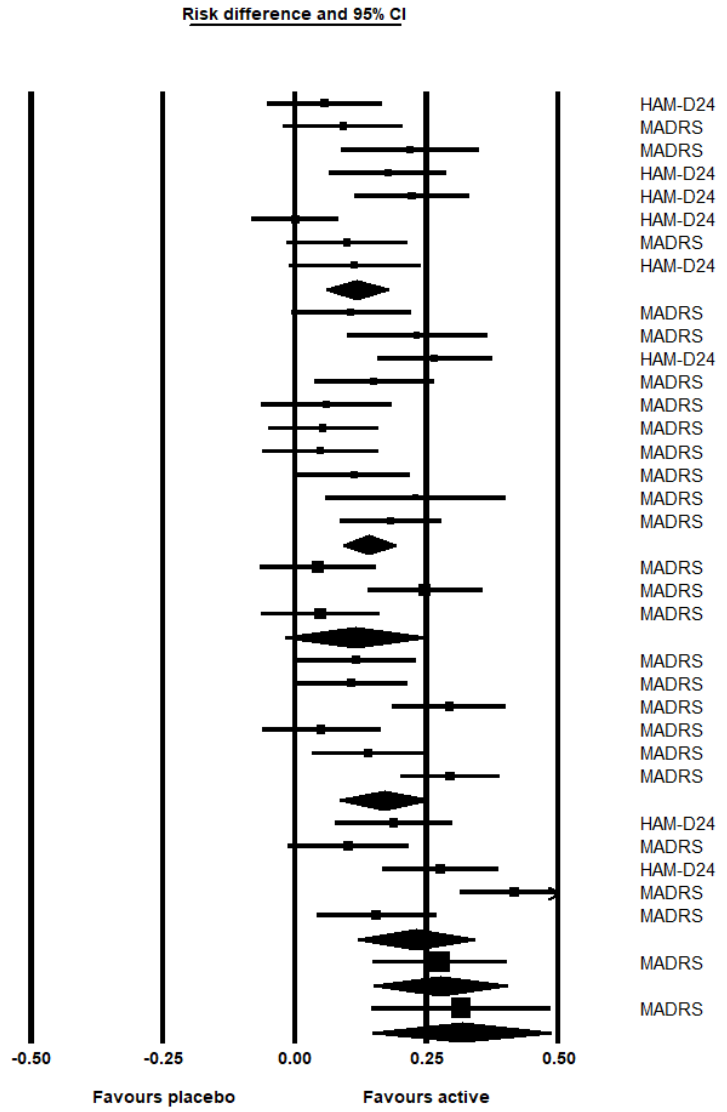


CI = confidence interval; HAM-D17 = 17-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Scale; VOR = vortioxetine.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 29.

Figure 11: Response – Active-Treatment Versus Placebo (Random-Effects Model)

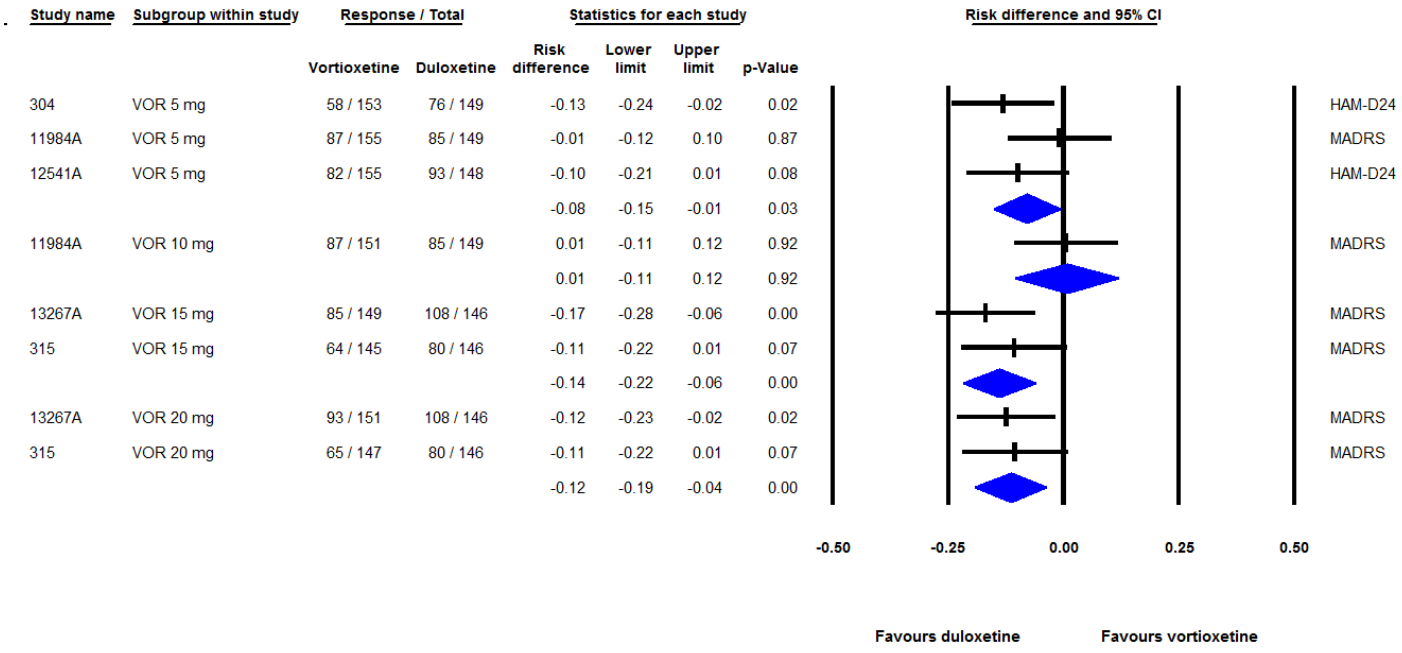
Study name	Subgroup within study	Risk difference	Lower limit	Upper limit	p-Value	
304	VOR 5 mg	0.06	-0.05	0.16	0.30	HAM-D24
11984A	VOR 5 mg	0.09	-0.02	0.21	0.11	MADRS
11492A	VOR 5 mg	0.22	0.09	0.35	0.00	MADRS
12541A	VOR 5 mg	0.18	0.07	0.29	0.00	HAM-D24
305	VOR 5 mg	0.22	0.11	0.33	0.00	HAM-D24
303	VOR 5 mg	0.00	-0.08	0.08	0.98	HAM-D24
CCT-002	VOR 5 mg	0.10	-0.01	0.21	0.09	MADRS
CCT-003	VOR 5 mg	0.11	-0.01	0.24	0.07	HAM-D24
		0.12	0.06	0.18	0.00	
11984A	VOR 10 mg	0.11	-0.01	0.22	0.06	MADRS
11492A	VOR 10 mg	0.23	0.10	0.36	0.00	MADRS
305	VOR 10 mg	0.27	0.16	0.37	0.00	HAM-D24
CCT-002	VOR 10 mg	0.15	0.04	0.26	0.01	MADRS
CCT-003	VOR 10 mg	0.06	-0.06	0.18	0.34	MADRS
316	VOR 10 mg	0.05	-0.05	0.16	0.31	MADRS
317	VOR 10 mg	0.05	-0.06	0.16	0.38	MADRS
CCT-004	VOR 10 mg	0.11	0.01	0.22	0.04	MADRS
15906A	VOR 10 mg	0.23	0.06	0.40	0.01	MADRS
14122A	VOR 10 mg	0.18	0.09	0.28	0.00	MADRS
		0.14	0.09	0.19	0.00	
317	VOR 15 mg	0.04	-0.07	0.15	0.43	MADRS
13267A	VOR 15 mg	0.25	0.14	0.36	0.00	MADRS
315	VOR 15 mg	0.05	-0.06	0.16	0.39	MADRS
		0.11	-0.02	0.25	0.09	
CCT-002	VOR 20 mg	0.12	0.00	0.23	0.04	MADRS
316	VOR 20 mg	0.11	0.00	0.21	0.05	MADRS
13267A	VOR 20 mg	0.29	0.19	0.40	0.00	MADRS
315	VOR 20 mg	0.05	-0.06	0.16	0.38	MADRS
CCT-004	VOR 20 mg	0.14	0.03	0.25	0.01	MADRS
14122A	VOR 20 mg	0.29	0.20	0.39	0.00	MADRS
		0.17	0.09	0.25	0.00	
304	DUL 60 mg	0.19	0.08	0.30	0.00	HAM-D24
11984A	DUL 60 mg	0.10	-0.01	0.22	0.08	MADRS
12541A	DUL 60 mg	0.28	0.17	0.39	0.00	HAM-D24
13267A	DUL 60 mg	0.42	0.32	0.52	0.00	MADRS
315	DUL 60 mg	0.16	0.04	0.27	0.01	MADRS
		0.23	0.12	0.34	0.00	
11492A	VEN 225 mg	0.28	0.15	0.40	0.00	MADRS
		0.28	0.15	0.40	0.00	
15906A	PAR 10 mg	0.32	0.15	0.48	0.00	MADRS
		0.32	0.15	0.48	0.00	



CI = confidence interval; DUL = duloxetine; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; PAR = paroxetine VEN = venlafaxine extended release; VOR = vortioxetine.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 29.

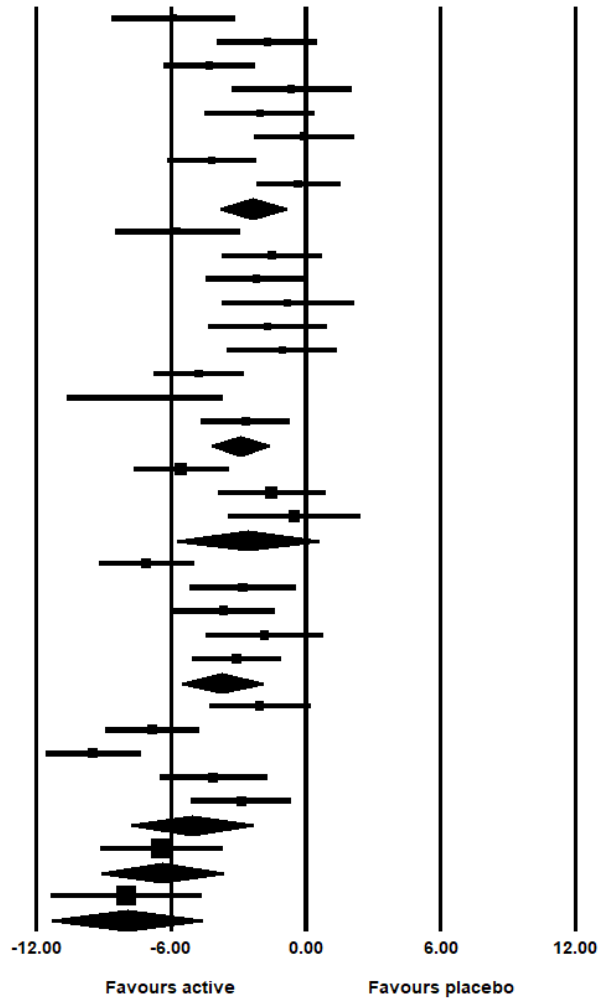
Figure 12: Response – Vortioxetine Versus Duloxetine (Random-Effects Model)



CI = confidence interval; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Scale; VOR = vortioxetine.
Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 29.

Figure 13: Change from Baseline in MADRS Score – Active-Treatment Versus Placebo (Random-Effects Model)

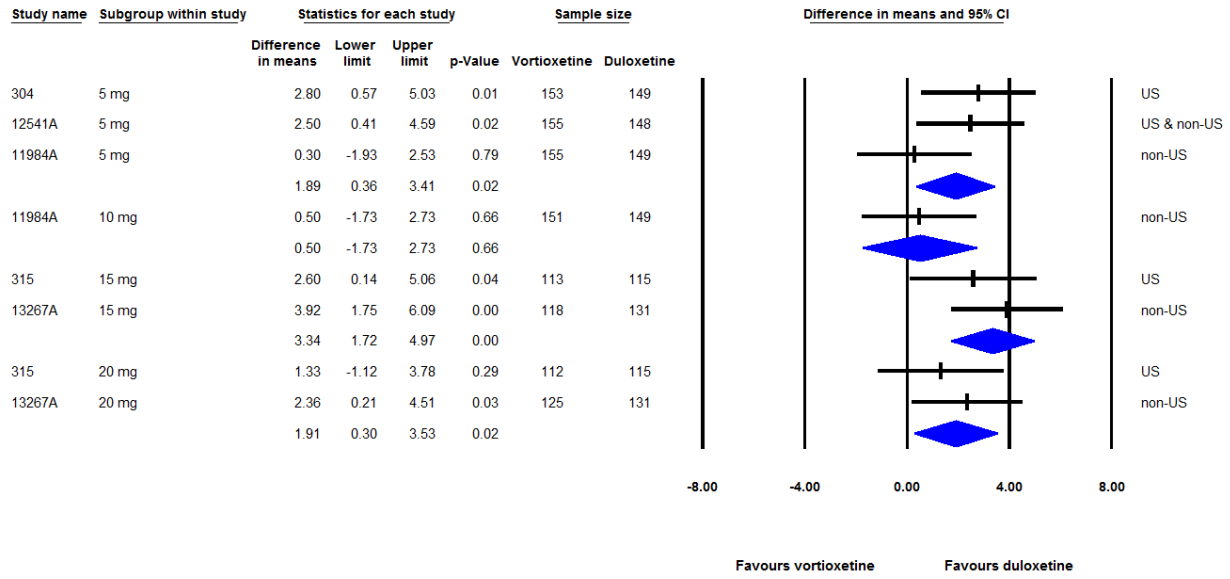
Study name	Dose	Difference in means	Lower limit	Upper limit	p-Value	
11492A	VOR 5 mg	-5.90	-8.62	-3.18	0.00	non-US
11984A	VOR 5 mg	-1.70	-3.91	0.51	0.13	non-US
12541A	VOR 5 mg	-4.29	-6.31	-2.27	0.00	US & non-US
CCT-002	VOR 5 mg	-0.61	-3.25	2.03	0.65	non-US
CCT-003	VOR 5 mg	-2.03	-4.46	0.40	0.10	non-US
304	VOR 5 mg	-0.08	-2.28	2.12	0.94	US
305	VOR 5 mg	-4.18	-6.14	-2.22	0.00	non-US
303	VOR 5 mg	-0.32	-2.18	1.54	0.74	US
		-2.36	-3.82	-0.90	0.00	
11492A	VOR 10 mg	-5.70	-8.47	-2.93	0.00	non-US
11984A	VOR 10 mg	-1.50	-3.72	0.72	0.18	non-US
316	VOR 10 mg	-2.19	-4.44	0.06	0.06	US
317	VOR 10 mg	-0.79	-3.70	2.12	0.59	US
CCT-002	VOR 10 mg	-1.69	-4.30	0.92	0.21	non-US
CCT-003	VOR 10 mg	-1.04	-3.46	1.38	0.40	non-US
305	VOR 10 mg	-4.75	-6.73	-2.77	0.00	non-US
15906A	VOR 10 mg	-7.15	-10.62	-3.68	0.00	non-US
CCT-004	VOR 10 mg	-2.66	-4.62	-0.70	0.01	non-US
		-2.93	-4.22	-1.64	0.00	
13267A	VOR 15 mg	-5.53	-7.65	-3.41	0.00	non-US
315	VOR 15 mg	-1.50	-3.87	0.87	0.22	US
317	VOR 15 mg	-0.49	-3.42	2.44	0.74	US
		-2.61	-5.75	0.53	0.10	
13267A	VOR 20 mg	-7.09	-9.20	-4.98	0.00	non-US
315	VOR 20 mg	-2.80	-5.16	-0.44	0.02	US
316	VOR 20 mg	-3.64	-5.91	-1.37	0.00	US
CCT-002	VOR 20 mg	-1.82	-4.42	0.78	0.17	non-US
CCT-004	VOR 20 mg	-3.07	-5.03	-1.11	0.00	non-US
		-3.74	-5.54	-1.95	0.00	
11984A	DUL 60 mg	-2.04	-4.27	0.19	0.07	non-US
12541A	DUL 60 mg	-6.83	-8.89	-4.77	0.00	US & non-US
13267A	DUL 60 mg	-9.45	-11.55	-7.35	0.00	non-US
315	DUL 60 mg	-4.10	-6.47	-1.73	0.00	US
304	DUL 60 mg	-2.87	-5.09	-0.65	0.01	US
		-5.08	-7.81	-2.36	0.00	
11492A	VEN 225 mg	-6.42	-9.12	-3.72	0.00	non-US
		-6.42	-9.12	-3.72	0.00	
15906A	PAR 10 mg	-7.97	-11.30	-4.64	0.00	non-US
		-7.97	-11.30	-4.64	0.00	



CI = confidence interval; DUL = duloxetine; MADRS = Montgomery–Åsberg Depression Rating Scale; PAR = paroxetine; VEN = venlafaxine extended release; VOR = vortioxetine.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 32.

Figure 14: MADRS – Vortioxetine Versus Duloxetine (Random-Effects Model)



CI = confidence interval.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 32 and Table 35.

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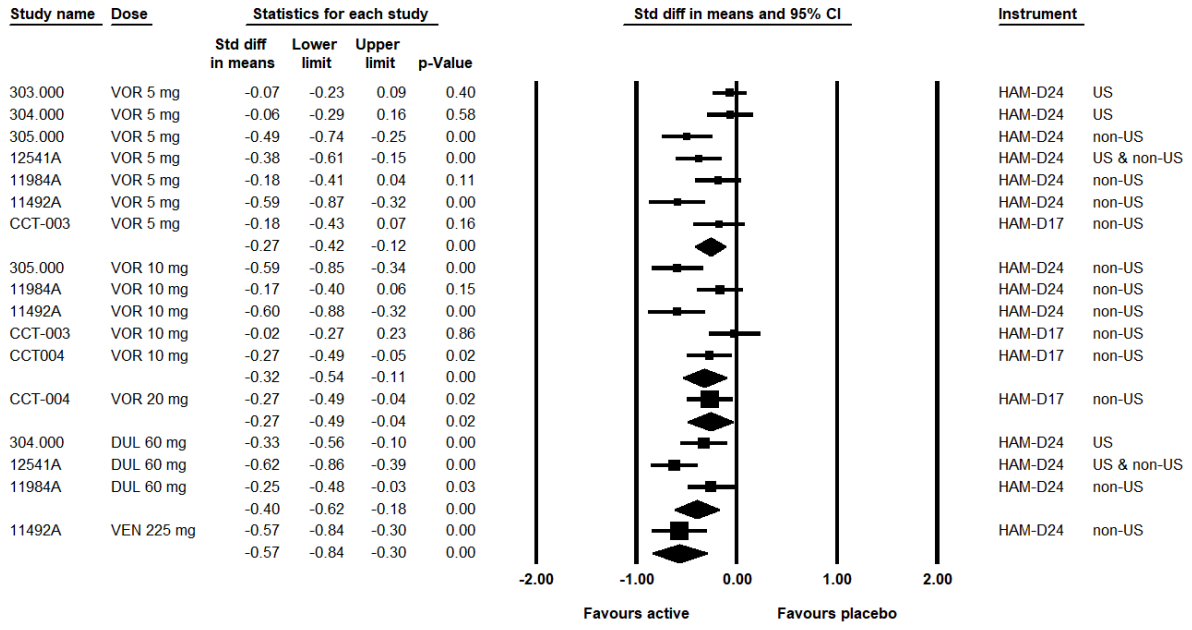
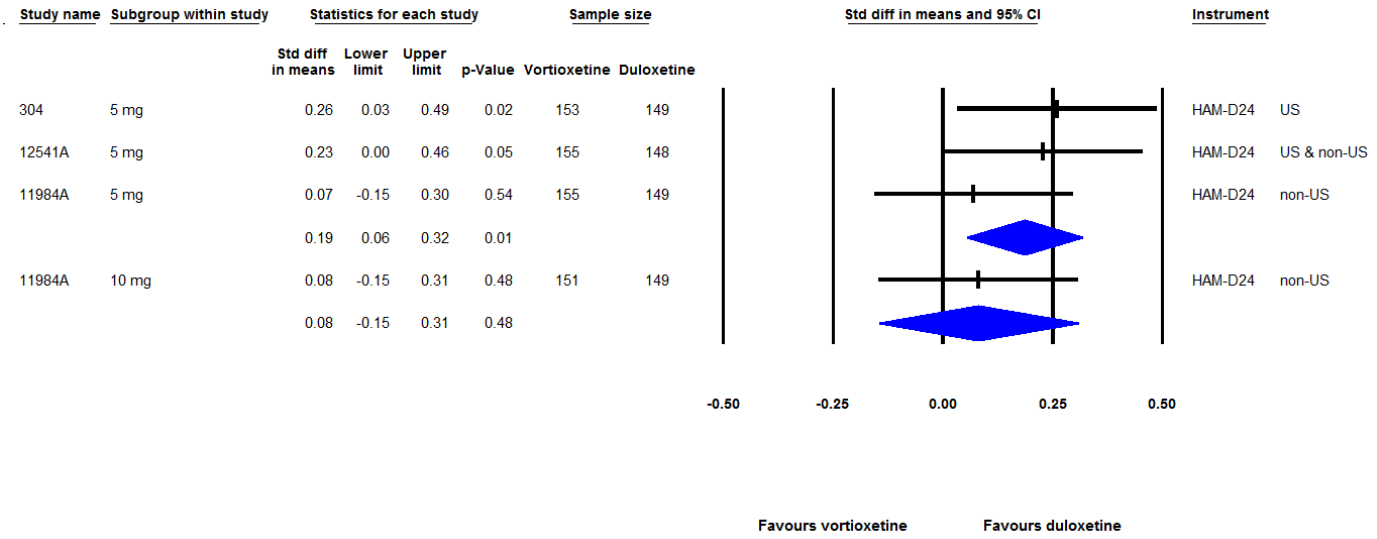
Figure 15: Change from Baseline in HAM-D17 and HAM-D24 scores – Active-Treatment Versus Placebo (Random-Effects Model)



CI = confidence interval; DUL = duloxetine; HAM-D17 = 17-item Hamilton Depression Rating Scale; HAM-D24 = 24-item Hamilton Depression Rating Scale; Std diff = standardized difference; VEN = venlafaxine extended release; VOR = vortioxetine.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 35.

Figure 16: HAM-D24 – Vortioxetine Versus Duloxetine (Random-Effects Model)

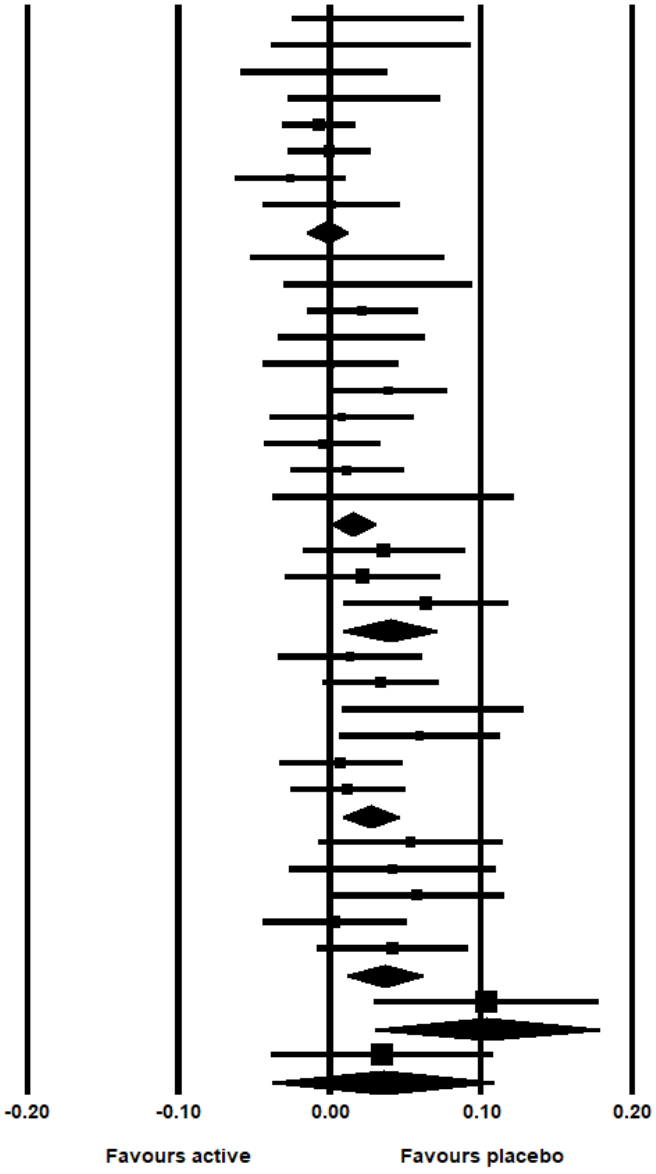


CI = confidence interval; HAM-D24 = 24-item Hamilton Depression Rating Scale; std diff = standard difference.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 32 and Table 35.

Figure 17: Withdrawals Due to Adverse Events – Active-Treatment Versus Placebo (Random-Effects Model)

Study name	Subgroup within study	Risk difference	Lower limit	Upper limit
304	VOR 5 mg	0.03	-0.02	0.09
11984A	VOR 5 mg	0.03	-0.04	0.09
11492A	VOR 5 mg	-0.01	-0.06	0.04
12541A	VOR 5 mg	0.02	-0.03	0.07
305	VOR 5 mg	-0.01	-0.03	0.02
303	VOR 5 mg	-0.00	-0.03	0.03
CCT-002	VOR 5 mg	-0.03	-0.06	0.01
CCT-003	VOR 5 mg	0.00	-0.04	0.05
		-0.00	-0.02	0.01
11984A	VOR 10 mg	0.01	-0.05	0.08
11492A	VOR 10 mg	0.03	-0.03	0.09
305	VOR 10 mg	0.02	-0.01	0.06
CCT-002	VOR 10 mg	0.01	-0.03	0.06
CCT-003	VOR 10 mg	0.00	-0.04	0.04
316	VOR 10 mg	0.04	-0.00	0.08
317	VOR 10 mg	0.01	-0.04	0.06
14122A	VOR 10 mg	-0.00	-0.04	0.03
CCT-004	VOR 10 mg	0.01	-0.03	0.05
15906A	VOR 10 mg	0.04	-0.04	0.12
		0.02	0.00	0.03
317	VOR 15 mg	0.04	-0.02	0.09
13267A	VOR 15 mg	0.02	-0.03	0.07
315	VOR 15 mg	0.06	0.01	0.12
		0.04	0.01	0.07
CCT-002	VOR 20 mg	0.01	-0.03	0.06
316	VOR 20 mg	0.03	-0.00	0.07
13267A	VOR 20 mg	0.07	0.01	0.13
315	VOR 20 mg	0.06	0.01	0.11
14122A	VOR 20 mg	0.01	-0.03	0.05
CCT-004	VOR 20 mg	0.01	-0.03	0.05
		0.03	0.01	0.05
304	DUL 60 mg	0.05	-0.01	0.11
11984A	DUL 60 mg	0.04	-0.03	0.11
12541A	DUL 60 mg	0.06	0.00	0.12
13267A	DUL 60 mg	0.00	-0.04	0.05
315	DUL 60 mg	0.04	-0.01	0.09
		0.04	0.01	0.06
11492A	VEN 225 mg	0.10	0.03	0.18
		0.10	0.03	0.18
15906A	PAR 10 mg	0.03	-0.04	0.11
		0.03	-0.04	0.11

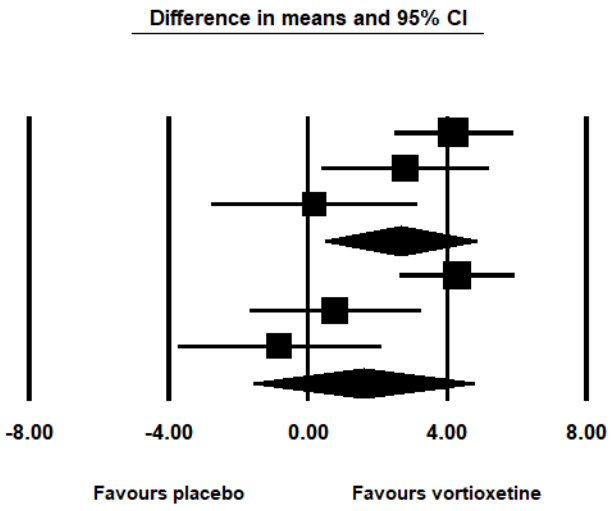


CI = confidence interval; DUL = duloxetine; PAR = paroxetine; VEN = venlafaxine extended release; VOR = vortioxetine.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 based on data from Table 40.

Figure 18: Change From Baseline in DSST – Vortioxetine Versus Placebo Excluding CCT-004 (Random-Effects Model)

Study name	Dose	Statistics for each study			
		Difference in means	Lower limit	Upper limit	p-Value
14122A	VOR 10 mg	4.20	2.51	5.89	0.00
12541A	VOR 10 mg	2.80	0.41	5.19	0.02
15906A	VOR 10 mg	0.20	-2.76	3.16	0.89
		2.67	0.48	4.85	0.02
14122A	VOR 20 mg	4.30	2.66	5.94	0.00
12541A	VOR 20 mg	0.80	-1.64	3.24	0.52
15906A	VOR 20 mg	-0.80	-3.71	2.11	0.59
		1.60	-1.56	4.77	0.32



CI = confidence interval; DSST = Digit Symbol Substitution Test; VOR = vortioxetine.

Source: Calculated by CADTH using Comprehensive Meta-Analysis software v2 using data from (Appendix 4, Table 36 and Table 37).

Appendix 6: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Hamilton Rating Scale for Depression (HAM-D)
- Montgomery–Åsberg Depression Rating Scale (MADRS)
- Sheehan Disability Scale (SDS)
- Changes in Sexual Functioning Questionnaire (CSFQ)
- Arizona Sexual Experience Scale (ASEX)
- Digit Symbol Substitution Test (DSST)
- Rey Auditory Verbal Learning Test (RAVLT)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- University of San Diego Performance-Based Skills Assessment (UPSA-B)
- Short-Form (36) Health Survey (SF-36)

Findings

The 17- and 24-item HAM-D, MADRS, SDS, CSFQ, ASEX, DSST, RAVLT, C-SSRS, UPSA, and SF-36 are briefly summarized in Table 56.

Table 56: Summary of Outcome Measures

Instrument	Type	Evidence of validity	MCID	References
HAM-D17 HAM-D24	HAM-D17 addresses both somatic and psychological symptoms of depression. The HAM-D24 includes seven additional items to capture cognitive symptoms. The scale is clinician-rated, in which ratings are made on the basis of a clinical interview and additional available information, such as family reports. Items are either rated on a 5-point scale (0 to 4) or a 3-point scale (0 to 2), where increasing scores represent increasing severity of symptoms. Scores are summed to obtain a total score of 52 or 53 on the HAM-D17 and 75 or 76 on the HAM-D24.	HAM-D17: Yes HAM-D24: Unknown	HAM-D17: 2 to 3[a] HAM-D24: Unspecified	Zimmerman et al. (2005)[79] Bagby et al. (2004)[80] Montgomery and Möller (2009)[81] O'Sullivan et al. (1997)[82]
MADRS	MADRS assesses depressive symptomology, particularly change in patients treated with antidepressants. This scale is clinician-rated and consists of 10 items. Each item is rated on a 0 to 6 scale, resulting in a maximum total score of 60 points, in which higher scores are indicative of greater depressive symptomology.	Yes	2	Zimmerman et al. (2004)[83] Lam et al. (2005)[84]
SDS	The SDS is a short, 3-item self-reported measure developed to assess the degree to which symptoms of depression, anxiety, panic, and phobia interfere with the patient's work, family and social life. Each of the items	No	Unspecified	Lam et al. (2005)[84] Sheehan et al. (1996)[85]

Instrument	Type	Evidence of validity	MCID	References
	is scored on a 1 to 10 scale, where 0 indicates no impairment, 1 to 3 mild impairment, 4 to 6 moderate impairment, 7 to 9 marked impairment and 10 extreme impairment. The items may also be summed into a total measure of global impairment, ranging from 0 to 30 points.			
CSFQ-14	The CSFQ-14 is a 14-item self-reported measure of illness- or medication-related changes in sexual functioning. It also gathers supporting clinical information to help identify the etiology of sexual dysfunction. Items are rated on a 5-point Likert scale to evaluate the frequency of the event in question (1 = never to 5 = every day), with higher scores indicating higher sexual functioning.	Yes, in patients with MDD	Unspecified	Keller et al. (2006)[86]
ASEX	The ASEX is a 5-item clinician-or self-administered measure of current sexual dysfunction. The items are related to sexual drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm. Scoring for each item is based on a 6-point Likert scale (1 = hyperfunction to 6 = hypofunction). Total scores may range from 5 to 30, with higher scores indicating increased sexual dysfunction.	Yes, in patients with MDD	Unspecified	McGahuey et al. (2000)[87]
DSST	The DSST is a measure of cognitive functioning focused on psychomotor speed. It is a timed task requiring subjects to match geometric symbols to corresponding numbers as designated by an answer key. The number of correct symbol-number pairs given within the prescribed time limit determines the raw DSST score, ranging from 0 to 133.	No	Unspecified	Betcher et al. (2011)[88]
RAVLT	The RAVLT is a brief cognitive function test that assesses immediate memory span, capacity for new learning and recognition, as well as susceptibility to interference. Subjects are asked to recall two or more lists of 15 nouns that have been read out loud to them after various lengths of time and in various formats, with one point awarded for every correctly recalled word.	No	Unspecified	Spreen and Straus (1998)[89]
C-SSRS	The C-SSRS is an interview-based measure of suicidal ideation and behaviour with four subscales (ideation severity, ideation intensity, behaviour, and lethality). The items on each subscale are rated on 3- to 6-point ordinal scales.	Yes, in adolescents with MDD	Unspecified	Posner et al. (2011)[90]
UPSA-B	A clinician-rated measure to assess everyday functional capacity in adults with mental illness. The full version examines the	Yes, in patients with MDD	UPSA summary score: 6.4 to 6.7 points[b]	Patterson et al. (2001)[91] Harvey (2017)[61]

Instrument	Type	Evidence of validity	MCID	References
	functioning in 5 areas, while the UPSA-B includes two subscales from the full version: communication and finance.			Christensen (2019)[92]
SF-36	The SF-36 is a generic measure of health-related quality of life. It consists of eight subdomains and provides two component summaries (PCS and MCS). The eight subdomains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status.	Yes, in patients with MDD	PCS: 2 points[c] MCS: 3 points[c] Subdomains: 2 to 4 points[c]	Ware and Gandek (1998)[93] Maruish (2011)[94] Ware et al. (2007)[95]

ASEX = Arizona Sexual Experience Scale; CPFQ = Cognitive and Physical Functioning Questionnaire; CSFQ-14 = Changes in Sexual Functioning Questionnaire; C-SSRS = Columbia Suicide Severity Rating Scale; Digit Symbol Substitution Test; HAM-D17 = 17-item Hamilton Rating Scale for Depression; HAM-D24 = 24-item Hamilton Rating Scale for Depression; MADRS = Montgomery–Åsberg Depression Rating Scale; MCID = minimal clinically important difference; MCS = mental component summary; MDD = major depressive disorder; PCS = physical component summary; RAVLT = Rey Auditory Verbal Learning Test; SDS = Sheehan Disability Scale; UPSA-B = University of San Diego Performance-Based Skills Assessment – Brief.

[a] Reported values are not MCIDs. For clinical trials, the National Institute for Health and Clinical Excellence recommends a three-point difference on the HAM-D17 between drug and placebo arms as a criterion for clinical significance.[96] In a separate report, Montgomery et al. (2009) suggested that a difference of 2 points between antidepressant and placebo might be clinically relevant.[81]

[b] Reported values are clinically important differences, not MCIDs.

[c] MCIDs not specific to MDD.

Hamilton Rating Scale for Depression

The HAM-D (or HDRS) is the most frequently utilized outcome measure in clinical trials of major depressive disorder (MDD) and is considered by many to be the standard for assessment of depression.[79] While numerous versions of this scale exist, the 17-item scale (HAM-D17) is most frequently used in efficacy trials.[79] The scale is clinician-rated, in which ratings are made on the basis of a clinical interview and additional available information, such as family report.[84] As a measure of the severity of depression symptoms, the HAM-D17 addresses both somatic and psychological symptoms of depression.[97] When the HAM-D17 was introduced, Hamilton had identified four additional variables that were not included in total scoring (diurnal variation, derealization, paranoid symptoms, and obsessive-compulsive symptoms), as these items reflected depression type rather than severity, or occurred too infrequently to warrant inclusion.[98] A 24-item version of this scale (HAM-D24) that included three more variables (helplessness, hopelessness, and worthlessness was later introduced with the goal of addressing general psychiatric distress.[82] A list of items included in the HAM-D17 and HAM-D24 is provided in

Table 57.

Items on both the HAM-D17 and HAM-D24 are either rated on a five-point scale (0 to 4) or a three-point scale (0 to 2), where increasing scores represent increasing severity of symptoms.[80,82] Depending on the version, scores are summed to obtain a total score out of 52 or 53 for the HAM-D17 and 75 or 76 for the HAM-D24.[99,100] Because the number of response options varies between items, certain items contribute more to the total score than others.[80] In HAM-D24 scoring, a total score ranging from 0 to 7 indicates that the patient is in the normal range (no depression), 8 to 13 indicates “mild depression,” 14 to 18 indicates “moderate depression,” 19 to 22 indicates “severe depression,” and a total score of 23 or greater indicates “very severe depression.”[79] Scoring instructions for the HAM-D24 were not identified; however, one study developed metrics to approximate the relationship between HAM-D17 and HAM-D24 scores and reported the conversions.[100]

Table 57: Items Included on the HAM-D17, HAM-D24, and MADRS

Domain	HAM-D17 or HAM-D24	MADRS (10 items)
Mood	• Depressed mood • Suicidal ideation	• Depression (apparent) • Depression (reported) • Loss of interest • Suicidal ideation
Anxiety	• Psychic anxiety • Somatic anxiety	• Tension
Appetite	• Somatic symptoms, gastrointestinal (appetite) • Weight loss	• Reduced appetite
Sleep	• Insomnia early • Insomnia middle • Insomnia late	• Insomnia
Functional status	• Work and activities • Psychomotor retardation • Psychomotor agitation	• Difficulties in activities
Ability to think	NA	• Concentration
Physical symptoms	• Somatic symptoms, general (e.g., pain, fatigue)	NA
Hypochondriasis	• Hypochondriasis (somatization)	NA
Sexual function	• Sexual disturbances (e.g., loss of libido)	NA
Diurnal variation	• Diurnal variation[a]	NA
General psychiatric distress	• Feelings of guilt and low self-esteem • Insight • Depersonalization and derealization[a] • Paranoid symptoms[a] • Obsessional and compulsive symptoms[a] • Helplessness[a] • Hopelessness[a] • Worthlessness[a]	• Pessimism

HAM-D17 = 17-item Hamilton Depression Rating Scale; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; NA = not applicable.

[a] Item included on the HAM-D24 but not the HAM-D17.

Source: Clinical Psychometrics, Appendix 3a: HAM-D_{17},[101] Clinical Psychometrics, Appendix 3b: HAM-D_{24},[102] FDA Description of the HAM-D and the MADRS.[103]

While many of the psychometric properties of the HAM-D17 are adequate and consistently meet established criteria, some psychometric and conceptual limitations have also been identified.[80] Reliability coefficients for internal consistency, inter-rater and test-retest reliability are generally good for the overall scale, as are the internal reliability estimates for the individual items of the scale. Although numerous items have weak inter-rater and retest reliability at the item level, the use of structured interview guides may increase the item and total scale reliability.[80] The content validity of the HAM-D24 is poor, as there is only partial overlap between the content of this scale and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) symptom inclusion diagnostic criteria for MDD.[79] Some symptoms on the HAM-D17 are not official DSM-IV criteria and, while some such symptoms are recognized as associated with depression (e.g., psychotic anxiety), the link to depression is more tenuous for other symptoms (e.g., loss of insight, hypochondriasis).[80] Conversely, important features of DSM-IV depression, such as concentration difficulties, feelings of worthlessness and reversed vegetative symptoms, are either buried within

complex items or not captured at all.[80] Notably, the HAM-D24 contains an item pertaining to feelings of worthlessness, which was originally added to improve the usefulness of the HAM-D17.[104] The convergent validity of the HAM-D17 has been shown to be adequate, as this scale has moderate-to-high correlation with many other depression scales.[80] Similarly, the discriminant validity of this scale has been shown to be adequate.[80] Several meta-analyses have also found the HAM-D17 to be more sensitive to change (responsive) in patients' conditions compared to other depression scales, such as the Beck Depression Inventory.[105,106] However, the multidimensional nature of the HAM-D17 may somewhat reduce its sensitivity to detecting changes in depression severity over time.[107] For instance, the full HAM-D17 scale has been shown to be less sensitive than unidimensional subscales of its items.[108] Frequently used subscales include the core, which incorporates items related to core depressive symptoms (depressed mood, guilt, suicidal behaviours and ideation, work/activities, and psychomotor retardation) and the Maier, which includes core items in addition to items related to anxiety and agitation. Overall, some of the psychometric properties of the HAM- D17 are adequate, yet some inherent psychometric and conceptual limitations remain.[80]

Little information specifically regarding the validity of the HAM-D24 was identified; however, some evidence suggests that its performance is comparable to that of the HAM-D17. One study reported similarly high internal consistencies for the HAM-D17 (0.83) and the HAM-D24 (0.88).[100] Another study that compared the treatment effects of fluoxetine in patients with MDD as assessed by multiple HAM-D versions reported a strong correlation between the HAM- D17 and HAM-D24 scores at baseline (0.86) and post-treatment (0.98).[82]

Response and remission are the two clinically important outcomes on the HAM-D17 that are frequently reported in efficacy trials. Response is defined as a 50% reduction from baseline HAM-D17 total score,[79] and this definition of response has also been applied to the HAM-D24 in clinical trials.[100] Remission was defined as a score of 7 or less on the HAM-D17 total score by a consensus panel in 1991,[109] and since then, this level has been widely adopted in clinical research.[79] However, more recent evidence has suggested that, based on a narrow definition of DSM-IV remission, which requires an absence of clinically significant symptoms of depression, the optimal cut-off should be 2 or lower on the HAM-D17 total score.[79] A score of 7 or lower was found to be an appropriate level when using a broader definition of remission.[79] No information about the HAM-D24 cut-off score for remission was identified. For clinical trials, the National Institute for Health and Clinical Excellence (NICE) recommends a three-point difference between drug and placebo arms as a criterion for clinical significance,[96] although no justification for this figure was provided.[99] The updated NICE guidelines[110] includes no mention of what constitutes a clinically significant difference. A separate report by Montgomery et al. suggested a difference of 2 points between antidepressant and placebo might be clinically relevant.[81] Although similar to the NICE guidelines, it appears that this figure was opinion-based. Therefore, neither a formally derived minimal clinically important difference (MCID) nor an evidence-based clinically significant difference for the HAM-D17 or HAM-D24 was identified.

Montgomery–Åsberg Depression Rating Scale

Next to the HAM-D17, the MADRS is the most commonly used outcome measure in antidepressant efficacy trials and has been used with increasing frequency during the past decade.[83] The main purpose of this scale is to assess depressive symptomology, particularly change in patients treated with antidepressants.[83] While the HAM-D17 includes items that address somatic symptoms, the MADRS focuses on the psychological symptoms

of depression (e.g., sadness, tension, pessimistic thoughts).[97] This scale is clinician-rated and consists of 10 items, in which each item is rated on a 0 to 6 scale, resulting in a maximum total score of 60 points, in which higher scores are indicative of greater depressive symptomology.[84] The MADRS scoring instructions indicate that a total score ranging from 0 to 6 indicates that the patient is in the normal range (no depression), a score ranging from 7 to 19 indicates "mild depression," 20 to 34 indicates "moderate depression," and scores of 35 and higher indicate "severe depression."[111] There is evidence to support that an improvement of 2 points or more on the MADRS can be considered clinically relevant[112]

The psychometric properties of the MADRS scale have been evaluated in numerous studies and compared to those of other scales, such as the HAM-D17. The MADRS has an internal consistency slightly higher than that of the HAM-D17.[107] The clinician inter-rater reliability of this scale was also acceptable on individual items as well as the total score.[113] With respect to its content validity, most of the items are highly related to the core concept of depression. However, similar to the HAM-D17, not all of the core criteria symptoms used in the DSM-IV are assessed by the MADRS and therefore neither scale is completely adequate to define the severity of depression or remission.[107] There is a high degree of correlation between scores of the MADRS and other measures, such as the HAM-D17 and the six-item version of the HAM-D, thereby showing good convergent validity.[97,107,113] The MADRS has also shown high ability to discriminate between various levels of depression severity.[107] Studies have repeatedly found the MADRS to have greater sensitivity to treatment-related change compared to the HAM-D17;[113-115] however, at least one study involving patients with MDD found its sensitivity to be lower than that of the HAM-D17.[116] This high capability of the MADRS to detect change in patients' conditions over time may be related to its more uniform structure compared to the HAM-D17.[117] Overall, the MADRS has been found to have sound psychometric properties and be at least comparable to, if not somewhat exceeding, the HAM-D17 in certain psychometric aspects. No comparison between the MADRS and the HAM-D24 was identified.

Response to treatment is usually defined as a reduction in the MADRS total score of least 50% from baseline.[118] No consensus has emerged regarding a cut-off value on the MADRS for defining remission in clinical trials.[119] Criterion scores to identify patients who have experienced remission have ranged from 6 through 12 in various trials.[118,120] However, one recent study that set out to establish an empirically based cut-off based on a narrow definition of remission concluded that the optimal MADRS cut-off was no more than 4 points. On the basis of a less-conservative definition of remission, the recommended cut-off was no more than 9 points.[119] There is evidence to support that a MADRS score of less than 10 is a valid cut point for remission.[121]

Sheehan Disability Scale

The SDS is a short, three-item, self-reported measure developed to assess the degree to which symptoms of depression, anxiety, panic, and phobia interfere with the patient's work, family, and social life.[84] Each of the items is scored on a 0 to 10 scale, where 0 indicates no impairment, 1 to 3 mild impairment, 4 to 6 moderate impairment, 7 to 9 marked impairment, and 10 extreme impairment. Scores exceeding 5 points on any of the items are indicative of functional impairment and heightened risk of mental disorder.[84] The items may also be summed into a total measure of global impairment, ranging from 0 to 30 points.[84] There is some evidence that the SDS is a sensitive measure of disability for patients with psychiatric disorders in primary care. One study evaluated this scale in a sample of 1,001 primary care

psychiatric patients (the proportion of patients with MDD was not specified) and found that a higher score (≥ 5) was associated with an increased risk of psychiatric impairment.[85] Also, more than 80% of patients with a diagnosis of a mental disorder were shown to have an elevated SDS score.[85] An MCID has not been specified.

Changes in Sexual Functioning Questionnaire

The CSFQ is a clinician interview-based or self-reported measure of sexual desire, activity, and satisfaction. It was developed to incorporate information on comorbid conditions and concomitant medications that may be relevant to sexual functioning in clinical trial populations with psychiatric illnesses, including MDD.[122] The original version contains 36 questions for men and 35 questions for women; the first 21 are common to both sexes.[122] The CSFQ was initially validated in a group of medical students and residents, demonstrating moderate-to-high internal consistency and test-retest reliability, as well as face validity (compared with the DSM-IV) and good concurrent validity with the Derogatis Interview for Sexual Functioning — Self-Report.[122] A study of CSFQ responsiveness in patients with MDD or dysthymia treated with antidepressants showed sensitivity to both improving and worsening changes in sexual function, and that neither the total score nor subscales were subject to substantial (greater than 30%) floor or ceiling effects.[123] The percentage of dimensions recording positive changes in sexual functioning following treatment was greater in women than in men (80% versus 20%), whereas the percentage of dimensions recording negative changes was greater in men than in women (40% versus 20%); however, this was consistent with the previously observed effects of the antidepressants used in this study and supported suggestions that male and female sexual functioning are different constructs.[123] A lack of sensitivity to change in the sexual desire/interest domain was observed in both men and women, as well as in the pleasure dimension for men only.[123]

The CSFQ-14 is a 14-item, sex-specific, self-reported questionnaire derived from the original CSFQ.[86] Each item is scored on a five-point Likert scale to evaluate the frequency (ranging from 1 = never to 5 = every day) or intensity (1 = nothing to 5 = very much) of the event in question, with higher scores indicating higher sexual functioning. A total score ranging from 14 to 70, as well as eight subscale scores, can be obtained with the CSFQ-14. Five dimensions are the same as on the original CSFQ, and three additional subscales that overlap with the five dimension items are related to phases of the sexual response cycle: desire, arousal, and orgasm or completion. In a validation study of patients with depression, the original scales and the three sexual response cycle-related scales of the CSFQ-14 demonstrated strong internal reliability for both the male and female versions.[86] Construct validity of the subdomains was also confirmed by factor analysis across sex and sexual dysfunction status subgroups.[86] The total CSFQ threshold scores for sexual dysfunction were established as less than or equal to 41 for males and 47 for females, which have been maintained for the CSFQ-14.[86] However, no formal MCID was identified for patients with MDD.

Arizona Sexual Experience Scale

The ASEX is a brief self- or clinician-administered measure of current sexual dysfunction.[87] The ASEX contains five items related to sexual drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm.[87] Scoring for each item is based on a six-point Likert scale (1 = hyperfunction to 6 = hypofunction). Total scores may range from 5 to 30, with higher scores indicating increased sexual dysfunction. It is suitable for use in heterosexual or homosexual populations, including people without sexual

partners. Unlike the CSFQ-14, the ASEX does not provide any information regarding the probable cause for sexual dysfunction. The ASEX demonstrated strong internal consistency and reliability in a validation study of psychiatric patients (the majority with depression and on antidepressants) and controls.[87] In support of convergent validity, the ASEX correlated well with the Brief Index of Sexual Functioning, an established measure of sexual functioning.[87] A single set of thresholds for sexual dysfunction was defined as greater than or equal to 19 for total ASEX score, any single item with a score of 5 or higher, or any three items with a score of 4 or higher. Female total ASEX scores were significantly higher than male total scores in both the depressed and control groups.[87] However, no formal MCID was identified for patients with MDD.

Digit Symbol Substitution Test

The DSST is one of a suite of cognitive functioning tests contained within various editions of the Wechsler Adult Intelligence Scale (WAIS).[88] Participants are shown a series of geometric symbols corresponding to the numbers one to nine, followed by a grid with numbers in the top boxes and blank boxes directly underneath. They are then asked to copy the corresponding geometric symbol in the blank box under its paired number. The test consists of 133 digits to be matched within either a 90-second or two-minute period.[17,22] The number of correct symbol-number pairs provided within the prescribed time limit determines the raw DSST score, ranging from 0 to 133, with a higher score indicating higher cognitive functioning.[22]

While it has been reported that no “gold standard” cognitive test has been validated for the evaluation of cognitive functioning in MDD, the DSST has been applied as a measure of processing speed in a number of clinical trials involving depressed patients.[124] In a study examining the performance of patients with and without MDD on 11 tests from the third edition of the WAIS, only the DSST and one other subtest related to speed demands had significantly different test scores between groups.[125] The authors concluded that the depression-related impairments identified by the third edition of the WAIS were concentrated in the processing speed domain, although the DSST’s responsiveness with improvement in depressive symptoms was not addressed in this study.[125] The ability of the DSST to differentiate between depressed and non-depressed patients was confirmed by a meta-analysis of cognitive function tests for MDD; however, a substantial degree of heterogeneity in the included studies was noted.[126] An MCID for the DSST was not identified.

Rey Auditory Verbal Learning Test

The RAVLT is a brief cognitive function test that assesses verbal learning and memory. The most common version of this test involves reading 15 nouns out loud to the test subject, followed by a free-recall test; this process is repeated multiple times. Another list of 15 new words is read, immediately followed by a free-recall test and a delayed-recall test of the first list, without repetition of the first list items. Additional recall tests can be performed after a longer time interval, and by presenting the nouns in different formats, such as in the context of a story. One point is awarded for every noun recalled correctly, with the maximum possible acquisition score depending on how many lists of 15 nouns were used (i.e., when three lists are used, the acquisition score may range from 0 to 45). The delayed-recall score refers to the number of words correctly recalled from only one list at the end of the test battery, with a score ranging from 0 to 15.[22] The objective is to determine immediate memory span, capacity for new learning and recognition, as well as susceptibility to interference.[89]

The RAVLT has been used as a measure of the memory domain of cognitive functioning in several clinical trials involving depressed patients.[22] The RAVLT was one of the included memory tests in a meta-analysis of cognitive test sensitivity to discriminate between patients with MDD and healthy controls; the results showed a significant between-group difference in immediate but not delayed verbal memory.[126] A high degree of heterogeneity was observed for the studies of verbal memory that were included in the meta-analysis.[126] No evidence regarding the psychometric validity of the RAVLT in MDD was identified.

Columbia Suicide Severity Rating Scale

The C-SSRS is an interview-based assessment tool for measuring suicidality as represented by the domains of suicidal behaviour and ideation.[90] It was developed to monitor changes in suicidality over time by incorporating assessments of lifetime suicidal ideation and behaviour as well as between-visit changes. The C-SSRS has four subscales: severity of ideation (e.g., specificity of suicidal thoughts or intent with methods or plans), intensity of ideation (e.g., frequency and duration of suicidal thoughts), behaviour (e.g., preparatory actions, suicide attempts, and non-suicidal injurious behaviour), and lethality (assessment of actual suicide attempts). The items on the ideation and lethality subscales are rated on three- to six-point ordinal scales, and the behaviour subscale uses a nominal scale. A higher total score indicates a higher level of suicidality.

The psychometric properties of the C-SSRS were assessed in three studies that were presented in one publication.[90] Study 1 included adolescents who had previously attempted suicide, Study 2 involved adolescents with a diagnosis of MDD, and Study 3 was conducted in adult patients who presented to the emergency department for psychiatric reasons.[90] The intensity of ideation subscale demonstrated moderate-to-high internal consistency in all three studies. In support of convergent validity, the suicidal ideation and behaviour subscales on the C-SSRS correlated moderately to strongly with the corresponding suicide-related items on the MADRS and Beck Depression Inventory, as well as with the Scale for Suicide Ideation and the Columbia Suicide History Form in Studies 1 and 3. Further analysis in Studies 1 and 2 showed that the change in the severity and intensity of ideation subscale scores over time significantly corresponded with Scale for Suicide Ideation or Suicidal Ideation Questionnaire – Junior score changes. Similarly, the classification of suicidal behaviours on the C-SSRS over time in Study 1 demonstrated moderate-to-full agreement with the classification of the same behaviour using the Columbia Suicide History Form. The divergent validity of the C-SSRS severity and intensity of ideation subscales was analyzed in Study 1, and a weak-to-moderate correlation between these subscales and somatic depression items on the Beck Depression Inventory and the MADRS was observed; however, this study population did not include adults with MDD.[90]

Although an MCID was not reported for the C-SSRS, predictive validity was examined in two studies. For each increase in C-SSRS level of lifetime suicide ideation by one standard deviation in an adolescent population, the odds of attempting suicide during the 24-week study increased by 45%.[90] A validation study of the electronic version of the C-SSRS evaluated an existing set of assessments extracted from multiple studies in which the majority (91%) of total patients had MDD, and demonstrated that patients who reported severe lifetime suicidal ideation or a history of suicidal behaviour at baseline were up to nine times more likely to report suicidal behaviour during their study participation.[127]

The University of California San Diego Performance-Based Skills Assessment

The University of California San Diego Performance-Based Skills Assessment (USPA) was developed to assess everyday functional capacity in older, community-dwelling patients diagnosed with severe mental illness (e.g., schizophrenia, post-traumatic stress disorder or MDD), other patient populations (e.g., type 2 diabetes and Alzheimer disease), as well as in healthy older adults.[61] There are several versions of the UPSA, varying in length and comprehensiveness. The original full UPSA assesses skills in five areas: household chores such as cooking and shopping, communication, finance, transportation, and planning recreational activities.[61] For household chores, raw scores ranging from 0 to 4 are yielded. Communication tasks, such as making phone calls, yield raw scores ranging from 0 to 9. The scores for both financial and transportation skills range from 0 to 6. For the task of planning recreational activities, people are asked to participate in two role-playing scenarios. Points are given for each appropriate response. The raw scores for this task for the two scenarios range from 0 to 27. Total scores for each subscale are calculated by transforming the raw scores into a 0-to-10 scale, yielding comparable scores on each scale. Each subscale score is multiplied by 2, generating subscale scores ranging from 0 to 20. Finally, by summing the five subscale scores, a UPSA summary score ranging from 0 to 100 is calculated. Higher scores indicate better functional capacity.[91] The University of California San Diego Performance-Based Skills Assessment – Brief (UPSA-B) is a shorter version that includes two subscales (communication and finance) from the original full version. This shorter version has been demonstrated to be highly correlated with the full UPSA (r = 0.91).[61]

The UPSA has demonstrated adequate test-retest reliability and validity to be used as a co-primary end point for treatment response to cognitive enhancement studies of schizophrenia.[61] Furthermore, psychometric properties of UPSA have been examined in 602 adult patients with moderate-to-severe recurrent MDD and self-reported cognitive dysfunction (Study 202). The full UPSA was administered to English-speaking US patients, and the UPSA-B was administered to patients in non-English-speaking countries. Each of the five subscales on the full UPSA were scored on a 0-to-20 scale and each of the two subscales on UPSA-B were scored on a 0-to-50 scale and then summed to yield a total score ranging from 0 to 100 for both versions. The results showed that the correlation between the full UPSA and UPSA-B was 0.80 in the US patients. The UPSA summary score correlated with cognitive functioning (DSST, r = 0.36, P < 0.001) and workplace productivity (Work Limitations Questionnaire: r = −0.17, P = 0.008) at baseline, but not depressive symptoms (MADRS: r = 0.02, P = 0.71) or subjective cognitive dysfunction (Perceived Deficits Questionnaire: r = −0.02, P = 0.70). The results supported the construct validity of UPSA for assessing functional capacity independent of mood symptoms. An increase of 6.4 points (distribution-based method) or 6.7 points (anchor-based method) on the UPSA summary score was determined to be the clinically important difference to show a treatment response in patients with MDD.[61] A recent study supported the initial validation of UPSA-B by incorporating additional trial data. The results showed that UPSA-B summary scores correlated with those of the DSST (r = 0.32, P < 0.0001), but not the MADRS (r = −0.07, P = 0.30) or the Perceived Deficits Questionnaire: r = −0.10, P = 0.11). The clinically important difference was estimated to be 7.0 points and 6.4 points for anchor- and distribution-based methods, respectively.[92]

Short-Form (36) Health Survey

The SF-36 is a generic health assessment questionnaire that has been used in clinical trials for a variety of diseases to study the impact of treatment on health-related quality of life (HRQoL). The SF-36 is a patient self-reported measure consisting of eight health concept subdomains: physical functioning (PF), bodily pain (BP), vitality (VT), social functioning (SF), mental health (MH), general health (GH), and role limitations due to physical and emotional problems (role physical [RP] and role emotional [RE], respectively).[93] The eight subdomains are each measured on a scale of 0 to 100, with higher scores indicating better HRQoL, and an increase in score indicates an improvement in health status. The SF-36 also provides two summary measures of the subdomains, the physical component summary (PCS) and the mental component summary (MCS). Each of the summary measures correlates more highly with and receive greater scoring contribution from some subscales than others, though the VT, GH, and SF correlate moderately to substantially with both the PCS and MCS.[93] An evaluation of the validity of the two summary measures instead of using all eight subdomains to measure HRQoL in adult patients with several conditions, including depression, showed that the MCS performed as well or better than individual scales to measure mental health, whereas the PCS demonstrated about 80% empirical validity of the best individual scale measure of physical health.[128]

Studies of the psychometric properties of the SF-36 subscales in patients with depression have shown that the internal consistencies of each subscale range from 0.60 (GH) to 0.92 (BP).[129] The most precise scales have at least 20 levels defining a wide range of health states with less skewed distributions (PF, GH, VT, and MH), and the least precise scales have five or fewer levels (RE and RP) and are subject to high standard deviations as well as floor and ceiling effects.[93] Marked differences in construct validity have been observed among the eight subscales, which have been supported by results from clinical studies comparing patient scores before and after treatment. For example, the MH, RE, and SF scales, which contain the most mental factor content from factor analysis studies, have demonstrated greater responsiveness to change in some studies of patients with depression following treatment.[93,128] However, Pukrop et al. showed a significant improvement in all SF-36 subdomain scores from hospital admission to discharge in patients with depression.[129] When the HAM-D score was included as a covariate in this analysis, the only remaining scales with significantly improved scores were MH and VT; this indicated that standard hospital treatment was associated with improved HRQoL overall, and that this improvement was linked to improvement of the patients' depression. The SF-36 scales have demonstrated at least moderate correlation with most GH concepts and symptoms, with the exception of sexual functioning, warranting the addition of supplemental sexual functioning questionnaires in clinical trials.[93]

Based on comparisons of SF-36 scores in dysfunctional and functional populations (e.g., populations representing those with and without a diagnosis of an affective or mood disorder, respectively), Newnham et al. calculated cut-off scores distinguishing dysfunctional and functional populations for the subscales relevant to the MCS in psychiatric inpatients, such that a score above the defined thresholds suggests that a patient is statistically more likely to be part of the functional population.[130] These cut-off scores were defined as 45 for VT, 55 for SF, 46 for role function (unclear whether this meant RE, RP, or both), and 55 for MH.[130] However, the authors indicated that an improvement in the score above the identified thresholds did not necessarily signify a reliable clinical change. They reported that clinically significant improvement relies on both a score increase above the cut-off and a reliable change index, which depends on the

change in score over time and the standard error of the difference between the functional and dysfunctional populations from which the cut-off scores were derived. Therefore, no absolute MCIDs for the SF-36 subscales or component summaries for depression were identified. General MCIDs (not specific to MDD) for the PCS and MCS of the SF-36 have been identified by the instrument developer and reported as 2 points and 3 points, respectively.[94] In general use of SF-36, a change of 2 to 4 points in each dimension indicates a clinically meaningful improvement as determined by the patient.[95]

Appendix 7: Summary of Extension Studies

Objective

To summarize the long-term safety and efficacy outcomes from the open-label extension studies by Alam et al.,[131] Baldwin et al. (2012[132] and 2016[133]), Inoue et al.,[41] Jacobsen et al.,[134] and Vieta et al.,[135] in which flexible doses of vortioxetine once daily were administered to adults with major depressive disorder (MDD) who had completed participation in a short-term vortioxetine randomized controlled trial (RCT).

Study Characteristics

Details of the included open-label extension studies are described in Table 58.

Table 58: Details of Open-Label Extension Studies

		Alam et al. (2014)	Baldwin et al. (2012)	Baldwin et al. (2016)[a]	Inoue et al. (2018)	Jacobsen et al. (2015)	Vieta et al. (2017)[a]
Designs & Populations	**Objectives**	• To evaluate the long-term safety and tolerability of flexible dosing of VOR over 52 weeks in patients with MDD who had completed short-term RCTs • To evaluate the maintenance of clinical effectiveness of VOR over a long-term treatment period. The Baldwin et al. (2016) study evaluated long-term safety only					
	Study design	Open-label, uncontrolled study					
	Population	Patients who completed Studies 304 and 305	Patients who completed Study 11984A	Patients who completed Studies 11492A, 11984A, 304, 305, 13267A, 315, 316, and 317 (pooled analysis of 5 extension studies)	Patients who completed CCT-003 in Japanese patients with MDD	Patients who completed Studies 315, 316, and 317	Patients who completed 11492A, 11984A, 304, 305, 13267A, 315, 316, and 317 (pooled analysis of 5 extension studies), and were previously treated with VOR 5 mg to 20 mg
	N	836	535	2457	120	1,075	1,231
	Inclusion criteria	• Completed 304 and 305 • Had clinical indication for 12 months of continued treatment	• Completed 11984A • Had clinical indication for 12 months of continued treatment	• Completers of one of the acute studies • Had clinical indication for 12 months of continued treatment	• 20 to 75 years of age • Completed the preceding 8-week DB RCT • Improvement of CGI-S score ≥ 1 from baseline	• Completed 315, 316, and 317	• Completed the lead-in studies and were treated with VOR at an approved therapeutic dose (5 mg to 20 mg)

		Alam et al. (2014)	Baldwin et al. (2012)	Baldwin et al. (2016)[a]	Inoue et al. (2018)	Jacobsen et al. (2015)	Vieta et al. (2017)[a]
	Exclusion criteria	• Diagnosis of other psychiatric disorders during lead-in studies • Significant risk of suicide or score ≥ 5 on MADRS item 10 (suicidal thoughts) • Moderate or severe AE related to study drug from prior study • Patient had used or were anticipated to take disallowed concomitant medication In the Inoue et al. (2018) study, patients with clinically significant neurological disorder, substance-related disorder, or a confirmed positive urine drug screen were also excluded. The Baldwin et al. (2016) and Vieta et al. (2017) studies did not specify exclusion criteria in the published articles.					
Drug	**VOR daily flexible dose**	2.5 mg 5 mg 10 mg	2.5 mg 5 mg 10 mg	2.5 mg 5 mg 10 mg 15 mg 20 mg	5 mg 10 mg 20 mg	10 mg 15 mg 20 mg	5 mg 10 mg 15 mg 20 mg
Duration	**Treatment duration**	52 weeks					
	VOR fixed daily dose	1 week 5 mg	1 week 5 mg	NR	2 weeks 10 mg	1 week 10 mg	NR
	VOR flexible daily dose	51 weeks 2.5 mg, 5 mg, or 10 mg	51 weeks 2.5 mg, 5 mg, or 10 mg	2.5 mg, 5 mg, 10 mg, 15 mg, and 20 mg (duration NR)	50 weeks 5 mg, 10 mg, or 20 mg	51 weeks 15 mg or 20 mg	5 mg, 10 mg, 15 mg, and 20 mg (duration NR)
	Follow-up	4 weeks	4 weeks	NR	4 weeks	4 weeks	< 30 days
Outcomes	**Outcomes**	Harms MADRS HAM-D24 CGI-S SDS SF-36 C-SSRS	Harms MADRS HAM-D24 SDS CGI-S	Harms	Harms MADRS CGI-S	Harms MADRS SDS CGI-S	Harms MADRS CGI-S
	Publications	Alam et al. (2014)	Baldwin et al. (2012)	Baldwin et al. (2016)	Inoue (2018)	Jacobsen (2015)	Vieta (2017)

AE = adverse event; CGI-S = Clinical Global Impression Scale – Severity; C-SSRS = Columbia Suicide Severity Rating Scale; DB= double-blind; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; NR = not reported; RCT = randomized controlled trial; SDS = Sheehan Disability Scale; SF-36 = Short-Form (36) Health Survey; VOR = vortioxetine.

[a] Baldwin et al. (2016) and Vieta et al. (2017) included the same five extension studies. The Vieta et al. (2017) study only included patients who were previously treated with VOR, after excluding those treated with placebo, duloxetine, venlafaxine or VOR at subtherapeutic doses (e.g., 1 mg or 2.5 mg per day).

Source: Alam et al. (2014),[131] Baldwin et al. (2012)[132] and (2016)[133], Inoue et al. (2018),[41] Jacobsen et al. (2015),[134] and Vieta et al. (2017).[135]

All open-label study participants had previously completed a double-blind, placebo-controlled trial evaluating the short-term (six to eight weeks of treatment) efficacy and safety of VOR in adults with major depressive disorder (MDD), regardless of the treatment received in the feeder study. Both the Baldwin et al. study (2012) and the Inoue et al. study enrolled patients who had completed one single preceding RCT, while the others enrolled patients from multiple RCTs. The Baldwin et al. (2016) study and Vieta et al. study were pooled analyses of the same five extension studies (Table 58). The Baldwin et al. (2016) study included the 2.5 mg dose for vortioxetine (not a Health Canada–approved dose) and did not report the therapeutic effect of vortioxetine in the study population. The Vieta et al. study included the Health Canada–approved doses (5 mg to 20 mg) and reported both long-term safety and clinical benefit of vortioxetine in patients with MDD. Results of the Vieta et al. study are presented in this review.

Table 59 summarizes the disposition of study participants for the five open-label extension studies. Among these studies, the proportions of patients who completed the 52-week extended treatment with vortioxetine ranged from 50% to 73%. Approximately 27% to 50% of the patients withdrew from treatment. The main reasons for early withdrawal were consent withdrawal, adverse events, and lost to follow-up.

Table 59: Patient Disposition – Open-Label Extension Studies

	Alam et al. (2014)	Baldwin et al. (2012)	Inoue et al. (2018)	Jacobsen et al. (2015)	Vieta et al. (2017)
Enrolled, N	836	535	120	1,075	1,231
Completed, n (%)	524 (62.8)[a]	328 (61.3)	88 (73.3)	538 (50.1)	706 (57)
Early withdrawal, n (%)	310 (37.2)	207 (38.7)	32 (26.7)	537 (50.0)	525 (43)
Reasons for withdrawal, N					
Adverse event	49 (5.9)	42 (7.9)	12 (10)	115 (21.4)	97 (7.9)
Lack of efficacy	35 (4.2)	35 (6.5)	2 (1.7)	NR	68 (5.5)
Withdrew consent	81 (9.7)	61 (11.4)	10 (8.3)	143 (26.4)	145 (11.8)
Lost to follow-up	59 (7.1)	15 (2.8)	2 (1.7)	112 (20.9)	88 (7.1)
Protocol violation	19 (2.3)	6 (1.1)	NR	NR	26 (2.1)
Non-compliance	28 (3.4)	16 (3.0)	3 (2.5)	NR	43 (3.5)
Other	39 (4.7)	32 (6.0)	3 (2.5)	NR	58 (4.7)
Analysis Sets					
Enrolled but not treated, N (%)	2 (0.2)	0	1 (0.8)	2 (0.2)	NR
Safety set, n (%)	834 (99.8)	535 (100)	119 (99.2)	1073 (99.8)	1,231 (100)
Efficacy set, n (%)	834 (99.8)	535 (100)	119 (99.2)	NR	1,230 (99.9)

NR = not reported.

[a] Two patients did not receive allocated intervention and were excluded from analysis.

Source: Alam et al. (2014),[131] Baldwin et al. (2012),[132] Inoue et al. (2018),[41] Jacobsen et al. (2015),[134] and Vieta et al. (2017).[135]

The demographics and baseline characteristics of patients in the extension studies are supplied in Table 60. The demographics of open-label study patients were similar across the studies, except for the Japanese study by Inoue et al., in which patients were relatively younger, and a higher proportion of male patients was observed compared with the other extension studies. The baseline scores for the main efficacy outcome measures, the Montgomery–Åsberg Depression Rating Scale (MADRS), and the 24-item Hamilton Depression Rating Scale (HAM-D24) were lower in the extension studies than in their respective original short-term RCTs.

Table 60: Summary of Demographics and Baseline Characteristics – Extension Studies

	Alam et al. (2014) (N = 836)	Baldwin et al. (2012) (N = 535)	Inoue et al. (2018) (N = 119)	Jacobsen et al. (2015) (N = 1,075)	Vieta et al. (2017) (N = 1,231)
Age, years, mean (SD)	45.5 (12.8)	46 (19-76)	39.5 (11.2)	44.5 (12.1)	NR
Male, n (%)	310 (37.1)	169 (31.6)	67 (56.3)	285 (26.5)	
Baseline Scores, Original Double-Blind RCT(s)					
Mean baseline MADRS total score (SD)	NR	NR	32.4 (4.7)	32.8 (4.3)	32.2 (4.2)
Mean baseline HAM-D24 score (SD)	31.2 (5.5)	NR	NR	NR	NR
Mean baseline CGI-S score (SD)	4.7 (0.7)	NR	4.5 (0.7)	4.6 (0.6)	4.7 (0.7)
Baseline Scores, Open-Label Extension Study					
Mean baseline MADRS total score (SD)	NR	13.5 (8.7)	14.8 (7.5)	19.9 (10.7)	17.1 (10.2)
Mean baseline HAM-D24 score (SD)	17.6 (9.4)	13.4 (8.7)	NR	NR	NR
Mean baseline CGI-S score (SD)	3.2 (1.3)	2.7 (1.2)	2.8 (0.8)	3.3 (1.2)	3.1 (1.2)

CGI-S = Clinical Global Impression Scale – Severity; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; NR = not reported; RCT = randomized controlled trial; SD = standard deviation.

Source: Alam et al. (2014),[131] Baldwin et al. (2012),[132] Inoue et al. (2018),[41] Jacobsen et al. (2015),[134] and Vieta et al. (2017).[135]

Results

In the extension studies, safety and efficacy data were summarized using descriptive statistics. Mean MADRS total score, HAM-D24 total score, Clinical Global Impression Scale – Severity (CGI-S) total score, and SDS score were calculated where applicable. In the study by Vieta et al., patient-level data from five long-term, open-label, flexible-dose extension studies were pooled, and the mean MADRS total scores and CGI-S scores were calculated.

The main efficacy results after 52 weeks of open-label vortioxetine treatment are presented in Table 61. For all extension studies, patients demonstrated a decrease from both double-blind and open-label baseline MADRS scores at week 52 (MADRS data were not available in the Alam et al. study); this indicated an improvement in depressive symptoms that was initiated during the preceding RCTs and continued through the one-year extension studies. Likewise, decreased HAM-D24 scores from the double-blind and open-label baseline scores were observed for the Alam et al. study and the Baldwin et al. (2012) study. All extension studies presented results for CGI-S scores, and the improvements achieved during the double-blind phase of the original RCTs were maintained when patients were continued on or switched to vortioxetine, with scores decreasing further from the open-label baseline values regardless of the original double-blind assigned treatment.

Studies by Baldwin et al. (2012), Inuoue et al., and Jacobsen et al. used the Sheehan Disability Scale as a measure of patient disability and reported a decrease in total scores at week 52 relative to both double-blind and open-label baseline scores, indicating a reduction in psychiatric impairment.

Table 61: Summary of Efficacy Outcomes at Week 52

	Alam et al. (N = 834)	Baldwin et al. (2012) (N = 535)	Inoue et al. (N = 119)	Jacobsen et al. (N = 1,073)	Vieta et al. (N = 1,230)
MADRS Total Score					
DBB, mean (SD)	NR	31.9 (4.1) N = 535	32.4 (4.7) N = 366	32.8 (4.3) N = 1063	32.2 (4.2)
OLB, mean (SD)		13.5 (8.7) N = 535	14.8 (7.5) N = 119	19.9 (10.7) N = 1063	17.1 (10.2)
Week 52, mean (SD)		5.5 (6.0) N = 329	4.9 (SD NR)	9.0 (9.0) N = 534	7.6 (8.2)
HAM-D24 Total Score					
DBB, mean (SD)	31.2 (5.5) N = 829	30.3 (5.5) N = 535	NR	NR	NR
OLB, mean (SD)	17.6 (9.4) N = 829	13.4 (8.7) N = 353			
Week 52, mean (SD)	8.2 (7.1) N = 522	6.2 (7.4) N = 342			
CGI-S Score					
DBB, mean (SD)	4.7 (0.7) N = 818	4.8 (0.7)	4.5 (0.7) N = 366	4.6 (0.6) N = 1032	4.7 (0.7)
OLB, mean (SD)	3.2 (1.3) N = 818	2.7 (1.2)	2.8 (0.8) N = 119	3.3 (1.2) N = 1032	3.1 (1.2)
Week 52, mean (SD)	2.0 (1.0) N = 527	1.7 (1.0)	Decreased from DBB and OLB (data graphically reported)	2.0 (1.1) N = 549	1.9 (1.1)
SDS Total Scores					
DBB, mean (SD)	NR	20.0 (5.9) N = 456	15.4 (5.8) N = 366	Data graphically reported	NR
OLB, mean (SD)		12.4 (8.1) N = 456	Decreased from DBB (data graphically reported)	11.3 (7.7) N = 694	
Week 52, mean (SD)		6.3 (6.8) N = 292	Decreased from DBB and OLB (data graphically reported)	5.7 (6.4) N = 381	

CGI-S = Clinical Global Impression Scale – Severity of Illness; DBB = double-blind baseline; HAM-D24 = 24-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; NR = not reported; OLB = open-label baseline; SD = standard deviation; SDS = Sheehan Disability Scale.

Source: Alam et al. (2014),[131] Baldwin et al. (2012),[132] Inoue et al. (2018),[41] Jacobsen et al. (2015),[134] and Vieta et al. (2017).[135]

A summary of the main safety results from the extension studies is presented in Table 62. No new safety signals were reported in any of these studies.

The proportion of patients experiencing at least one treatment-emergent adverse event during the 52-week treatment with VOR ranged from 71% to 87% across the five extension studies. The most common adverse events included nausea (15% to 24%), headache (11% to 15%), nasopharyngitis (6% to 40%) and increased weight (4% to 8%). The risk of suicide behaviours ranged from 0.6% to 10%. In general, most of the reported treatment-emergent adverse events were considered mild or moderate in intensity by the investigator.

Rates of serious adverse events ranged from 2.7% to 3.5% among the five extension studies. Suicidal ideation and behaviour were reported as a serious adverse event in most of the studies. Columbia Suicide Severity Rating Scale (C-SSRS) assessments were used to identify suicide attempts or suicidal behaviour in Studies by Alam et al., Inoue et al. or Jacobsen et al. The C-SSRS total scores were not provided in the study. The number of positive reports for suicidal ideation and attempts were generally low; however, this risk was higher in the Alam et al. study (10%) compared with other extension studies. No suicide-related adverse events were reported for the Vieta et al. study.

No deaths were reported in the extension studies, except for Baldwin et al. (2012),[132] in which two patients died during 52 weeks of treatment with vortioxetine. One death was related to a motorcycle accident, and the other was due to multiple traumas resulting from falling from a balcony. None of the deaths were considered to be related to the study drug by the investigator.

Rates of withdrawals due to adverse events ranged from 6% to 11% in the five extension studies. Nausea was the most common reason for study drug discontinuation in most of the studies (1% to 2%).

Table 62: Summary of Treatment Duration and Harms During Open-Label Extension Studies (Safety Set)

	Alam et al. (N = 834)	Baldwin et al. (2012) (N = 535)	Inoue et al. (2018) (N = 119)	Jacobsen et al. (2015) (N = 1,073)	Vieta et al. (2017) (N = 1,231)
Mean duration of study drug exposure (SD)	VOR 2.5 mg: 22.9 weeks (NR) VOR 5 mg: 15.5 weeks (NR) VOR 10 mg: 31.1 weeks (NR)	268 days (NR)	NR	35.1 weeks (19.6)	NR
Patient-years of exposure to study drug	NR	393	NR	NR	NR
TEAEs, n (%)	589 (70.6)	389 (72.7)	103 (86.6)	854 (79.6)	895 (72.7)
Nausea, n (%)	127 (15.2)	106 (19.8)	25 (21.0)	258 (24.0)	204 (16.6)
Headache, n (%)	103 (12.4)	82 (15.3)	13 (10.9)	136 (12.7)	159 (12.9)
Nasopharyngitis, n (%)	82 (9.8)	56 (10.5)	48 (40.3)	68 (6.3)	116 (9.4)
Weight increased, n (%)	36 (4.3)	31 (5.8)	10 (8.4)	65 (6.1)	65 (5.3)
Suicidal ideation or suicide attempt	83 (10.0)	6 (1.1)	5 (4.2)	6 (0.6)	NR

	Alam et al. (N = 834)	Baldwin et al. (2012) (N = 535)	Inoue et al. (2018) (N = 119)	Jacobsen et al. (2015) (N = 1,073)	Vieta et al. (2017) (N = 1,231)
SAEs, n (%)	29 (3.5)	18 (3.4)	4 (3.4)	29 (2.7)	34 (2.8)
	Suicide ideation, suicide attempt, left hemispheric ischemic stroke, depression, major depression, supraventricular tachycardia, and paroxysmal tachycardia.	Suicidal behaviours or self-harm, worsening of depression.	Suicidal ideation	Acute cholecystitis, breast cancer, suicide attempt.	NR
WDAEs, n (%)	50 (6.0)	7 (10)	11 (9.2)	117 (10.9)	96 (7.8)
Deaths, n (%)	0	2 (0.4)	0	0	0
		Motorcycle accident, multiple trauma due to fall from balcony			

NR = not reported; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event; VOR = vortioxetine; WDAE = withdrawal due to adverse event.

Source: Alam et al. (2014),[131] Baldwin et al. (2012),[132] Inoue et al. (2018),[41] Jacobsen et al. (2015),[134] and Vieta et al. (2017).[135]

Critical Appraisal

The longer-term treatment duration (e.g., one year) in studies performed by Alam et al., Baldwin et al. (2012), Inoue et al., Jacobsen et al. and Vieta et al. is generally more reflective of the management of MDD in clinical practice, compared to the six- to eight-week treatment duration in the RCTs. However, the main limitations associated with these studies arise from their open-label study design, which lacks randomization, blinding, and comparators. The absence of a comparator group makes it challenging to interpret small changes from baseline. Although the open-label baseline patient demographic characteristics were generally similar to those in their respective lead-in RCTs, extension studies typically represent a selective population of patients who have responded and tolerated treatment well during the initial RCTs. The proportions of patients who continued on from the lead-in RCTs ranged widely among the extension studies. For example, in the study by Inoue et al., 366 patients were randomized in the original short-term RCT, but less than one-third of them were enrolled in the extension phase.

All extension studies had substantial withdrawal rates, which ranged from 27% in the Inoue et al. study to 50% in Jacobsen et al., which led to a further reduced patient population that remained on therapy until week 52 for inclusion in the efficacy data reporting. The generalizability of the results is limited by these high withdrawal rates, as patients who do not tolerate or respond well to the study drug tend to withdraw from a study, resulting in a selective population of patients with favourable outcomes remaining for inclusion in the efficacy and safety analyses. This may overestimate the effectiveness of study treatment.

Conclusion

The results of the five extension studies (Alam et al., Baldwin et al. [2012], Inoue et al., Jacobsen et al., and Vieta et al.) suggested that flexible dosing of vortioxetine for 52 weeks was generally safe and tolerated by patients with MDD. Nausea was a common adverse event with treatment. The risk of suicidal behaviours was low. The efficacy results reported in the original RCTs appeared to be maintained throughout an additional 52 weeks of vortioxetine treatment, albeit in select patients who were enrolled and able to remain on treatment. Due to the non-randomized and uncontrolled open-label study design, as well as potential selection bias, there is a high degree of uncertainty with respect to the findings of the extension studies, in particular for the efficacy results.

Appendix 8: Summary of Other Studies

In addition to the randomized controlled trials (RCTs) and their extension studies evaluating the short-term and long-term efficacy and safety of vortioxetine in adults with major depressive disorder (MDD), the manufacturer submitted five non-randomized trials examining the clinical effectiveness or related health care resource utilization in real-world settings.

Table 63: Summary of Trial Characteristics of Manufacturer-Submitted Non-Randomized Trials

Studies	Study design	Population	Intervention and comparator	Primary outcome measures	Authors' conclusions
Cao (2019)	Post hoc analysis of a phase II/III, open-label study 8 weeks	Patients with moderate-to-severe depressive symptoms. Key exclusion criteria: current alcohol or substance use disorder; major psychiatric disorders other than MDD; at high suicide risk.	MDD patients: VOR 10 mg to 20 mg per day + assessment using a THINC-it tool (N = 100) Healthy control: THINC-it tool (N = 50)	Change in anhedonia	VOR significantly improved anhedonia in SHAPS and MADRS anhedonia factor scores. Improvements in the SHAPS and the MADRS anhedonia factor correlated with improvements in general function and quality of life.
Chokka (2019)	Phase IV, open-label, single-arm 52 weeks	Working patients with MDD, treatment-naive, or had inadequate response to previous antidepressants Key exclusion criteria: major psychiatric disorders other than MDD; resistant to 2 adequate antidepressant treatments of ≥ 6 weeks duration.	VOR 10 mg to 20 mg per day (N = 199) No comparator	Correlation between changes in PDQ-D20 and changes in WLQ at week 12	Improvements in cognitive dysfunction were significantly associated with improvements in workplace productivity in patients with MDD at week 12 and week 52.
McCue (2018)	Phase IV, open-label, single-arm 12 weeks	Adult patients with MDD and previously treated with any antidepressant but switched to VOR due to inadequate response or tolerability issues.	VOR 10 mg to 20 mg per day (N = 123) No comparator	% of patients achieved pre-identified goals at week 12	Significant proportion of patients treated with VOR reached their personalized treatment goals at week 12.

Studies	Study design	Population	Intervention and comparator	Primary outcome measures	Authors' conclusions
RWE research report (2019)	Observational study (pre- post-intervention)	Adult patients with MDD and had ≥ 1 medication dispensation record for VOR in Alberta, between October 2014 and December 2016.	≥ 1 dose of VOR	Health care resource utilization related to VOR	% of patients with all-cause or mental health-related hospitalizations was statistically significantly lower during the post-VOR period compared with pre-VOR period.
RWE feasibility report (2018)				Treatment patterns Health care resource utilization	% of patients with all-cause or mental health-related emergency department visits was statistically significantly lower during the post-VOR period compared with pre-VOR period. % of patients with all-cause or mental health-related physician visits was similar for pre-VOR and post-VOR periods.

MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; PDQ-D20 = 20-item Perceived Deficits Questionnaire; RWE = real-world evidence; SHAPS = Snaith-Hamilton Pleasure Scale; VOR = vortioxetine; WLQ = Work Limitations Questionnaire.

Source: Cao (2019),[136] Chokka (2019),[137,138] McCue (2018),[139] RWE research report (2019),[140] and RWE feasibility report (2018).[141]

The purpose of the Cao study was to evaluate the sensitivity of the THINC-integrated tool (THINC-it) in MDD patients with moderate-to-severe depressive symptoms.[136] This was a post hoc analysis of a Canadian study (NCT03053362), in which patients with MDD received daily vortioxetine 10 mg to 20 mg plus the THINC-it tool for eight weeks (n = 100), and healthy controls received the THINC-it tool only (n = 50). The THINC-it tool was a computerized cognitive test application administering the following cognitive test components: Digit Symbol Substitution Test, the Choice Reaction Time task, the one-back working memory tool, the Trail Making Test Part B, and the five-item Perceived Deficits Questionnaire Depression. This tool covers the dimensions of executive function, learning and memory, attention, and processing speed, all of which have been shown to be impaired by MDD. The authors of this tool indicated that it is a valid and sensitive tool for detecting cognitive dysfunction in patients with MDD.[142] The primary outcome measure of the post hoc analysis was change in anhedonia in patients with MDD, measured by the change from baseline to end point in the Snaith-Hamilton Pleasure Scale total score and the Montgomery–Åsberg Depression Rating Scale (MADRS) anhedonia factor. The results showed that improvements both correlated with improvements in general function (e.g., Sheehan Disability Scale) and health-related quality of life (e.g., WHO-5 Well-Being Index) ($P < 0.0001$).

The Chokka study was a phase IV, open-label, single-arm study.[137,138] In total, 199 working adult patients (living in Canada) diagnosed with MDD, either treatment-naive or switched from a previous antidepressant due to inadequate response, were treated with vortioxetine 10 mg to 20 mg daily. Results were assessed over 52 weeks. The primary end point in this study was the correlation between changes in patient-reported cognitive symptoms (measured with the 20-item Perceived Deficits Questionnaire [PDQ-D20]) and changes in

work productivity loss (measured with Work Limitations Questionnaire [WLQ]) at week 12. This was also assessed at week 52. Additional outcome measures included depression severity, cognitive performance, patient-reported functioning, and safety. At week 12, statistically highly significant association between the changes in PDQ-D20 and WLQ productivity loss scores assessed by the partial correlation coefficient was observed, after being adjusted for age, sex, baseline PDQ-D20, baseline WLQ productivity loss, disease duration, and disease severity ($r = 0.61$, $P < 0.001$), and this association between PDQ-D20 and WLQ productivity loss scores persisted at week 52 ($r = 0.73$; $P < 0.001$). Safety analysis indicated that long-term treatment with vortioxetine was well tolerated. The most common treatment-emergent adverse events were nausea (29.2% of treated patients), headache (11.9%), insomnia (9.1%), nasopharyngitis (6.8%), anxiety (6.4%), and dizziness (5.9%). The authors concluded that the study results demonstrated the long-term (up to week 52) benefits of vortioxetine treatment in working patients with MDD and emphasized the strong association between cognitive symptoms and functioning in real-world setting.

McCue and colleagues evaluated the real-world effectiveness of 12 weeks of vortioxetine 10 mg to 20 mg per day on patient goal achievement, measured by a Goal Attainment Scale Adapted for Depression score of at least 50.[139] Eligible patients were those with MDD and previously treated with any antidepressant but switched to vortioxetine due to inadequate response or tolerability issues. All patients received vortioxetine 10 mg to 20 mg per day. Results of the interim analysis of the first 60 patients suggested that 62.3% of patients achieved a score of 50 of greater, indicating successful goal attainment. Data are available from an abstract only; a full report of this study was not available at the time of this review.

The manufacturer submitted two reports concerning patients diagnosed with MDD or dysthymic disorder in a real-world setting. The first one is a feasibility assessment of patients receiving vortioxetine, where treatment patterns of vortioxetine and health care resource utilization in Alberta were described.[141] Multiple databases were used to retrieve data, including the Discharge Abstract Database, National Ambulatory Care Reporting System Database, Physician Claim Database, and Pharmaceutical Information Network Database. The inclusion criteria of this study were adult patients who had at least one medication dispensation record for vortioxetine between October 28, 2014, and December 28, 2016. The number of patients with MDD and/or dysthymic disorder in this study was 623 (MDD: 372 patients; dysthymic disorder: 313). The second report is a retrospective, observational study that describes the health care resource utilization in the same patient population as the first study.[140] Results from both reports indicate that the proportion of patients with hospitalizations and emergency department visits and physician visits in the six-month period before and the six-month period after initiation of vortioxetine therapy were described. The results suggested that the proportion of patients with depression using the resource intensive medical services of inpatient admissions and emergency department visits in Alberta was lower following vortioxetine initiation compared to before (inpatient admission: 24.6% before versus 15.7% after; $P < 0.001$; emergency department visits: 40.0% before versus 33.7% after; $P = 0.006$). There were no significant pre-post differences in the proportion of patients with physician visits (97.8% before versus 97.3% after).

Critical Appraisal

These non-randomized studies were provided as supportive evidence for the clinical effectiveness and safety of vortioxetine therapy in patients with MDD in real-world settings; two of them reported health care resource utilization information. However, they are subject to limitations due to the nature of their study design. First, the lack of a control group or active comparator means conclusions regarding comparative effectiveness cannot be made. Second, an open-label study design may result in bias with subjective outcomes. Third, in the pre-post comparison in the two Alberta real-world evidence reports that evaluated health care resource utilization related to treatment with vortioxetine, it is unclear whether practice patterns (e.g., prescription of concomitant medications, treatment modalities, and routine for follow-up visits) remained the same before and after the approval of vortioxetine in Alberta. Fourth, when using an existing database, some important patient characteristics may not be available, such as over-the-counter medications and treatment adherence. As a result of these limitations, detailed results of these studies are not presented in this Appendix and no concrete conclusions have been made.

Appendix 9: Summary of Indirect Comparisons

Introduction

Given the limited availability of head-to-head studies comparing vortioxetine with other antidepressants approved for use in Canada, the objective of this Appendix was to summarize and critically appraise the indirect treatment comparisons (ITCs) submitted by the manufacturer and identified in the literature.

The manufacturer submitted six published ITCs,[8,72,74,143-145] as well as a supplemental analysis of the Cipriani et al.[8] ITC that was prepared for Lundbeck.[7] Two additional ITCs were identified in the literature search conducted by CADTH.[73,146] Two ITCs[73,146] were excluded from this summary because they were less comprehensive than the ITC by Cipriani et al.[8] One report submitted by the manufacturer was a pairwise meta-analysis and not an ITC.[145] Five ITCs were included in this Appendix, although the summary focuses on the ITC by Cipriani et al. and the manufacturer-submitted supplemental analysis, as these data were used to inform the manufacturer-submitted pharmacoeconomic analysis.[7,8,72-74]

Summary of ITC by Cipriani et al. and Manufacturer-Submitted Reanalysis

Methods

Study Eligibility and Selection Process

Literature Search

Cipriani et al.[8] conducted a systematic review of several databases, including: "Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, AMED, the UK National Research Register, and PSYNDEX." The time frame of the search was from inception of each database until January 8, 2016, with no language restriction. In addition to the database search, they also conducted an expanded search of "published, unpublished, and ongoing randomized controlled trials (RCTs) in international trial registers, websites of drug approval agencies, and key scientific journals in the field." They also contacted drug manufacturers and study authors to request unpublished information including missing data from included studies, and unpublished pre- and post-market studies.

Table 64: Population, Interventions, Comparisons, Outcomes, and Study Design Criteria for Study Inclusion in Cipriani et al. (2018)

Criteria	Monotherapy
Population	Adults (≥ 18 years old) with a primary diagnosis of major depressive disorder based on "standard operationalized diagnostic criteria (Feighner criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-5, and ICD-10)"
Interventions	Any of the following active antidepressants as oral monotherapy: • Second-generation antidepressants with regulatory approval in the US, Europe, or Japan: agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine, vilazodone, and vortioxetine • Tricyclic antidepressants (included in World Health Organization List of Essential Medicines): amitriptyline and clomipramine

Criteria	Monotherapy
	• Trazodone and nefazodone
Comparators	Any active antidepressant monotherapy or placebo
Outcomes	**Primary Efficacy Outcome:** "response rate measured by the total number of patients who had a reduction of ≥ 50% of the total score on a standardized observer-rating scale for depression" **Primary Acceptability Outcome:** "treatment discontinuation measured by the proportion of patients who withdrew for any reason" **Secondary outcomes:** 1. Efficacy – defined as a continuous outcome from Hamilton or Montgomery–Åsberg rating scales 2. Remission – defined as the proportion of patients with remission of depressive symptoms 3. Tolerability – defined as the proportion of patients who discontinue due to an adverse event Outcomes were measured at 8 weeks if possible (range 4 to 12 weeks)
Study design and factors	• Double-blind RCTs • Included trials that allowed rescue medication (usually benzodiazepines or sedative-hypnotic agents) for both the intervention and comparison groups • Only included doses within therapeutic range • Excluded quasi-randomized trials, crossover trials, and cluster randomized trials • Excluded trials that were incomplete • Excluded trials with "20% or more of participants with bipolar disorder, psychotic depression, or treatment-resistant depression; or patients with a serious concomitant medical illness"
Language	No language restriction
Search period	Database inception to January 8, 2016

DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third edition; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third edition, Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth edition; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th edition; RCT = randomized controlled trial.

Source: Cipriani et al. (2018).[8]

Eligibility Criteria and Study Selection

Studies were eligible for inclusion that were double-blind RCTs and enrolled patients with a diagnosis of major depressive disorder (Table 64). The diagnosis had to be according to standard diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders, International Statistical Classification of Diseases and Related Health Problems, 10th edition, or Feighner criteria. Studies were included if they allowed rescue medications to all randomized groups. Data were only included for groups receiving medications within established therapeutic ranges. Studies were excluded if they were quasi-randomized trials, were incomplete or "included 20% or more of participants with bipolar disorder, psychotic depression, or treatment-resistant depression; or patients with a serious concomitant medical illness."

Data Extraction

Six pairs of investigators independently selected the studies, reviewed materials, extracted the relevant information, and assessed the risk of bias. Discrepancies "were resolved by consensus and arbitration by a panel of investigators within the review team."

Comparators

Comparators of interest were placebo and other currently available treatments:

1. Agomelatine[a]
2. Amitriptyline
3. Bupropion
4. Citalopram
5. Clomipramine
6. Desvenlafaxine
7. Duloxetine
8. Escitalopram
9. Fluoxetine
10. Fluvoxamine
11. Levomilnacipran
12. Milnaciprana
13. Mirtazapine
14. Nefazodonea
15. Paroxetine
16. Reboxetinea
17. Sertraline
18. Trazodone
19. Venlafaxine
20. Vilazodone
21. Vortioxetine

[a] Not available in Canada.

Outcomes

The primary outcomes were efficacy and acceptability. Efficacy was defined as "the total number of patients who had a reduction of at least 50% of the total score on a standardized observer-rating scale for depression." Acceptability was defined as the proportion of patients discontinuing treatment for any reason. The authors also reported on several secondary outcomes, including changes to depression score from baseline, remission rate, and discontinuation due to adverse events. When studies reported more than one standardized rating scale, a predefined hierarchy, based on psychometric properties and consistency of use across included trials, was used. This hierarchy placed the Hamilton and Montgomery–Åsberg Depression rating scales at the top of the hierarchy.[147] If the response rate was not reported, the response rate was calculated using validated imputation methods. Outcomes were reported at eight weeks when possible. If information at eight weeks was not available, data ranging between four and 12 weeks was used, with whatever data were closest to eight weeks.

Quality Assessment of Included Studies

The general risk of bias in included studies was assessed using the Cochrane risk of bias tool. The study authors also assessed the certainty of evidence contributing to estimates with the Grading of Recommendations Assessment, Development and Evaluation framework.[148] The risk of bias was reported for each component, including sequence generation, allocation concealment, blinding of participants, blinding of therapist, blinding of assessors, selective reporting, and attrition bias. Risk of bias was categorized as low, moderate, and high using the following definition:

> Studies were classified as having low risk of bias if none of the domains above was rated as high risk of bias and three or less were rated as unclear risk; moderate if one was rated as high risk of bias or none was rated as high risk of bias but four or more were rated as unclear risk, and all other cases were assumed to pertain to high risk of bias.

This information was planned to be used for sensitivity analyses.

Analytical Methods

Cipriani et al. conducted both pairwise and network meta-analysis (NMA). They reported estimated summary odds ratios (ORs) for dichotomous outcomes and standardized mean differences (SMDs) for continuous outcomes. Ranking was reported using the surface under the cumulative ranking curve (SUCRA) and the mean ranks. The NMAs used group-level data and a random-effects model. Heterogeneity was assessed by comparing "the posterior distribution of the estimated heterogeneity variance with its predictive distribution." Transitivity assumption was assessed by comparing the distribution of variables that could act as potential effect modifiers. Effect modifiers included variables related to year of publication, sponsorship, dosing schedule, probability of receiving placebo, baseline disease severity, whether the study was multi-centre, dose ranges, and unpublished data. Funnel plots were also used to assess if results differ based on the precision of included trials. Lastly, they evaluated consistency in the network "using the design-by-treatment test and by separating direct evidence from indirect evidence."

For the two primary outcomes, "subgroup analyses and network meta-regression using study year, sponsorship, depressive severity at baseline, dosing schedule, study precision (i.e., small study effect), and novelty effect" were conducted to assess the robustness of results. The NMAs used "binomial likelihood for dichotomous outcomes, uninformative prior distributions for the treatment effects, and a minimally informative prior distribution for the common heterogeneity SD [standard deviation]." Models assumed uninformative priors for all meta-regression coefficients, and model convergence was evaluated using the Brooks-Gelman-Rubin diagnostic and the visual inspection of three chains. The analysis was completed using OpenBUGS (version 3.2.2) and replicated in R (version 3.4.0). "Statistical evaluation of inconsistency and production of network graphs and result figures were done using the network and network graphs packages in Stata (version 14.2)." All code was shared as part of the protocol.

The primary analysis included 474 placebo and active-controlled trials. A secondary analysis was conducted based on head-to-head studies only (194 trials with at least two active-treatment groups at licensed doses).

Manufacturer-Submitted ITC

The manufacturer-submitted ITC further expanded on the analysis conducted by Cipriani et al. to explore if adjusting for dose would affect results. The ITC included all studies identified by the Cipriani et al. systematic review and used similar methods to conduct the analysis. First they replicated the Cipriani et al. analysis to ensure consistency of the results, and then they conducted an analysis that was stratified by dose. All drugs were stratified into two distinct categories: "standard dose or above" and "lower than standard dose" based on WHO defined daily doses. [redacted]
Outcomes were defined using the same definitions as the original study. NMA outputs were the median values from all iterations along with their 95% credible intervals (CrI). These median values were ORs for dichotomous outcomes and SMDs for continuous outcomes.

Results of ITC by Cipriani et al.

The systematic review by Cipriani et al. identified a total of 28,552 unique publications. Overall, 522 trials met the criteria for inclusion. All of the included trials were randomized, double-blind, parallel-group design clinical trials. They included studies conducted from 1979 to 2016 across 21 different antidepressants and placebo. Of the trials, 304 (58%) were placebo-controlled. The majority (83%) were multi-centre studies, with 48% recruiting patients from North America. Overall, "46 (9%) of 522 trials were rated as high risk of bias, 380 (73%) trials as moderate, and 96 (18%) as low."

The 522 trials included a total of 116,447 participants; 87,052 patients were randomized to active treatment, and 29,425 were randomly assigned to placebo. The average study size was 224 patients with a median study duration of eight weeks (interquartile range: 6-8) (Table 65). The mean patient age was 44 years (standard deviation [SD] 9) and 62.3% of patients were women. A total of 464 (89%) studies evaluated baseline depression with the 17-item Hamilton Depression Rating Scale, and the mean baseline score was 25.7 (3.97), indicating moderate-to-severe depression.

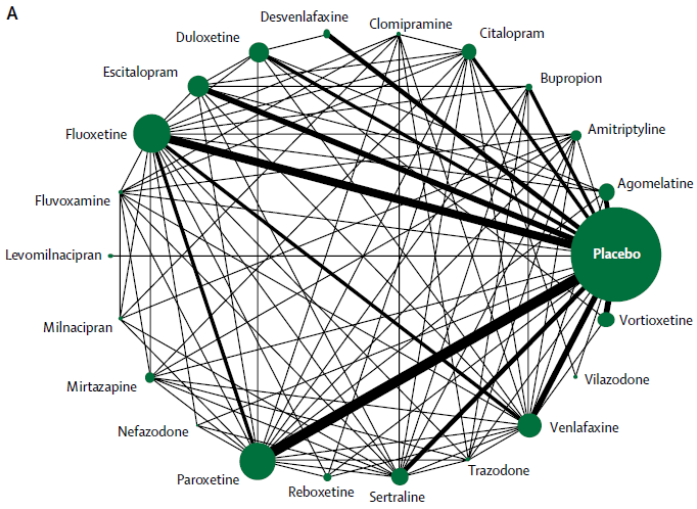
Table 65: Summary of Studies Included and Baseline Characteristics

Characteristics	
Number of studies	522
Total number of patients	87,052
Average number of patients per study (SD)	224 (186)
Total number assigned to placebo	29,425
Median duration of studies, weeks (IQR)	8 (6-8)
Multi-centre studies	391 (83%)
Proportion outpatient	335 (77%)
Industry funding	409 (78%)
Unpublished information retrieved	274 (52%)
Average age, years (SD)	44 (9)
Proportion female	62.3%

IQR = interquartile range; SD = standard deviation.

Source: Cipriani et al. (2018).[8]

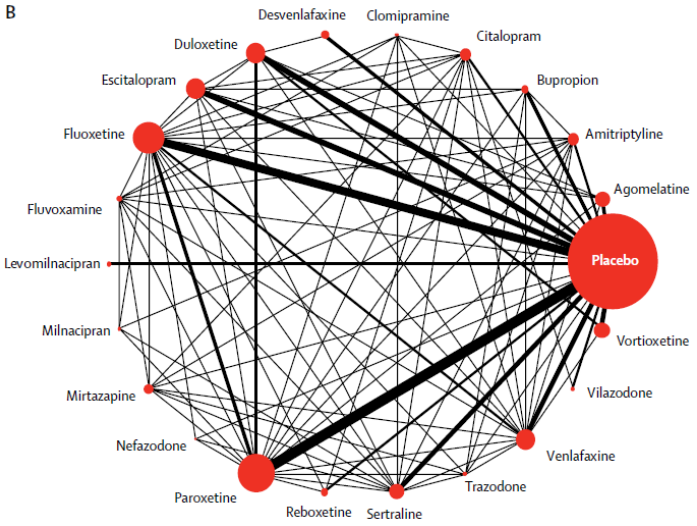
Figure 19: Evidence Network for Primary Outcomes of Efficacy (Response)



Note: Included 432 randomized controlled trials and 102,443 patients.

Reprinted from Lancet, Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. 2018 Apr 7;391(10128):1357-1366. https://doi.org/10.1016/S0140-6736(17)32802-7. Creative Commons Attribution Licence 4.0. http://creativecommons.org/licenses/by/4.0

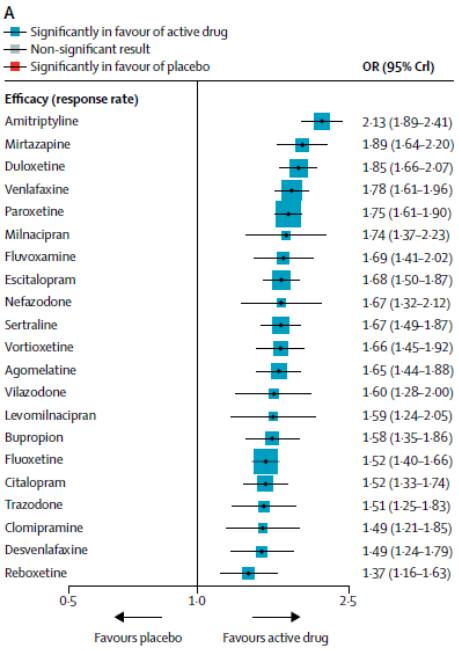
Figure 20: Evidence Network for Primary Outcome of Acceptability (All-Cause Withdrawals)



Note: Included 422 randomized controlled trials and 99,787 patients.

Reprinted from Lancet, Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. 2018 Apr 7;391(10128):1357-1366. https://doi.org/10.1016/S0140-6736(17)32802-7. Creative Commons Attribution Licence 4.0. http://creativecommons.org/licenses/by/4.0

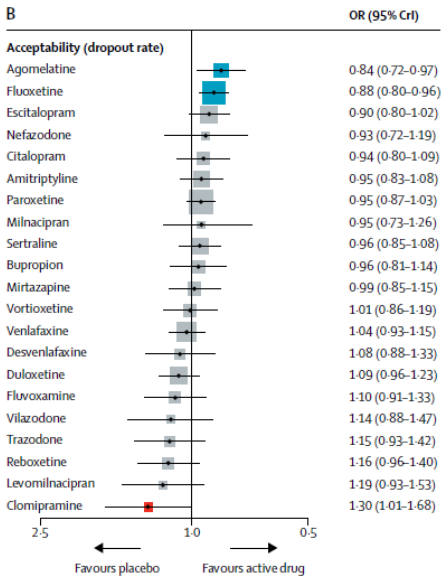
Figure 21: Forrest Plot of Primary Outcomes of Efficacy Compared to Placebo



CrI = credible interval.

Reprinted from Lancet, Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. 2018 Apr 7;391(10128):1357-1366. https://doi.org/10.1016/S0140-6736(17)32802-7. Creative Commons Attribution Licence 4.0. http://creativecommons.org/licenses/by/4.0

Figure 22: Forrest Plot of Primary Outcomes of Acceptability Compared to Placebo



CrI = credible interval.

Reprinted from Lancet, Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. 2018 Apr 7;391(10128):1357-1366. https://doi.org/10.1016/S0140-6736(17)32802-7. Creative Commons Attribution Licence 4.0. http://creativecommons.org/licenses/by/4.0

Figure 23: Indirect Treatment Comparison Results for Primary Outcomes of Efficacy and Acceptability (Head-to-Head Comparisons)

Efficacy (response rate) | Comparison | Acceptability (dropout rate)

Agom	**0·72* (0·55–0·92)**	0·80* (0·54–1·15)	0·89* (0·66–1·19)	**0·57* (0·42–0·77)**	**0·62† (0·47–0·82)**	0·97* (0·74–1·27)	0·85† (0·68–1·05)	**0·69† (0·51–0·97)**	0·79* (0·58–1·09)	0·81* (0·61–1·05)	0·70* (0·44–1·14)	0·81* (0·65–1·00)	**0·53* (0·36–0·80)**	0·86* (0·66–1·13)	**0·69* (0·48–0·98)**	**0·74† (0·58–0·92)**	1·24† (0·71–2·19)
0·96* (0·76–1·24)	**Amit**	1·10‡ (0·78–1·58)	1·23* (0·94–1·64)	0·79† (0·60–1·05)	0·87† (0·66–1·15)	**1·35* (1·05–1·74)**	1·18† (0·99–1·42)	0·97† (0·74–1·24)	1·10† (0·84–1·45)	1·12* (0·89–1·42)	0·98‡ (0·62–1·55)	1·12† (0·95–1·34)	0·74† (0·51–1·10)	1·20* (0·97–1·47)	0·96‡ (0·70–1·31)	1·02† (0·83–1·26)	**1·72† (1·00–3·05)**
0·87† (0·59–1·30)	0·91‡ (0·62–1·31)	**Bupr**	1·11‡ (0·76–1·67)	0·71† (0·49–1·07)	0·78† (0·53–1·18)	1·23* (0·84–1·80)	1·07‡ (0·76–1·50)	0·87‡ (0·59–1·30)	1·00‡ (0·66–1·49)	1·01† (0·70–1·47)	0·89‡ (0·51–1·54)	1·02‡ (0·73–1·43)	0·67† (0·42–1·08)	1·08‡ (0·75–1·56)	0·87‡ (0·57–1·30)	0·92‡ (0·66–1·30)	1·55† (0·85–2·94)
1·13* (0·88–1·47)	1·18* (0·93–1·49)	1·30† (0·88–1·93)	**Cita**	**0·64† (0·47–0·87)**	**0·70* (0·51–0·95)**	1·09* (0·85–1·42)	0·96* (0·76–1·21)	0·78* (0·57–1·06)	0·89* (0·64–1·23)	0·91† (0·68–1·21)	0·79‡ (0·49–1·32)	0·91* (0·71–1·17)	**0·60† (0·41–0·87)**	0·97‡ (0·74–1·25)	0·77* (0·53–1·13)	0·83† (0·64–1·07)	1·40† (0·78–2·48)
1·20* (0·91–1·59)	1·24† (0·98–1·58)	1·37† (0·93–2·04)	1·06* (0·82–1·38)	**Clom**	1·10† (0·80–1·51)	**1·71* (1·27–2·29)**	**1·49† (1·16–1·90)**	1·22† (0·88–1·67)	**1·40† (1·00–1·92)**	**1·41* (1·05–1·91)**	1·24‡ (0·76–2·00)	**1·42† (1·12–1·79)**	0·94‡ (0·62–1·41)	**1·51† (1·15–1·96)**	1·21† (0·83–1·73)	1·29† (0·99–1·67)	**2·20† (1·22–3·90)**
1·06* (0·82–1·37)	1·10† (0·84–1·42)	1·21† (0·81–1·81)	0·93* (0·71–1·22)	0·88† (0·66–1·18)	**Dulo**	**1·56* (1·19–2·01)**	**1·37* (1·06–1·73)**	1·12* (0·80–1·53)	1·28† (0·91–1·75)	1·30* (0·96–1·72)	1·13‡ (0·69–1·83)	**1·30* (1·02–1·63)**	0·86† (0·57–1·29)	**1·38† (1·04–1·80)**	1·10† (0·76–1·59)	1·18† (0·92–1·49)	**1·99† (1·13–3·52)**
0·90* (0·71–1·14)	0·93* (0·74–1·17)	1·03† (0·70–1·51)	**0·79* (0·65–0·97)**	**0·75* (0·58–0·97)**	0·85* (0·67–1·08)	**Esci**	0·87* (0·70–1·09)	**0·71* (0·53–0·96)**	0·81* (0·60–1·11)	0·83* (0·63–1·08)	0·72† (0·45–1·18)	0·83* (0·67–1·03)	**0·55* (0·37–0·81)**	0·88* (0·69–1·12)	0·70* (0·49–1·00)	**0·75* (0·60–0·94)**	1·27‡ (0·73–2·25)
1·20* (0·99–1·48)	**1·25† (1·06–1·48)**	1·38† (0·97–1·97)	1·06* (0·87–1·29)	1·00‡ (0·81–1·24)	1·14* (0·91–1·44)	**1·34* (1·11–1·61)**	**Fluo**	0·82* (0·64–1·04)	0·94* (0·72–1·20)	0·95* (0·77–1·16)	0·83† (0·54–1·30)	0·95* (0·83–1·09)	**0·63† (0·44–0·90)**	1·01† (0·84–1·21)	0·81* (0·60–1·09)	0·87† (0·74–1·01)	1·46† (0·85–2·53)
1·20* (0·91–1·61)	1·25† (0·99–1·59)	1·38† (0·93–2·07)	1·06* (0·82–1·39)	1·01‡ (0·76–1·32)	1·14† (0·85–1·54)	**1·34* (1·03–1·75)**	1·00* (0·80–1·25)	**Fluv**	1·14† (0·84–1·56)	1·16* (0·89–1·52)	1·01‡ (0·62–1·71)	1·16* (0·90–1·49)	0·77† (0·51–1·17)	1·23* (0·94–1·63)	0·99‡ (0·69–1·42)	1·06* (0·80–1·38)	**1·78‡ (1·00–3·24)**
1·07* (0·80–1·44)	1·11† (0·86–1·43)	1·23† (0·81–1·85)	0·94† (0·71–1·26)	0·89† (0·67–1·19)	1·01‡ (0·74–1·38)	1·19* (0·90–1·58)	0·89* (0·70–1·13)	0·89† (0·67–1·17)	**Miln**	1·02† (0·75–1·37)	0·88‡ (0·54–1·44)	1·02‡ (0·80–1·31)	0·67† (0·45–1·03)	1·08* (0·82–1·44)	0·86* (0·60–1·25)	0·93* (0·71–1·22)	1·56† (0·89–2·84)
0·93* (0·72–1·21)	0·97* (0·77–1·21)	1·07† (0·73–1·57)	0·82* (0·65–1·05)	0·78* (0·60–1·01)	0·88* (0·67–1·16)	1·04* (0·82–1·32)	**0·78* (0·64–0·94)**	**0·78* (0·60–0·99)**	0·87* (0·66–1·15)	**Mirt**	0·87† (0·55–1·41)	1·00* (0·82–1·23)	**0·66* (0·45–0·99)**	1·06* (0·84–1·35)	0·85* (0·62–1·18)	0·91* (0·73–1·13)	1·53† (0·89–2·72)
1·15† (0·76–1·76)	1·19† (0·80–1·78)	1·32‡ (0·80–2·20)	1·01‡ (0·67–1·54)	0·96‡ (0·63–1·45)	1·09‡ (0·71–1·68)	1·28* (0·86–1·94)	0·96‡ (0·66–1·40)	0·95‡ (0·63–1·46)	1·07‡ (0·70–1·67)	1·23* (0·82–1·86)	**Nefa**	1·15‡ (0·74–1·78)	0·75‡ (0·43–1·32)	1·23† (0·77–1·90)	0·98‡ (0·57–1·64)	1·04‡ (0·66–1·65)	1·76† (0·90–3·56)
1·01* (0·82–1·24)	1·05† (0·89–1·23)	1·16† (0·81–1·64)	0·89* (0·72–1·09)	0·84† (0·68–1·03)	0·95† (0·76–1·19)	1·12* (0·93–1·35)	**0·84* (0·73–0·95)**	0·84* (0·67–1·04)	0·94† (0·75–1·18)	1·08* (0·89–1·30)	0·88‡ (0·60–1·27)	**Paro**	**0·66† (0·46–0·94)**	1·06* (0·88–1·28)	0·85† (0·63–1·15)	0·91* (0·77–1·07)	1·53† (0·90–2·66)
1·44* (1·02–2·04)	**1·50† (1·07–2·07)**	**1·65† (1·05–2·60)**	1·27† (0·92–1·75)	1·20† (0·84–1·70)	1·36† (0·95–1·95)	**1·60* (1·14–2·23)**	1·20† (0·88–1·62)	1·20† (0·83–1·71)	1·35† (0·92–1·95)	**1·54* (1·09–2·17)**	1·25‡ (0·77–2·01)	**1·43† (1·05–1·94)**	**Rebo**	**1·61† (1·09–2·34)**	1·29† (0·81–2·01)	1·38† (0·94–1·99)	**2·32† (1·24–4·41)**
1·07* (0·85–1·37)	1·11* (0·92–1·35)	1·23† (0·85–1·79)	0·95† (0·76–1·18)	0·90† (0·71–1·13)	1·02‡ (0·79–1·32)	1·20* (0·97–1·48)	0·89‡ (0·76–1·05)	0·89† (0·70–1·13)	1·00† (0·77–1·30)	1·15* (0·93–1·43)	0·93‡ (0·63–1·37)	1·07* (0·90–1·26)	0·75† (0·54–1·04)	**Sert**	0·80* (0·58–1·11)	0·86* (0·70–1·05)	1·45† (0·84–2·54)
1·36* (0·99–1·87)	**1·41† (1·06–1·86)**	**1·56† (1·04–2·31)**	1·20* (0·88–1·63)	1·13† (0·83–1·54)	1·28† (0·92–1·79)	**1·51* (1·12–2·04)**	1·13† (0·87–1·46)	1·13† (0·82–1·55)	1·27* (0·91–1·76)	**1·45* (1·09–1·94)**	1·18‡ (0·75–1·84)	**1·35* (1·04–1·75)**	0·94‡ (0·64–1·39)	1·26† (0·95–1·67)	**Traz**	1·07‡ (0·77–1·47)	1·80† (0·98–3·38)
1·01* (0·82–1·26)	1·05† (0·87–1·27)	1·16† (0·82–1·65)	0·90† (0·72–1·10)	0·85† (0·67–1·06)	0·96† (0·77–1·21)	1·13* (0·93–1·37)	**0·84† (0·73–0·97)**	0·84* (0·66–1·07)	0·95* (0·73–1·23)	1·09* (0·89–1·33)	0·88‡ (0·59–1·30)	1·01† (0·86–1·17)	**0·70† (0·51–0·97)**	0·94* (0·78–1·13)	**0·75† (0·57–0·98)**	**Venl**	**1·69† (1·01–2·86)**
0·73‡ (0·42–1·26)	0·76‡ (0·44–1·29)	0·83‡ (0·45–1·54)	0·64† (0·37–1·11)	0·61† (0·35–1·05)	0·69† (0·40–1·20)	0·81‡ (0·47–1·39)	0·60† (0·36–1·02)	0·60† (0·34–1·05)	0·68† (0·39–1·20)	0·78‡ (0·45–1·34)	0·63† (0·33–1·19)	0·72† (0·43–1·22)	**0·51† (0·28–0·92)**	0·68† (0·39–1·16)	**0·54† (0·30–0·95)**	0·72† (0·43–1·19)	**Vort**

Agom = agomelatine; Amit = amitriptyline; Bupr = bupropion; Cita = citalopram; Clom = clomipramine; Dulo = duloxetine; Esci = escitalopram; Fluo = fluoxetine; Fluv = fluvoxamine; Miln = milnacipran; Mirt = mirtazapine; Nefa = nefazodone; OR = odds ratio; Paro = paroxetine; Rebo = reboxetine; Sert = sertraline; Traz = trazodone; Venl = venlafaxine; Vort = vortioxetine.

Note: Includes 194 randomized controlled trials and 34,196 patients. Drugs are reported in alphabetical order. Data are odds ratios (ORs) (95% credible interval) in the column-defining treatment compared with the row-defining treatment. For efficacy, ORs higher than 1 favour the column-defining treatment (i.e., the first in alphabetical order). For acceptability, ORs lower than 1 favour the first drug in alphabetical order. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored. The certainty of the evidence (according to the Grading of Recommendations Assessment, Development and Evaluation) was incorporated in this figure (Appendix pp. 231–65).

* Moderate quality of evidence.

† Low quality of evidence.

‡ Very low quality of evidence.

Analysis Results: The network for the primary analyses included 432 RCTs comprising 102,443 patients (Figure 19 and Figure 20). The most commonly studied antidepressants were fluoxetine and paroxetine. A total of 179 of the studies were head-to-head trials of active comparators. All antidepressants in the network had a placebo-controlled trial except

milnacipran. A small proportion of studies (n = 51, 11.8%) required imputation of response rates.

Results of the NMA found that all treatments were more efficacious than placebo (Figure 21). For acceptability only two drugs — agomelatine (OR 0.84; 95% CrI, 0.72 to 0.97) and fluoxetine (OR 0.88; 95% CrI, 0.80 to 0.96) — were more acceptable than placebo (Figure 22). In head-to-head comparisons from the NMA, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more efficacious than other antidepressants (ORs ranging between 1.19 and 1.96) and agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were more acceptable than other antidepressants (ORs ranging between 0.43 and 0.77) (Figure 23).

Secondary outcomes for response and remission also found that all treatments were more efficacious than placebo. Analysis of patient withdrawals due to adverse events found that all drugs had greater rates of dropouts compared to placebo except agomelatine (OR 1.21; 95% CrI, 0.94 to 1.56). Meta-regression and subgroup analyses did not show any changes from the primary analysis. Preplanned sensitivity analysis limiting the network to only studies with a low risk of bias was not performed due to the small sample size (n = 39).

Vortioxetine-Specific Results: Vortioxetine was found to be more efficacious than placebo in achieving response, defined as reduction in the total score of 50% or greater on a standardized observer-rating scale for depression (OR 1.66; 95% CrI, 1.45 to1.92) and as acceptable as placebo (OR 1.01; 95% CrI, 0.86 to 1.19), based on the proportion of patients who withdrew for any reason (Table 66). Based on the primary analysis that included placebo and active-controlled trials, the response rate and acceptability of vortioxetine was similar to other antidepressants. Based on the secondary analysis that included only head-to-head studies, vortioxetine was found to be more efficacious than trazodone (OR 0.54; 95% CrI, 0.30 to 0.95) and reboxetine (OR 0.51; 95% CrI, 0.28 to 0.92) (Figure 23). Vortioxetine was also found to be more acceptable than venlafaxine (OR 1.69; 95% CrI, 1.01 to 2.86), reboxetine (OR 2.32; 95% CrI, 1.24 to 4.41), fluvoxamine (OR 1.78; 95% CrI, 1.00 to 3.24), duloxetine (OR 1.99, 95% CrI, 1.13 to 3.52), clomipramine (OR 2.20; 95% CrI, 1.22 to 3.90), and amitriptyline (OR 1.72; 95% CrI, 1.00 to 3.05). Vortioxetine was not in the top five treatments in terms of SUCRA but was found to have a SUCRA of 54.6% for efficacy (mean rank = 10.5) and 47.9% for acceptability (mean rank = 11.9).

For secondary outcomes for response (change in depression symptom score from baseline) (SMD −0.28; 95% CrI, −0.36 to −0.20) and remission (OR 1.49; 95% CrI, 1.29 to 1.72) vortioxetine was more efficacious than placebo. Vortioxetine was found to have a greater likelihood of dropouts due to side effects compared to placebo (OR 1.64; 95% CrI, 1.25 to 2.14).

Table 66: Summary of Vortioxetine Results Compared to Placebo

Outcome	Odds ratio (95% CrI)
Primary Outcomes	
Efficacy	1.66 (1.45 to 1.92)
Acceptability	1.01 (0.86 to 1.19)
Secondary Outcomes	
Efficacy- Change in depression symptom score from baseline	SMD −0.28 (−0.36 to −0.20)
Remission	OR 1.49 (1.29 to 1.72)
Dropouts due to adverse events	OR 1.64 (1.25 to 2.14)

CrI = credible interval; OR = odds ratio; SMD = standardized mean difference.

Source: Cipriani et al. (2018).[8]

Manufacturer-Submitted Analysis: Of the 522 studies included in the Cipriani ITC, [redacted] were excluded from the manufacturer-submitted dose-stratified analysis because [redacted].

The additional analysis conducted by the manufacturer had similar findings to the Cipriani et al. report (Figure 24 and Figure 25). [redacted]

Figure 24: Indirect Treatment Comparison of Response Stratified by Dose – Active Treatment Versus Placebo

Figure redacted as per the sponsor's request.

Agom = agomelatine; Amit = amitriptyline; Bupr = bupropion; Cita = citalopram; Clom = clomipramine; CrI = credible interval; Desv = desvenlafaxine; Dulo = duloxetine; Esci = escitalopram; Fluo = fluoxetine; Fluv = fluvoxamine; Levo = levomilnacipran; Miln = milnacipran; Mirt = mirtazapine; Nefa = nefazodone; OR = odds ratio; Paro = paroxetine; Rebo = reboxetine; Sert = sertraline; Traz = trazodone; Venl = venlafaxine; Vort = vortioxetine.

Source: Manufacturer submission for Trintellix.[7]

Figure 25: Indirect Treatment Comparison of Withdrawals Stratified by Dose – Active Treatments Versus Placebo

Figure redacted as per the sponsor's request.

Agom = agomelatine; Amit = amitriptyline; Bupr = bupropion; Cita = citalopram; Clom = clomipramine; CrI = credible interval; Desv = desvenlafaxine; Dulo = duloxetine; Esci = escitalopram; Fluo = fluoxetine; Fluv = fluvoxamine; Levo = levomilnacipran; Miln = milnacipran; Mirt = mirtazapine; Nefa = nefazodone; OR = odds ratio; Paro = paroxetine; Rebo = reboxetine; Sert = sertraline; Traz = trazodone; Venl = venlafaxine; Vort = vortioxetine.

Source: Manufacturer submission for Trintellix.[7]

Critical Appraisal

Cipriani et al. presented a transparent synthesis of the current evidence for the acute treatment of major depressive disorder. They conducted a comprehensive search of multiple databases over a complete period of time. Overall, the methodology presented is in line with current methodological standards for systematic reviews. A number of steps were taken to ensure the inclusion of additional unpublished data and the authors conducted a comprehensive search of the grey literature. Screening of studies for eligibility occurred over multiple phases (titles/abstracts and full-text) by multiple teams of reviewers working independently. Additionally, the authors posted all their data in hopes that full transparency may allow for improvement of their work. The review was only conducted up until January 2016, potentially excluding recent evidence, especially for a newer drug. The analysis plan presented for the NMA presented is in line with current methodological standards. They assessed and measured all assumptions inherent in NMA, including consistency and transitivity, and explored the impacts of these assumptions on the results. Some variances in results indicate the heterogeneity of the data included. For example, there was greater variance in results for the head-to-head evidence than in the placebo-controlled evidence, highlighting the potential impact of publication bias and high rates of placebo response in this therapeutic area. The authors noted that, although the results of individual studies varied greatly (as seen by the sensitivity analysis), the overall conclusions remained robust.

The studies included in the analyses were heterogeneous with respect to the populations included. For example, differences in ages, previous treatments, and severity of MDD at baseline varied across studies. Additionally, due to the broad nature of the systematic review, studies from as early as 1979 were included, raising concerns that this may impact efficacy measures if outcome definitions and, for placebo-controlled studies, placebo response rates have changed over time. Meta-regression and a sensitivity analysis were conducted to attempt to control for these factors. The authors reported that controlling for study factors by meta-regression did not change results in a meaningful way. They explored the potential impact of study year and found minimal change in variance. One important factor that was not discussed that may affect the analysis is concurrent non-pharmacological treatments. It appears that they categorized studies that allowed non-pharmacological treatments as placebo-controlled if no drug was given concurrently. This information was not collected or reported and could present important variance across studies. Supportive medical management (e.g., sedative-hypnotics and anxiolytics) and inclusion of psychotherapy may affect placebo response rates and introduce heterogeneity across studies. Lastly, head-to-head comparisons were more likely to be affected by low-quality studies, based on results of risk of bias assessments, and some head-to-head comparisons must be interpreted carefully. The authors also found a significant novelty affect, in which newer drugs often performed better than older drugs.

A strength of this analysis is the broad inclusion of a wider evidence base. While limited in the traditional manner that all clinical trials are, there is variance in the baseline characteristics of included studies. The authors allowed broader inclusion of a variety of diagnosis tools realistic of what may occur globally in practice. Importantly, and as with most clinical trials, the patients were younger and healthier than would be expected in real practice.[149-152] It is also important to note that in many of these trials care is given by psychiatrists, which may be different from the care given by family doctors, who are the most common prescribers of antidepressants in Canada. Cipriani et al. only explored the acute use (eight weeks) of antidepressants in adults, and therefore their report cannot be used to inform the longer-term comparative efficacy and acceptability of these drugs.

However, efficacy and tolerability are quickly recognized after treatment initiation, and long-term use is strongly linked with initial response.[153] A study of UK antidepressants users found that nearly half of patients will have intermittent or chronic use of antidepressants.[149]

The study does have some important limitations worth noting when considering the applicability of the results. First, the evidence base presented is drawn from clinical trials and may not be reflective of real-world practice and use. Important factors such as concurrent non-pharmacological therapies used in general practice, and comorbidities were not explored and likely limited by inclusion. A large proportion of patients treated with antidepressants may have additional mental health comorbidities, but they were not included in many of the studies analyzed. The second limitation, which is acknowledged by Cipriani et al., is that some of the included evidence was of lower quality or did not have enough information reported to allow for analysis. The authors did attempt to account for this through a variety of analyses, including publication bias assessments. These sensitivity analyses did not greatly affect the main conclusions. Lastly, the authors were not able to investigate important clinical and demographic modifiers of treatment response. This information would be useful in helping develop more nuanced clinical recommendations in selecting antidepressants from among the 21 different options. The authors suggest that future research could leverage patient-level data to explore these important factors.

The additional analysis conducted by the manufacturer, although interesting, has some potential limitations. First, although the analysis does leverage both placebo-controlled and head-to-head studies, the analysis further stratifies the evidence base and relies more heavily on biased and dispersed head-to-head comparisons, as noted by Cipriani et al. The reduction in evidence for each group introduces greater uncertainty to estimates. Building on an analysis that is already highly variable introduces further variance by diluting the evidence base. Second, the results do not vary greatly from the base analysis, as concluded by the manufacturer-submitted report, and raises the question as to whether the additional analysis offers any further insight aside from adding further uncertainty. The results of the dose-stratified analysis align with the primary analysis conducted by Cipriani et al., supporting the robustness of the primary analysis. In light of both of these points, it is more appropriate to use the base analysis presented by Cipriani et al. as the primary estimate for vortioxetine and only use the dose-stratified analysis provided by the manufacturer as a potential sensitivity analysis.

Other Indirect Treatment Comparisons of Interest

Due to the broad nature and complexity of MDD treatment, a scan of other relevant ITCs in the literature was conducted to help contextualize other factors associated with MDD treatment with vortioxetine as well as help inform gaps that were not addressed by Cipriani et al. and the submitted indirect comparison. Three additional ITCs have been included in this summary.

Table 67: Summary of Additional Indirect Treatment Comparisons

Paper	Objective
Brignone (2016)[73]	**Objective:** To assess the relative efficacy and tolerability of vortioxetine against different antidepressant monotherapies in patients with MDD with inadequate response to other antidepressants. **Methods:** *Systematic review:* Systematic literature review of major databases up to March 2014. Limited to English-language studies. *Inclusion criteria:* Randomized and quasi-randomized trials (no blinding requirement) and observational studies (with comparator) for adults with MDD who have failed a prior first-line treatment. Included all interventions for the treatment of MDD, dysthymia, and subsyndromal depression. Interventions included all antidepressants and non-pharmacological treatments and placebo. *Outcomes:* Remission rates and withdrawal rates due to adverse events. *Analysis:* Adjusted indirect comparison using Bucher's method. **Summary of major results:** The systematic review located 27 studies (24 RCTs and three non-RCTs). Only three studies contributed to the evidence network. Analysis concluded that vortioxetine had a higher remission rate compared with other antidepressants. Vortioxetine was also found to be well tolerated, with statistically lower withdrawal rates due to adverse events compared with other antidepressants. **Funding:** Pharmaceutical companies (Lundbeck) **Interpretation:** Sparse network. All information was drawn from only three studies. Direct evidence with vortioxetine was limited to one trial compared with agomelatine. The trials included trials had significant heterogeneity in populations. Low-quality analysis based on scarce evidence network. Evidence does not support conclusions made by authors.
Baune (2017)[72]	**Objective:** To assess the comparative effect of antidepressants on cognitive dysfunction. **Methods:** *Systematic review:* Systematic literature review of major databases up to November 2014. Limited to English-language studies. *Inclusion criteria:* RCTs (no blinding requirement) for adults with MDD. Included all interventions for the treatment of MDD, including non-pharmacological treatments and placebo. *Outcomes:* Cognition and cognitive dysfunction, work productivity, and quality of life. *Analysis:* Frequentist-based NMA using random-effects models. Conducted both drug class and by-drug NMA. NMA was only conducted for DSST. **Summary of major results:** Final analysis included 72 randomized controlled trials. The review identified 86 different cognitive tests assessing the effect of antidepressants on cognitive functioning. DSST was selected for analysis based on its inclusion in 12 trials. Due to lack of data, it was not feasible to analyze other cognitive function tests. NMA of DSST found that vortioxetine was the only antidepressant that improved cognitive dysfunction on the DSST versus placebo (SMD 0.33; 95% CI, 0.12 to 0.53). **Funding:** Pharmaceutical companies (Lundbeck and Takeda) **Interpretation:** Large variability in measures used to assess cognitive functioning across trials limited the ability to conduct ITC and assess relative treatment effects. Finding of potential differential effects of vortioxetine versus various antidepressants is inconclusive due to an inability to test across different trials because of variation in tools used.

Paper	Objective
	Although the analysis was based on a comprehensive systematic literature review, the network of evidence for cognitive function outcomes was sparse, which limited the NMA. Further evidence development is needed.
Wagner (2017)[74]	**Objective:** To assess differences between vilazodone, levomilnacipran, and vortioxetine with one another and other antidepressants. **Methods:** *Systematic review:* Systematic literature review of major databases from January 2010 to September 2017. Limited to English-language studies. Conducted risk of bias assessment using Cochrane risk of bias tool. *Inclusion criteria:* Limited to double-blinded, RCTs comparing levomilnacipran, vilazodone, or vortioxetine with one another or with another second-generation antidepressant. Evidence base was expanded for harms to include non-randomized studies. *Outcomes:* Primary outcome was response to treatment in Hamilton Depression Rating Scale, defined as a ≥ 50% improvement. *Analysis:* Frequentist-based NMA using random-effects models. All major assumptions were addressed. **Summary of major results:** Final analysis included 24 publications, with seven head-to-head studies and 17 placebo- and active-controlled trials. No non-randomized studies were included. Overall, the authors concluded that the evidence suggested similar efficacy among levomilnacipran, vilazodone, or vortioxetine and other second-generation antidepressants. **Interpretation:** Findings of this study are in line with the conclusions made of the larger, more-robust analysis conducted by Cipriani et al. (2018)[8] This analysis was much more limited due to the scope of the question and thus included less evidence in the network.

AE = adverse event; CI = confidence interval; DSST = Digit Symbol Substitution Test; ITC = indirect treatment comparison; MDD = major depressive disorder; NMA = network meta-analysis; SMD = standardized mean difference; RCT = randomized controlled trial.

Source: Baune (2017),[72] Brignone (2016),[73] Wagner (2017).[74]

Overall Conclusion

The evidence presented supports a general finding in the literature that most drugs used in the acute treatments for MDD, including vortioxetine, have similar efficacy and all are more efficacious than placebo. In Cipriani et al.'s ITC the analysis based on head-to-head studies may be less robust than the primary analysis, which also included placebo-controlled trials. Head-to-head analyses are generally supportive of the existence of few differences between agents when all data are used. There is no evidence to suggest that vortioxetine presents any superiority or advantage, aside from presenting an additional treatment option, an advantage that all agents possess. The three other ITCs that were briefly summarized did not yield any added value to our understanding of the overall or comparative efficacy of vortioxetine. Specifically, studies aiming to assess the cognitive benefits of agents were limited by a large degree of heterogeneity in reporting cognitive measures in the literature, as well as a scarcity of evidence.

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Correction Notice

The footnotes for Tables 15 and 35 in this report have been reordered and renumbered. Also, table numbering throughout this report has been updated and is reflected in the Table of Contents and the List of Tables.