

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Vortioxetine for treating major depressive disorder

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Company's decision problem

- The marketing authorisation for vortioxetine is for 'the treatment of major depressive episodes in adults'. The company made a case for the use of vortioxetine in a more narrow population (that is, people whose condition has not responded to initial treatment with a serotonin-specific reuptake inhibitors (SSRI) or serotonin–norepinephrine reuptake inhibitors (SNRI) and who wish to change antidepressant because of an inadequate response or intolerability to the initial treatment). The company refers to this population as the 'switch population'. The company considered that this reflects clinical practice of switching to an agent with a different mechanism of action. NICE's clinical guideline on [Depression in adults](#) (CG 90) states consider switching to:
 - initially a different SSRI or a better tolerated newer-generation antidepressant;

- subsequently an antidepressant of a different pharmacological class that may be less well tolerated, for example venlafaxine.

At what point in the treatment pathway is vortioxetine likely to be offered in England (for example, after first SSRI, after two or more SSRIs, after SSRIs as a pharmacological class have been exhausted etc.)?

- The company considered that based on NICE clinical guideline 90, its own market share data and clinical opinion, citalopram (SSRI), venlafaxine (SNRI), sertraline (SSRI), mirtazapine (non-SSRI/SNRI) and fluoxetine (SSRI) were the most relevant comparators. The company presented direct evidence for vortioxetine compared with agomelatine (non-SSRI/SNRI) and escitalopram (SSRI), and indirect evidence for vortioxetine compared with agomelatine, sertraline, venlafaxine, bupropion and citalopram. No comparisons were made by the company with duloxetine (SNRI; included in ERG's exploratory analyses), fluoxetine and mirtazapine. What are the most relevant comparisons?

Clinical effectiveness

- The ERG commented that the baseline severity of depression in the population enrolled into REVIVE was broadly representative of the 'switch population' in England but:
 - Most participants were white (99.8%) which is unlikely to reflect the 'switch population' in England;
 - 23% of all participants had received a SNRI as initial treatment which is not reflective of clinical practice in England, where their use first-line is negligible;
 - Most participants were recruited from an out-patient setting (97%);
 - The proportion of participants from the UK was small (≈7%).

How generalisable are the results from the REVIVE trial to UK clinical practice?

- The company stated its indirect treatment comparison suggested vortioxetine is more efficacious and tolerable compared with other antidepressants in the proposed switch population. The company's indirect treatment comparison included 4 trials and 6 technologies, including vortioxetine (each arm of network was informed by 1 trial, see Figure 3). The trials included used different scales for measuring depressive symptoms and remission, and assessed outcomes at different time-points. The ERG stated that the heterogeneous nature of the data

meant that the company's indirect treatment comparison may not be reliable, and also the creation of a network relied upon the inclusion of Kasper et al. (2013) that may not have enrolled people only from the proposed 'switching' population.

- o Is the clinical evidence included in the company's indirect treatment comparison relevant for the company's proposed positioning of vortioxetine and its comparators (that is, after 1 SSRI therapy)?
 - o How robust are the estimates of relative effectiveness obtained from the company's indirect treatment comparison?
- The ERG considered that there was substantial uncertainty associated with the company's indirect treatment comparison. The ERG identified 2 alternative data sources for estimating the relative effectiveness of vortioxetine with other antidepressants from the company's response to the ERG's and NICE's clarification request. These included meta-analyses of placebo-controlled trials with active reference arms in the non-switch population (that is, first-line population [Pae et al. 2014]) and an indirect treatment comparison in the non-switch population (Llorca et al. 2015). Of these sources, the ERG felt that Llorca may be the most reliable, although it had limitations because of the lack of direct comparison between active therapies.
 - o Is evidence from the non-switching population relevant to inform relative effectiveness of vortioxetine compared with other antidepressants?
 - o Is it plausible that the relative effectiveness of vortioxetine compared with (i) SSRIs, (ii) non-SSRIs, is similar between the non-switch and switch populations?
 - o Which source, the company's indirect comparison, Pae or Lorca, is the most robust for estimating the effectiveness of vortioxetine compared with other antidepressants in people with major depressive disorder?
- The ERG concluded that based on the totality of evidence, vortioxetine is likely to be of similar efficacy as other antidepressants, but may be more efficacious than agomelatine but less efficacious than duloxetine for achieving remission.
 - o What differences between rates of remission and depression severity scores (for example, MADRS) are considered clinically significant?

- o Is there sufficient evidence to robustly suggest a difference in effectiveness between vortioxetine and any of the comparators?

Cost effectiveness

- The company's model was a decision-tree that included a Markov component for subsequent switches to third and later treatment options. The ERG considered that the company's model structure was unnecessarily complicated and introduced inconsistencies between the timing of events in the decision tree and Markov component. Is the company's model structure appropriate?
- The company's model used remission data at 8-weeks from the trials to inform switching decisions at 4-weeks. The ERG noted that this not only excludes 4-weeks of treatment costs for non-remitters and overestimates the health benefits for remitters, but does not reflect how decisions are made in clinical practice because response is also a basis for treatment continuation.
 - o Does the company's model adequately reflect clinical practice?
 - o Was there evidence available for the company to model response?
- The company used the STAR*D trial, a prospective, sequentially randomized controlled trial of outpatients with nonpsychotic major depressive disorder comparing various switching or augmenting strategies, to inform rates of remission and relapse for subsequent switches after initial treatment in the model. The ERG stated that the population of STAR*D was not generalisable to the population of REVIVE and had lower rates of remission and higher rates of relapse than would be expected in clinical practice. The ERG stated that using STAR*D favoured the most effective initial switch treatment and potentially overestimated the length of a major depressive episode. Therefore, the ERG explored several scenarios around the remission and relapses rates for subsequent switches after initial treatment.
 - o How long is an average major depression episode treated for?
 - o What is the preferred approach for modelling remission and relapse of subsequent switches?
- The company used utility values from 2 different sources for the acute phase (REVIVE) and the maintenance phase (Sapin et al. 2004), see table 8. The ERG noted that the utility value from Sapin used by the company for non-remitters was

lower than utility value reported for non-remitters at 8-weeks in the REVIVE trial. Therefore, the ERG preferred to use utility values from REVIVE for both phases, see table 9. What is the most appropriate source for utility values?

- The company based doses in the acute and maintenance phases on the World Health Organisation Defined Daily Dose (for example, 10 mg daily for vortioxetine), and the mean dose reported at the end of trials included in its indirect treatment comparison, respectively. The ERG also explored a scenario in which the doses were the same for the acute and maintenance phases. Which dosing assumption is most appropriate?

1 Remit and decision problems

- 1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of vortioxetine within its licensed indication for the treatment of major depressive disorder.

Table 1 Company's decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	Adults with major depressive disorder	The company's decision problem addresses a subset of the population defined in the scope and marketing authorisation: "Adult patients with moderate-to-severe major depressive disorder who are experiencing an major depressive episode, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to an alternative antidepressant."	Selective serotonin reuptake inhibitors (SSRIs) are recommended as initial antidepressant therapy and all members of this class are now available as generics at low cost (less than £2 per month). Trials show vortioxetine to be suitable for depression that has failed initial SSRI or serotonin-noradrenaline reuptake inhibitor (SNRI) treatment. The company stated that these factors suggest vortioxetine is more likely to be cost-effective in switch use (that is, after initial treatment) rather than in initial use. The efficacy and tolerability profile of vortioxetine qualifies it as a "newer generation, better-tolerated antidepressant" particularly suitable for switch use as per NICE clinical guideline 90.	The ERG acknowledged the justification from the company. However, the ERG considered that this was an important limitation of the company's submission from a clinical and cost-effectiveness perspective (see 'comparators' section of table 1). The ERG was of the opinion that it would have been more appropriate for the company to include the full evidence base rather than restricting the decision problem to evidence in the switch population from the outset. Therefore, the ERG noted that uncertainty exists around the optimal position of vortioxetine in the treatment pathway.
Intervention	Vortioxetine		No comments	No comments.

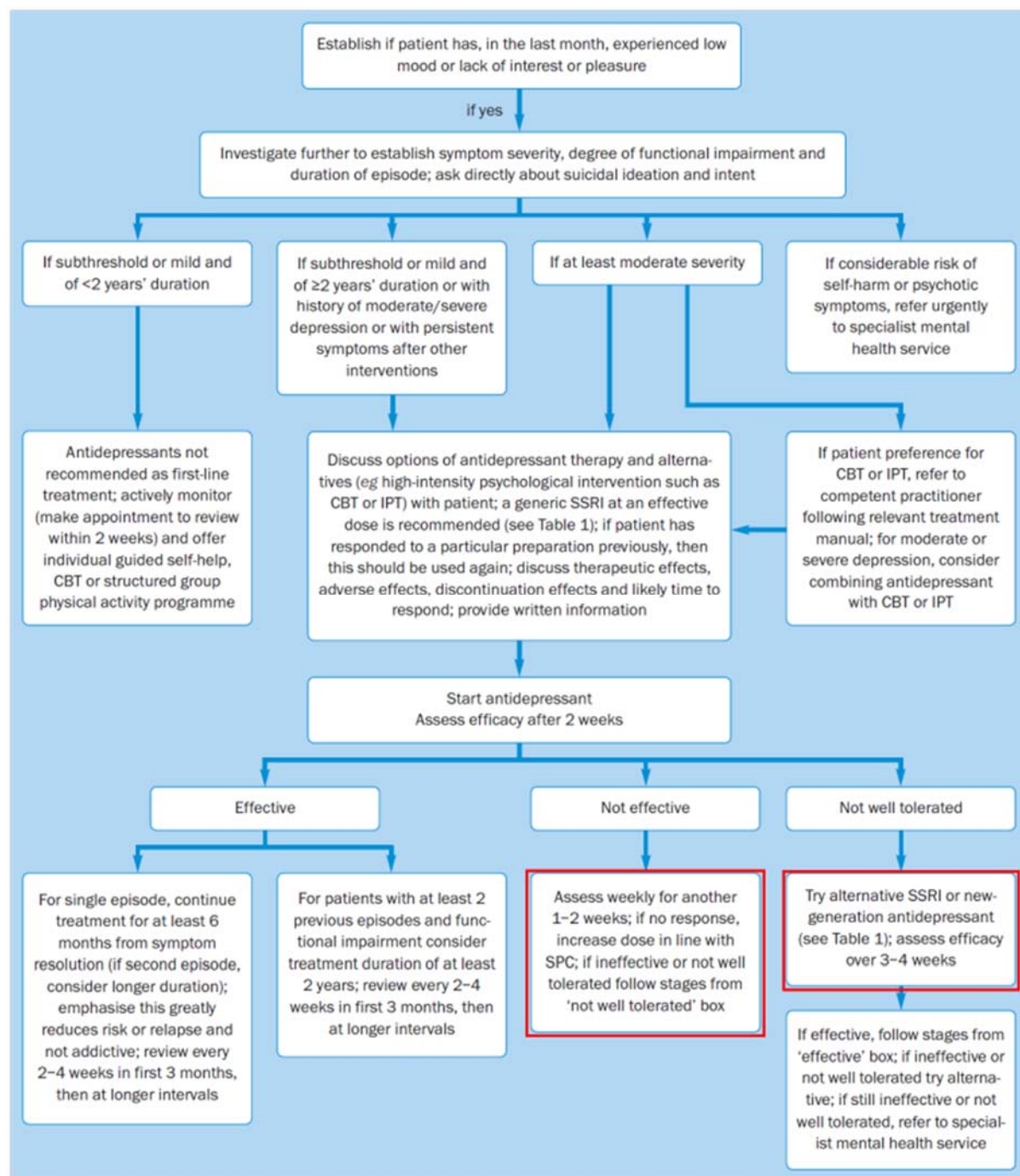
Comparators	- selective serotonin reuptake inhibitors (for example citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) - tricyclic antidepressants (for example clomipramine, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, and amitriptyline) - tricyclic-related antidepressants (for example mianserin and trazodone) - serotonin and noradrenaline reuptake inhibitors (for example venlafaxine, duloxetine and levomilnacipran) - other antidepressant drugs (for example agomelatine, mirtazapine, reboxetine and non-reversible mono-amine oxidase inhibitors [such as phenelzine]) - augmentation treatments (for example, with an antipsychotic such as quetiapine)	- agomelatine - citalopram - venlafaxine XL - sertraline - mirtazapine* - fluoxetine*	Based on its internal data, the company only included antidepressants with a UK second-line market share of 5% or more (source: Cegedim strategic data for the 12-month period April 2013-March 2014). Of these antidepressants, switch clinical data were available to support direct or indirect comparisons of efficacy and tolerability with agomelatine, citalopram, venlafaxine XL, sertraline. * No relevant data were identified by the company for mirtazapine or fluoxetine	Restricting the trial evidence to the switch population constrained the company's approaches to estimating the comparative efficacy. The restriction to consider only switch population evidence, and the small number of trials identified, meant that vortioxetine was compared directly only with agomelatine and escitalopram; and indirectly only with agomelatine, sertraline, venlafaxine (XR), bupropion and citalopram. No comparisons to duloxetine, fluoxetine or mirtazapine were made.

Outcomes	• response to treatment • relapse (including relapse rate and time from remission to relapse) • severity of depression • cognitive dysfunction • remission of symptoms • anxiety • sleep quality • hospitalisation • mortality • adverse effects of treatment • health-related quality of life.	The company stated it included all of these except mortality. In addition, the company stated it included outcomes of: • disability • family functioning • productivity (absenteeism and presenteeism).	Available clinical trial data are short-term (up to 1 year) and provide no direct evidence for longer-term course of major depressive disorder or differential mortality rates. The company considered that disability, family functioning, productivity are particularly relevant outcomes in major depressive disorder.	Outcomes measured in the short-term in trials. No data reported for relapse, cognitive dysfunction and sleep quality in REVIVE. No data on cognitive dysfunction, anxiety and sleep quality, or health-related quality of life outcomes (other than related to sexual dysfunction) reported in TAK318. Limited outcomes included in company's indirect treatment comparison (only 2: remission and withdrawal because of adverse reactions). In response to clarification, response and mean change from baseline were also presented by the company.
Other	If evidence allows, consider: • severity of depression (mild, moderate or severe) • clinical and cost effectiveness of vortioxetine in different positions in the treatment pathway.	Moderate-to-severe depression only. The cost-effectiveness analysis only considers the population indicated in the decision problem, that is, patients switching to switch antidepressant treatment.	The population for the decision problem is already limited by severity (moderate-to-severe) and by positioning (after inadequate response to an initial antidepressant). NICE CG90 step-care principle does not advocate use of antidepressants in mild depression (except persistent sub-threshold depression). No data are available for vortioxetine in mild depression.	The company's restriction to the switch population was potentially consistent with the "other considerations" section specified in the NICE scope.

2 The technology and the treatment pathway

- 2.1 Major depressive disorder is a broad and heterogeneous condition associated with a range of cognitive, behavioural, emotional, and physical symptoms. It is characterised by low mood and loss of pleasure in most activities. The severity of the disorder may vary from mild to severe depending on both the number of symptoms and the degree of functional impairment. In severe disease, psychotic symptoms may be present, and people may hallucinate or have delusions. Major depressive disorder often has a remitting and relapsing course, and symptoms may persist between episodes.
- 2.2 NICE guidance on [Depression in adults](#) (NICE clinical guideline 90; currently under review with expected date of publication May 2017) advocates a stepwise approach for managing major depressive disorder. NICE does not recommend routinely using antidepressants to treat mild major depressive disorder (hereafter called 'depression') except for people who have a past history of moderate or severe major depressive disorder or who have mild major depressive disorder that persists after other interventions. For people with moderate or severe depression, the guideline recommends combining an antidepressant medication and a high-intensity psychological intervention (cognitive behavioural therapy or interpersonal psychotherapy). NICE recommends that a clinician prescribes a generic selective serotonin reuptake inhibitor (SSRI) at first-line. Patients should be seen after 2 weeks of treatment and then every 2–4 weeks for the first 3 months. If the patient with depression develops side effects or his or her condition inadequately responds, NICE advocates switching to a different SSRI or a better tolerated newer-generation antidepressant may be considered (herein referred to as the "switch population"). If another treatment is subsequently needed, an antidepressant of a different pharmacological class may also be considered.

Figure 1 Interpretation of NICE CG90 recommended management & treatment pathway (Reid et al. 2014, Figure A5, page 36 of company's submission)



2.3 The company stated that based on the recommendations of NICE guidance on [Depression in adults](#), clinical opinion and its UK market share data, the most commonly used treatments for the “switch population” (that is, after initial treatment) are: sertraline, mirtazapine, citalopram, fluoxetine and venlafaxine (see table 2).

Table 2 Overview of vortioxetine and its comparators for treating major depressive episodes

	Vortioxetine (Brintellix®)	Sertraline (Lustral®)	Mirtazapine (Zispin SolTab®)	Citalopram (Cipramil®)	Fluoxetine (Prozac®)	Venlafaxine (Efexor® XL)
(related) Marketing authorisation	major depressive episodes in adults	- major depressive episodes - prevention of recurrence of major depressive episodes	episodes of major depression	major depressive episodes	symptoms of depressive illness, with or without associated anxiety symptoms, especially where sedation is not required	- treatment of major depressive episodes - prevention of recurrence of major depressive episodes
Administration	All technologies are orally administered					
Posology	Initially 10 mg daily in adults less than 65 years of age. Adjustments are made based on response & tolerability.	Initially 50 mg daily, increased if necessary by increments of 50 mg at intervals of at least 1 week to max. 200 mg daily.	Initially 15–30 mg daily at bedtime increased within 2–4 weeks according to response; max. 45 mg daily.	Initially 20 mg once daily increased if necessary in steps of 20 mg daily at intervals of 3–4 weeks; max. 40 mg daily.	Initially 20 mg daily increased after 3–4 weeks if necessary, and at appropriate intervals thereafter; max. 60 mg daily.	Initially 75 mg daily in 2 divided doses increased if necessary at intervals of at least 2 weeks; max. 375 mg daily.
Cost	5 mg x 28: £27.72 10 mg x 28: £27.72 20 mg x 28: £27.72	50 mg x 28: £17.82 100 mg x 28: £29.16	15 mg x 30: £15.06 30 mg x 30: £15.06 45 mg x 30: £15.06	20 mg x 28: £8.95	20 mg x 30: £1.50	37.5 mg x 56: £2.32 75 mg x 56: £2.59 Modified release: 75 mg x 28: £22.08 150 mg x 28: £36.81

Source: Company's submission and British National Formulary (March 2015). XL, extended release.

See vortioxetine's [summary of product characteristics](#) for details on adverse reactions and contraindications.

3 Comments from consultees

- 3.1 No statements from professional or patient groups were submitted to NICE.

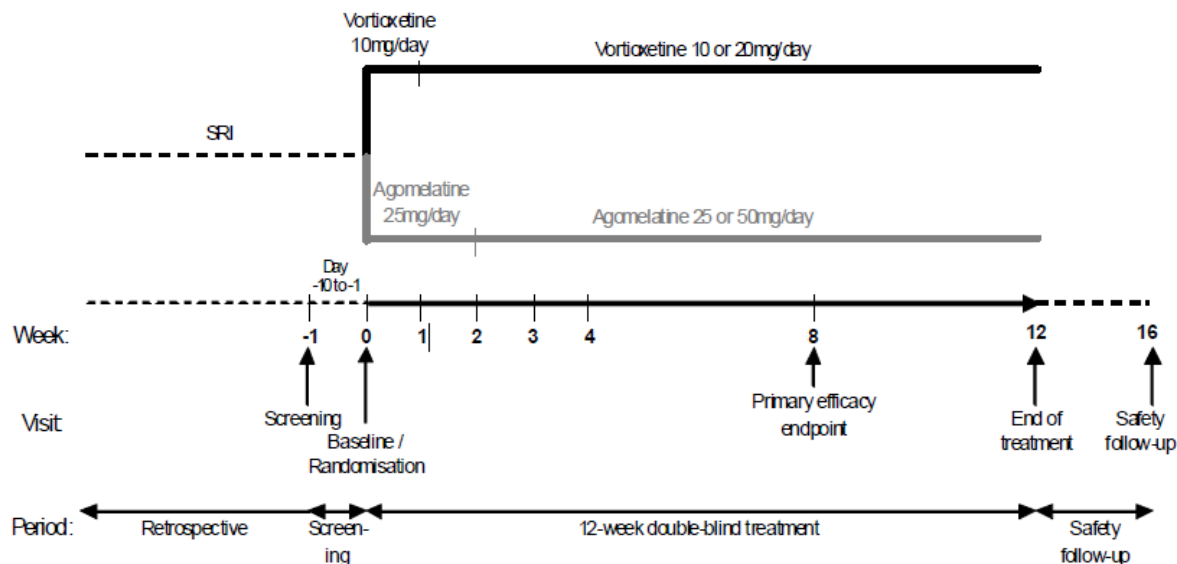
4 Clinical-effectiveness evidence

Overview of the clinical trials

- 4.1 The company conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of vortioxetine for treating adults experiencing a moderate-to-severe major depressive episode, whose condition has responded inadequately or has not tolerated the initial antidepressant treatment, and requires further antidepressant therapy (hereafter referred to as the 'switch population'). The company did not consider all adults with major depressive disorder as specified in NICE's final scope and vortioxetine's marketing authorisation. It identified 2 phase III randomised controlled trials, REVIVE and TAK318.
- 4.2 REVIVE was an international (14 European countries including those in the UK), double-blind, randomised active-control trial in 495 adults with moderate-to-severe major depressive disorder whose condition had inadequately responded to monotherapy with a serotonin reuptake inhibitor (SRI) [see Figure 2]. Patients were randomised 1:1 to flexible doses of vortioxetine (10–20 mg daily; starting dose 10 mg daily), or agomelatine (25–50 mg daily; starting dose 25 mg daily). Patients were assessed weekly during the first 4 weeks of treatment and then every 4 weeks until the end of the 12-week treatment period. A further safety assessment was scheduled 4 weeks after completion or withdrawal from the study. Most patients enrolled into REVIVE were women (74.7%) or white (99.8%), with a mean age of 46.3 years and a mean of 2.5 prior major depressive episodes. The company stated that both groups had comparable baseline Montgomery-Åsberg Depression Rating Scale (MADRS) scores and prior antidepressant use. Most patients received the

maximum dosage of vortioxetine (20 mg, 64.7%) and agomelatine (50 mg, 71.7%) from weeks 4–12.

Figure 2 Design of REVIVE (Figure B2, page 67 of the company's submission)



- 4.3 The primary outcome measure in REVIVE was change from baseline in MADRS score at week 8 (MADRS is a rating scale consisting of 10 items, each rated 0 [no symptom] to 6 [severe symptom] contributing to a total score from 0 to 60; the higher the score, the more severe the condition). A ‘full analysis set’ population (that is, people who were randomised into the study and had a baseline assessment and at least 1 post-baseline assessment) was used to analyse the efficacy outcomes. The company tested a hypothesis of non-inferiority using estimates from a mixed model for repeated measurements, which included treatment, week, and centre as fixed factors and the baseline MADRS score as a covariate. Non-inferiority was considered established if the upper bound of the two-sided 95% confidence interval of the difference between treatment groups in MADRS total score at week 8 did not exceed +2 MADRS units compared with agomelatine.
- 4.4 TAK318 was a multicentre (62 centres in USA and Canada), double-blind, randomised active-control trial in 447 adults with stable major depressive disorder experiencing treatment-emergent sexual dysfunction. Patients

were randomised 1:1 to flexible doses of vortioxetine (10–20 mg daily; starting dose 10 mg daily), or escitalopram (10–20 mg daily; starting dose 10 mg daily). Patients were assessed at the end of the 8-week treatment period and had an additional safety assessment 3 weeks after study completion. For further information about the participants and methods of TAK318, see pages 67–70 and 72–77 of the company's submission.

- 4.5 The primary outcome measure in TAK318 was change from baseline in the Changes in Sexual Functioning Questionnaire Short-Form 14 (CSFQ-14) total score after 8 weeks of treatment (total score ranges from 14 to 70; higher scores reflect higher sexual functioning). A 'full analysis set' population was used to analyse the efficacy outcomes based on a mixed model for repeated measurements of covariance (no formal hypothesis stated).

ERG comments

- 4.6 The ERG stated that the reporting of the company's searches were clear and appropriate. The ERG noted that the company presented no evidence to suggest the relative efficacy of non-selective SRIs may vary between initial and switch use. It concluded that it would be more appropriate to include the full evidence base for vortioxetine and its comparators, rather than restricting the evidence base from the outset to the switch population, and thereby excluding 22 of 24 completed studies of vortioxetine.
- 4.7 The ERG commented that REVIVE and TAK318 appeared well conducted but raised the following concerns:
- Both trials included comparators of limited relevance to clinical practice in England (for example, NICE has not issued any guidance for agomelatine; [NICE technology appraisal 231 \[terminated\]](#)).
 - Both trials were short considering the duration of treatment recommended by NICE to achieve and consolidate remission, and so evidence of long-term efficacy was uncertain.

- Both trials evaluated the efficacy of vortioxetine 10-20 mg daily, so the efficacy of the licensed 5 mg daily regimen was uncertain.

4.8 The ERG commented that the population enrolled into REVIVE was broadly representative of the switch population in England. For example, baseline MADRS scores ranged from 22 to 43 points which is consistent with people experiencing moderate to severe major depressive disorder. However, the ERG noted that:

- Most participants were white (99.8%) which is unlikely to be reflective of the switch population in England.
- 23% of all participants had received a serotonin–norepinephrine reuptake inhibitor as initial treatment which is not reflective of clinical practice in England, where their use first-line is negligible.
- Most participants were recruited from an outpatient psychiatric setting (97.2%).
- The proportion of participants from the UK was small (approximately 7%).

4.9 The ERG noted that although the efficacy analyses in REVIVE and TAK318 used a modified intention-to-treat analysis (that is, full analysis set rather than inclusion of all randomised participants), the risk of bias was likely to be low because relatively few participants randomised were excluded.

Clinical trial results

REVIVE trial

4.10 The results of the primary outcome of REVIVE, the mean change from baseline in MADRS total score at week 8, were -16.5 and -14.4 points in the vortioxetine group and the agomelatine group respectively. This resulted in a mean difference of -2.16 points in favour of vortioxetine (95% confidence interval [CI] -3.51 to -0.81).

- 4.11 Pre-specified subgroup analyses of the primary outcome were carried out by the company for sex, age, baseline severity, baseline anxiety and class of prior antidepressant. The company stated that these analyses suggested vortioxetine improved MADRS score compared with agomelatine across all pre-specified subgroups. For further information, see pages 80, 92–3 of the company's submission.
- 4.12 The company stated that vortioxetine statistically significantly improved outcomes compared with agomelatine across the analyses of the secondary outcomes (see tables 3 and 4).

Table 3 Company's analysis of primary and secondary outcomes in REVIVE (Table B13, page 88 of company's submission; Table 12, ERG report)

Outcome	Vortioxetine: difference compared with agomelatine			
	Week 8		Week 12	
	MMRM	LOCF, ANCOVA	MMRM	LOCF, ANCOVA
Δ MADRS total score	-2.16*† (-3.51 to -0.81)	-3.1**	-2.03* (-3.45 to -0.60)	-3.5**
Δ HAM-A total score	-1.9**	-2.4**	-1.9**	-2.8**
Δ CGI-S score	-0.30* (-0.48 to -0.11)	-0.4**	-0.27* (-0.47 to -0.07)	-0.4**
Δ CGI-I score	-0.25* (-0.42 to -0.08)	-0.4**	-0.25* (-0.42 to -0.07)	-0.5**
Δ = mean change from baseline. † Primary efficacy analysis. *p<0.01; **p<0.001 compared with agomelatine. Vortioxetine: baseline n=252, week 8 n=220, week 12 n=200. Agomelatine: baseline n=241, week 8 n=190, week 12 n=178. ANCOVA, analysis of covariance; CGI-I, Clinical Global Impression - Improvement Scale; CGI-S, Clinical Global Impression - Severity Scale; HAM-A, Hamilton Anxiety Rating Scale; LOCF, last observation carried forward; MMRM, mixed model for repeated measures.				

Table 4 Proportion of responders and remitters in REVIVE: FAS LOCF LREG
(Table B14, page 89 of company's submission; Table 11, ERG report)

Outcome	Week 8				Adjusted OR (95% CI)	Week 12				Adjusted OR (95% CI)
	Vortioxetine		Agomelatine			Vortioxetine		Agomelatine		
	n	%	n	%		N	%	n	%	
Response										
MADRS	155	62%**	114	47%	1.81 (1.26 to 2.60)	176	70%**	135	56%	1.83 (1.26 to 2.65)
CGI-I	186	74%***	140	58%	2.03 (1.38 to 2.96)	187	74%*	154	64%	1.62 (1.10 to 2.39)
Remission										
MADRS	102	41%**	71	30%	1.72 (1.17 to 2.52)	139	55%***	95	39%	2.01 (1.39 to 2.90)
CGI-I	104	41%*	78	32%	1.55 (1.07 to 2.25)	140	56%**	106	44%	1.63 (1.14 to 2.33)
*p <0.05; **p <0.01; ***p <0.001 compared with agomelatine. CGI-I, Clinical Global Impression - Improvement Scale; CI, confidence interval; FAS, full analysis set; LOCF, last observation carried forward; LREG, logistic regression; OR, odds ratio.										

4.13 Health-related quality of life was measured at baseline and at weeks 4, 8 and 12 in the REVIVE trial using the EuroQol-5 dimensions survey (EQ-5D, see table 5). For the EQ-5D scores by status of remission, see pages 82–86 of the company's response to the clarification letter.

Table 5 EQ-5D summary scores and changes in EQ-5D score from baseline
(Table B15 and Figure B9, page 91 of company's submission)

Assessment	Vortioxetine			Agomelatine			p-value
	n	Mean (SD)	Change from baseline*	N	Mean (SD)	Change from baseline*	
Baseline	252	0.53 (0.28)		241	0.55 (0.27)		
Week 4	241	0.70 (0.22)	0.16	233	0.64 (0.27)	0.08	<0.001
Week 8	220	0.76 (0.19)	0.20	189	0.73 (0.23)	0.16	0.03
Week 12	200	0.81 (0.21)	0.25	178	0.78 (0.22)	0.20	0.01
SD, standard deviation.							
* Based on a mixed model for repeated measures analysis (see Figure B9 of company's submission).							

TAK318 trial

- 4.14 Sexual functioning improved in both the vortioxetine and escitalopram groups, with a mean change from baseline in CSFQ-14 score at week 8 of +8.8 and +6.6 points respectively. This resulted in a mean difference of 2.2 points in favour of vortioxetine compared with escitalopram ($p=0.013$). For further results from the TAK318 study, see pages 96–99 of company's submission.

ERG comments

- 4.15 The ERG commented that the results from the company's analysis of the primary and secondary outcomes from REVIVE had relatively wide confidence intervals, and therefore the size of the difference in efficacy between vortioxetine and agomelatine was uncertain (see tables 3 and 4).

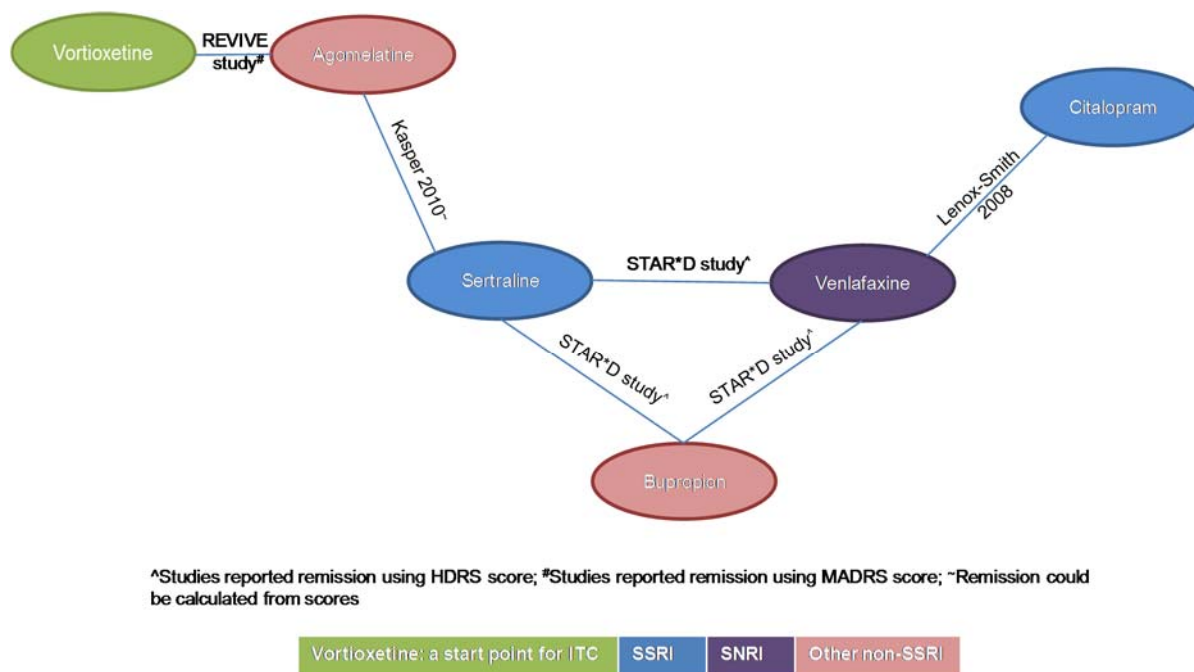
Indirect treatment comparison

- 4.16 In the absence of head-to-head data comparing vortioxetine with comparators other than agomelatine in the switch population, the company conducted both a Bayesian indirect treatment comparison and a frequentist indirect treatment comparison using the Bucher method for 2 outcomes: rate of remission; and the proportion of people who stop treatment because of adverse reactions. The company systematically searched the literature and identified the REVIVE trial plus 3 additional multicentre blinded randomised controlled trials, which compared agomelatine with sertraline (Kasper et al. 2010), venlafaxine with citalopram (Lenox-Smith et al. 2008), and bupropion (which does not have a marketing authorisation in the UK for treating major depressive disorder) with sertraline and venlafaxine (STAR*D) [see Figure 3]. The company excluded:
- Rosso et al. 2012, which compared bupropion with duloxetine because it considered the method of randomisation (by day of the week) and blinding (single-blind) inadequate.

- 2 placebo-controlled trials, because the company's clinical advisers suggested that people who enroll in placebo-controlled trials may be different from those in active-controlled studies, but the company included these trials in a sensitivity analysis.

The company stated that its searches did not identify any evidence that allowed 2 other relevant comparators (fluoxetine or mirtazapine) to be included in the indirect treatment comparison.

Figure 3 Company's base-case network for the indirect treatment comparison (Figure B16, page 116 of the company's submission)



4.17 Kasper et al. (2013) was a post hoc analysis of the 'pre-treated' population from 2 trials of agomelatine in people with major depressive disorder. The number of patients enrolled in each of the 4 trials ranged from fewer than 100 (Kasper) to 789 (STAR*D). Mean age of patients was reported for 3 of the 4 trials and ranged from 41.8 (STAR*D) to 46.3 years (REVIVE). Baseline severity measured by HAM-D was between 21 (REVIVE) to >31 (Lenox-Smith et al. 2008) but the company considered that the differences between the trials would not have an impact on the treatment effect. In general, STAR*D enrolled a higher proportion of men

who were younger and whose depression was less severe than populations in the other trials. Outcomes were assessed at different time-points in the trials, from 6 weeks (Kasper) to 14 weeks (STAR*D). Each study measured depressive symptoms (and hence remission) using different scales: MADRS (REVIVE), HAM-D₁₇ (Kasper, STAR*D) and HAM-D₂₁ (Lenox-Smith) but the company stated that each trial used clinically accepted cut-off rates for remission which are generalisable regardless of the scale used.

- 4.18 The company stated the results of its indirect treatment comparison suggested vortioxetine works better and is better tolerated than the comparators. The results of the company's indirect treatment comparison are presented in tables 6 and 7. The company stated that it did not assess heterogeneity because of the small number of studies included in the network.

Table 6 Summary of the results of the company's frequentist indirect treatment comparison (Table 17, page 63 of the ERG report)

Treatment	Remission rate			People stopping treatment because of adverse reactions (withdrawal)		
	Rate (%)	Risk difference vs vortioxetine (%)	95% CI	Rate (%)	Risk difference vs vortioxetine (%)	95% CI
Vortioxetine	40.5	–	–	5.9	–	–
Agomelatine	29.5	-11	-19.4 to -2.6	9.5	3.6	-1.1 to 8.3
Sertraline	26.1	-14.4	-29.9 to 1.1	18.0	12.1	3.1 to 21.1
Venlafaxine	33.3	-7.2	-24.3 to 9.9	18.2	12.3	0.8 to 23.8
Bupropion	29.8	-10.7	-27.8 to 6.4	24.2	18.3	6.4 to 30.1
Citalopram	23.7	-16.8	-41.1 to 7.5	18.0	12.1	-0.3 to 24.5
CI, confidence intervals.						

Table 7 Summary of the results of the company's Bayesian indirect treatment comparison (Table 18, page 63 of the ERG report)

Treatment	Remission rate			People stopping treatment because of adverse reactions (withdrawal)		
	Rate (%)	Odds ratio vs vortioxetine (%)	95% CrI	Rate (%)	Odds ratio vs vortioxetine (%)	95% CrI
Vortioxetine	40.5	–	–	5.9	–	–
Agomelatine	29.5	1.63	1.12 to 2.37	9.5	0.60	0.30 to 1.17
Sertraline	25.9	1.95	0.89 to 4.24	29.5	0.15	0.03 to 0.62
Venlafaxine	35.1	1.26	0.51 to 3.07	29.5	0.15	0.03 to 0.65
Bupropion	30.7	1.54	0.62 to 3.77	38.5	0.10	0.02 to 0.46
Citalopram	25.6	1.98	0.59 to 6.60	29.5	0.15	0.02 to 0.86
CrI, credible intervals.						

ERG comments

- 4.19 The ERG agreed with the company's assessment of bias for Rosso et al. (2012), so considered it was reasonable to exclude it, but noted it was the only trial that compared vortioxetine with duloxetine. The ERG stated that it was questionable whether Kasper et al. (2013) was suitable for inclusion in the indirect treatment comparison because it was unclear whether the population consisted entirely of patients who were switching treatments, or whether it also included those who had been treated for a previous depressive episode.
- 4.20 The ERG stated that it had significant concerns over the validity of the company's indirect treatment comparison because of the differences in the baseline patient characteristics and severity of depression of the populations across the 4 trials. It also stated that time of outcome assessment between trials (varying from 6 to 14 weeks) may also affect the results because rates of remission and withdrawal are likely to be time-dependent. The ERG concluded that the heterogeneous nature of data included in the network means that the results may not be reliable.
- 4.21 The ERG highlighted that there was little evidence of a statistically significant improvement in the efficacy for vortioxetine compared with the comparators, given that the results from the company's indirect treatment comparison had wide confidence intervals. It stated that the findings in

each specific trial drove the results of the company's indirect treatment comparison because of the sparse evidence network (that is, each arm of the network was informed by 1 trial). The ERG noted that basing results on risk differences was potentially inappropriate, because they may be sensitive to the heterogeneity across trials (see table 6), but acknowledged the company's results based on odds ratios were largely consistent (see table 7). The ERG also commented that the results from the company's sensitivity analysis including the 2 placebo-controlled trials were broadly similar to those that excluded them.

4.22 Because the ERG considered that there was no evidence to suggest the relative efficacy of non-selective SRIs varies between initial and switch use (see section 4.6), it sought from the company further evidence in a population at first-line treatment (that is, the 'non-switch population') during the clarification stage.

- The ERG re-analysed data from a published meta-analysis of placebo-controlled trials with active reference treatment arms (Pae et al. 2014). Pae compared vortioxetine with agomelatine (1 trial), duloxetine (5 trials) and venlafaxine (1 trial). The ERG noted that both the European Medicines Agency and the company have criticised the use of trials including active references because they are not true randomised comparisons given patients known to be non-responsive to the reference treatment are excluded, possibly biasing results in favour of the active reference. The ERG accepted the potential for such bias, but did not consider it substantial enough to exclude these trials. The ERG stated Pae found no evidence of any difference in efficacy between vortioxetine and venlafaxine, and that vortioxetine was worse than duloxetine in terms of reducing depression scores, or achieving response and remission.
- Llorca et al. (2015) published an indirect treatment comparison that found no evidence of any difference in efficacy between vortioxetine and its comparators. Llorca identified placebo controlled trials of the following drugs: vortioxetine, agomelatine, desvenlafaxine, duloxetine,

escitalopram, sertraline, venlafaxine, vilazodone. The ERG commented that there was evidence to suggest fewer people stop vortioxetine because of adverse reactions than other treatments, including sertraline and venlafaxine. The ERG considered that Llorca may represent the most reliable evidence for comparing vortioxetine with other treatments.

For further information around the additional analyses in non-switch populations, see pages 23–60 of the company's response to the clarification letter and pages 72–78 of the ERG report.

- 4.23 The ERG concluded that based on the totality of evidence, vortioxetine is likely to be of similar efficacy as other antidepressants, but may be superior to agomelatine and inferior to duloxetine.

Adverse effects

- 4.24 The company presented short-term safety data from REVIVE. Approximately half of the patients in each treatment group had 1 or more treatment-emergent adverse reaction over the 12-week treatment period. Adverse reactions with an incidence of 5% or more for vortioxetine or agomelatine, respectively, were: nausea (16.2% and 9.1%), headache (10.3% and 13.2%), dizziness (7.1% and 11.6%) and somnolence (4.0% and 7.9%). Fewer patients in the vortioxetine group (1.2%) compared with the agomelatine group (1.7%) experienced serious adverse reactions. Fewer patients stopped treatment because of adverse reactions in the vortioxetine group (5.9%) than in the agomelatine group (9.5%).
- 4.25 The company also presented safety data from 5 open-label long-term extension studies including a total of 2587 patients, of which 54% were exposed to vortioxetine for 52 weeks or more. The overall incidence of treatment emergent adverse reactions was 74.6%, and was higher in the 15-20 mg dose group (78.9%) compared with the 2.5-10 mg group (71.2%).

- 4.26 For further adverse reaction data, see pages 93–5, 99 and 128–134 of the company's submission.

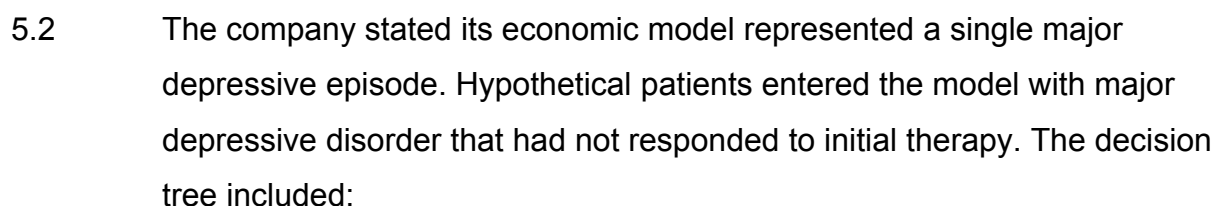
ERG comments

- 4.27 The ERG agreed that vortioxetine appears generally safe and tolerable in people with major depressive disorder. The ERG stated that although the incidence of adverse reactions was high in people taking vortioxetine, most were mild to moderate in nature, and there was no conclusive evidence that these were dose-dependent.
- 4.28 The ERG also concluded that vortioxetine may have a better overall safety profile than other antidepressants, but sparse comparative data for adverse reactions prevented the ERG making a firm conclusion.

5 Cost-effectiveness evidence

Model structure

- 5.1 The company did not identify any published studies of the cost effectiveness of vortioxetine for treating the 'switch population'. It submitted a decision tree model with a Markov component to include subsequent treatment switches to third and later lines (see Figures 4 and 5), and assumed a patient can be offered 1 of 5 treatments: vortioxetine, agomelatine, citalopram, sertraline and venlafaxine. The company conducted the economic analysis from an NHS and personal social services perspective and chose a time horizon of 12 months so did not discount costs and health effects. A half-cycle correction was applied to the health effects in the Markov part of the model (cycle length 2 months).



- an acute phase of treatment of 8 weeks (months 0–2)
- a maintenance phase of 6 months (months 2–8) and
- a recovery phase of 4 months duration (months 8–12).

The time patients spent in the decision tree varied and depended on whether treatment was successful in each phase. If treatment succeeded in all 3 phases, with remission achieved and sustained to recovery, a hypothetical patient spent the entire 12 months in the decision tree model. The company's economic model also included events in which treatment was not successful (lack of response or because of adverse reactions). These events led to a further switch, that is, to third-line treatment. Patients who did not complete the acute or maintenance phase left the decision tree model and entered the Markov component. In a given cycle of the Markov component, patients could either achieve remission or not. The company assumed that patients remained on treatment for 6 months after they achieved remission in the acute phase unless they experienced a long-term side-effect (insomnia, sexual dysfunction or weight gain).

ERG comments

5.3 The ERG stated that the company developed an unnecessarily complicated model structure. It was unclear why the company chose to:

- use different modelling approaches in the maintenance and recovery periods, rather than an initial decision tree for the acute phase and then a separate Markov component for all people in the subsequent 10 month period.
- assume in the maintenance phase different time-points for relapse (after 3 months) and stopping treatment because of adverse reactions (after 1 month) which favours those treatments with higher acquisition costs. The ERG noted that this introduced inconsistency between the timing of relapse for people within the decision tree and Markov components.

5.4 The ERG commented that basing the decision to switch treatments solely on remission data at 8-weeks was an important limitation. It stated that the company's model therefore excluded people whose condition responded to treatment, but who had not achieved full remission, and that in clinical practice, clinicians use response in deciding whether to continue treatments. The ERG commented that the company also used the 8-week remission data to inform switching decisions at 4-weeks in the model. The ERG explained that this ignores the costs of additional treatment for people whose disease responders (non-remitters) and may overestimate health benefits for people whose disease remits because it assigned a utility value based on improved health improvements demonstrated over 8 weeks rather than 4 weeks. The ERG concluded that the company's base case may underestimate vortioxetine's costs and overestimate vortioxetine's benefits.

5.5 The ERG noted the company's assumed that:

- Because in the recovery period, a person is not at risk of relapse or recurrence, this introduces a potential bias in favour of the most effective initial treatment. The ERG agreed that the risk of relapse may be different in later phases than in earlier phases of the condition, but that assuming no relapse seemed overly optimistic.
- patients remain on treatment for 6 months after remission in the maintenance phase was reasonable and consistent with [Depression in adults](#), but was aware that NICE recommends 2 years of continued treatment in people considered high risk of relapse.

The ERG acknowledged that the company explored both of these assumptions in the company's response to clarification by varying the time-horizon of the model from 8 months [no recovery period] up to 2 years [treatment and monitoring costs continued in the recovery period]. The ERG concluded that although the company's base case analysis was robust to these scenarios, the ICER for vortioxetine compared with the next most cost-effective treatment was higher than in the company's base

case analysis, suggesting that including these assumptions potentially favoured vortioxetine. For further details of these scenario analyses, see pages 120–122 of the ERG report.

- 5.6 The ERG stated the company should have used a half-cycle correction for both costs and utility values, rather than for utility values only, since different health states are associated with different costs for consultation or hospitalisation.
- 5.7 The ERG highlighted that using a 12-month time horizon was reasonable for the 'average' patient because an untreated episode of major depressive disorder is estimated to last between 5 to 6 months (World Health Organisation 2008). However, the ERG noted that some people may be treated for longer than 12 months and therefore 12 months may not be sufficient to capture all of the relevant costs and consequences.

Model details

- 5.8 The company took data on the probability of remission after 8 weeks of treatment (acute phase) from its indirect treatment comparison (see table 6). The company assumed that an individual's probability of relapse during the 6 months of treatment after remission depended on the line of therapy rather than specific drug: initial switch treatment (14.2%, from Limosin et al. 2004), third-line (25.0%, from STAR*D¹), fourth- and fifth-line (42.6%, from STAR*D). Patients who relapsed during the maintenance phase (which the company assumed occurred halfway

¹ STAR*D was a prospective, sequentially randomized controlled trial of outpatients with nonpsychotic major depressive disorder who received 1 (n=3671) to 4 (n=123) successive acute treatment steps. In level 1, participants received citalopram as their first treatment step. Level 2 and 3 treatments were randomly assigned. Level 2 provided 7 possible treatments involving 4 switch treatments (citalopram was stopped and new treatment initiated with sustained-release bupropion, cognitive therapy, sertraline or extended-release venlafaxine) and 3 augmentation options (citalopram plus bupropion, buspirone, or cognitive therapy). Level 3 included 2 medication switch strategies (mirtazapine or nortriptyline) or 2 medication augmentation strategies (lithium or T3 [25 mg]). Level 4 entailed only a single randomisation to either tranylcypromine or extended-release venlafaxine plus mirtazapine.

through the maintenance phase) could switch to third-line treatment. The company assumed that clinicians then assessed these patients for remission 2 months after starting third-line treatment, and took the data reflecting the proportion of patients in remission after each line of treatment from STAR*D: third- (13.7%), fourth- (13.0%) and fifth-line (13.0%). The company considered that patients who did not relapse after 6 months of maintenance treatment to have recovered. These patients stopped treatment and the company assumed that they could not experience recurrent depression.

- 5.9 Resource use and costs in the company's economic model included those for treatment (drug), adverse reactions and for each health state (that is, monitoring, inpatient and outpatient admissions). The company based drug costs on the list prices from the 'Monthly Index of Medical Specialities', and dosages in the acute on the World Health Organisation Defined Daily Dose (for example, 10 mg daily for vortioxetine), and dosages in the maintenance phase based on the mean dose reported at the end of trials included in the company's indirect treatment comparison. The company took data for health state resource use for the acute phases from an unpublished interim analysis of the PERFORM study (n=226, which included people on first-line treatment), and for the maintenance phase from Byford et al. (2011) General Practice Research Database 2001–06 of 88,935 people with depression and at least 2 antidepressant prescriptions,. The company took data for the health state costs from Unit Costs of Health and Social Care (2013) and NHS Reference Costs. The company assumed no treatments were prescribed to manage adverse reactions, but around one-third of people would incur an additional GP visit. Therefore, the company costed all adverse events based on an assumed 0.3 GP visits per patient per adverse reaction (£13.50).
- 5.10 To estimate health-related quality of life in the acute phase, the company used EQ-5D data from REVIVE (see table 8). However, for the maintenance phase, the company used EQ-5D data from Sapin et al. (2004). Sapin was a French study which enrolled 250 people with major

depressive disorder in primary care, and assessed health-related quality of life at baseline and after 8 weeks of treatment. The company noted that the mean MADRS score at baseline was 32.7 in Sapin compared with 29.1 in REVIVE, which may explain why the baseline EQ-5D score from Sapin was lower than the baseline EQ-5D score in REVIVE. The company included disutility values associated with adverse reactions from Sullivan et al. (2004), and applied them for 3 weeks in the company's base case analysis.

Table 8 Summary of utility values used in company's economic model (Table B59, page 168 of the company's submission)

Event	Utility value	Comment	Source
Acute phase (0-8 weeks)			
Depression (baseline)	0.54	None	REVIVE
Remission	0.85		
No remission	0.62	Weighted average of non-responders and responding non-remitters at 8 weeks	
Maintenance phase (after 8 weeks)			
Remission	0.85	EQ-5D score for ‘responders remitters’	Sapin et al. 2004
Relapse/no remission	0.58	EQ-5D score for non-responders	
Recovery	0.85	Assumed equal to remission	
Disutility values of side-effects			
Sexual dysfunction	0.049	None	Sullivan et al. 2004
Headache	0.115		
Diarrhoea	0.044		
Somnolence	0.085	Assumed equal to drowsiness	
Nausea	0.065	Assumed average of gastrointestinal adverse reactions	
Insomnia	0.129	Assumed equal to anxiety	
Dry mouth	0.000	No data available, so company assumed no decrement	N/A
Dizziness	0.000		
Sweating	0.000		
Weight gain	0.032	Company calculation	Dixon et al. 2004 & REVIVE

ERG comments

5.11 The ERG highlighted that there was uncertainty around whether STAR*D was an appropriate study to inform the prognosis of people with depression whose condition had not remitted after first switching treatment. The ERG considered that STAR*D included treatments that did not reflect the comparators in the model, and that the population of STAR*D was different from the population of REVIVE. It explained that using data from STAR*D for subsequent switches imposes a poorer prognosis (that is, lower remission rates and higher relapse rates) than expected for a population with the same characteristics as in REVIVE. The ERG stated that using STAR*D may make the most effective initial switch treatment look even better (that is, vortioxetine in the company's base case analysis).

5.12 The ERG disagreed with the company's decision to use the same utility value for:

- relapse and
- people whose condition was not in remission after third or subsequent treatment

because they are very different health states. It highlighted that the utility value from Sapin et al (2004) used by the company for people whose condition had not achieved remission was lower than the utility value reported for people whose condition had not achieved remission at week 8 in the REVIVE trial. The ERG considered it was not necessary to use a different source for the utility values in the maintenance phase, and that using these 2 sources (REVIVE and Sapin et al. 2004) favoured vortioxetine in the company's base-case analysis. It also felt that the relapse health state should reflect the recurrence of moderate-to-severe major depression and so these people should return to their baseline level of utility (that is, 0.54). The ERG proposed alternative utility values for the company's model, see table 9.

Table 9 ERG's preferred utility values (Table 50, page 128 of the ERG report)

Health state	Company's utility	Company's source	ERG's utility	ERG's source
No remission (0-8 weeks)	0.62	REVIVE	0.67	REVIVE (FAS, MMRM): table 37, clarification letter
No remission (after 8 weeks)	0.58	Sapin (2004)	0.67	
Relapse (after 8 weeks)	0.58	Sapin (2004)	0.54	REVIVE (baseline depression)

5.13 The ERG commented that the company used the proprietary price of venlafaxine (extended-release form) rather than the generic price (immediate-release form). It also noted that the maintenance phase dose of citalopram used by the company exceeded the dose stated in its marketing authorisation.

5.14 The ERG stated that the parameter used reflecting the proportion of people stopping treatment because of adverse reactions had no impact on the cost-effectiveness estimates because the company assumed these people did not achieve remission. Because adverse reactions may differ between people who stop or who switch treatment, the ERG considered that the results are potentially biased.

Company's base-case results and sensitivity analysis

5.15 The company's deterministic cost-effectiveness results for vortioxetine compared with the comparators are presented in table 10.

Table 10 Company's base-case cost effectiveness results (Table B82, page 188 of company's submission)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Venlafaxine	£964	0.675	-	-	-
Vortioxetine	£971	0.694	£7	0.019	£378
Citalopram	£976	0.664	£5	-0.030	Dominated
Sertraline	£977	0.664	£0	-0.001	Dominated
Agomelatine	£1082	0.676	£105	0.012	Dominated
QALY, quality-adjusted life year.					
Dominated, fewer QALYs at greater cost than comparator.					

5.16 The company explored parameter and structural uncertainty in its economic model by presenting the results of 1-way sensitivity analyses, scenario analyses and a threshold analysis. The 1-way sensitivity analyses suggested the company's cost effectiveness results was most sensitive to:

- the difference in remission rates at 8 weeks (acute phase) between vortioxetine and each comparator
- GP consultation cost and the utility values for remission at 8 weeks and
- the relapse health state in the maintenance phase after 8 weeks.

However, in all but 2 of the company's 1-way sensitivity analyses vortioxetine remained dominant or had an ICER below £15,670 per QALY gained: vortioxetine was dominated by venlafaxine and by citalopram when including the lower bound of the 95% CI for the differences in remission rates at 8 weeks in the company's economic model. The company commented that its scenario analyses indicated that its economic model was robust to all of the structural assumptions and remained the most cost-effective treatment. Because the remission rate at 8 weeks was the most influential driver of the company's cost effectiveness results, it explored a threshold analysis around this parameter for vortioxetine, see table 11.

Table 11 Company's threshold analysis of remission rate for vortioxetine
(Table B84, page 200 of company's submission)

Treatment	Remission rate at 8 weeks	£20,000 per QALY gained threshold	Remission at 8 weeks	£30,000 per QALY gained threshold
Vortioxetine (base case)	40.50%		40.50%	
Vortioxetine	30.53%		30.10%	
Venlafaxine	33.30%	£20,009	33.30%	£29,898
Vortioxetine	27.97%		28.54%	
Agomelatine	29.50%	£20,016*	29.50%	£29,973*
Vortioxetine	24.53%		24.00%	
Sertraline	26.10%	£20,075	26.10%	£30,062
Vortioxetine	24.10%		23.55%	
Citalopram	23.70%	£20,027	23.70%	£29,975
Figures in bold are base case remission rates. * Threshold ICERs between vortioxetine and agomelatine are based on lower cost and fewer QALYs for vortioxetine, so the ICERs should be interpreted as willingness to accept QALYs lost, not willingness to pay for QALYs gained.				

For further details around the company's sensitivity and scenario analyses, see pages 176–83, 188–202 and Appendix 19 of the company's submission.

ERG comments

- 5.17 Given the issues highlighted by the ERG around the company's indirect treatment comparison (see sections 4.19 to 4.21), the ERG stated that there was considerable uncertainty associated with the ICERs. It concluded that the company's base case analysis can only be reliably used for comparisons of vortioxetine with agomelatine.
- 5.18 The ERG was aware from the World Health Organisation (2008) that an untreated major depressive episode lasts on average 5 to 6 months. The ERG calculated the average duration of a major depressive episode for each treatment included in the company's model based on approximating the mean number of months not spent in the remission and recovery health states. The ERG highlighted that the lowest estimated duration for

a major depressive episode for any given treatment in the company's model was for vortioxetine (6.73 months; longer than the 5 to 6 months stated by the World Health Organisation). The ERG explained that this assumes implicitly that people who switch treatment have a poorer prognosis compared with the broader major depressive disorder population, highlighting that therefore the trial populations used to inform the parameters for remission and relapse in the company's model are crucially important (for example, STAR*D; see section 5.11).

ERG exploratory analyses

5.19 The ERG presented deterministic ICERs for several exploratory analyses that used alternative sources of evidence for the relative effectiveness of vortioxetine compared with its comparators (see section 4.22 and table 12) and used the company's preferred utility values (see table 9).

- Exploratory analysis 1 (see table 13):
 - o The dosage of treatment was up-titrated after 8 weeks (maintenance phase).
 - o STAR*D used to inform remission and relapses rates for subsequent switches after initial treatment.
- Exploratory analysis 2 (see table 14):
 - o The same dosage of treatment for the acute and maintenance phases rather than up-titrated after 8 weeks.
 - o STAR*D used to inform remission and relapses rates for subsequent switches after initial treatment.
- Exploratory analysis 3 (see table 15):
 - o The dosage of treatment was up-titrated after 8 weeks.
 - o Same rate of relapse applied for initial and subsequent switches rather than based on the line of treatment (relapse rate taken from Limosin et al. 2004).
 - o Assumed all treatments were equally effective for achieving remission at all stages of treatment (based on the average of the remission rates for the comparators at initial switch).

- Exploratory analysis 4 (see table 16):
 - o The dosage of treatment was up-titrated after 8 weeks.
 - o Same rate of relapse applied for initial and subsequent switches rather than based on the line of treatment (relapse rate taken from Limosin et al. 2004).
 - o Assumed a decline in the effectiveness of each subsequent treatment (applying the proportionate reduction in effectiveness from STAR*D at each subsequent switch to average of the remission rates for the comparators at initial switch).

For further information around the ERG's exploratory analyses, see pages 126–39 of the ERG report.

Table 12 ERG's alternative scenarios for relative effectiveness: proportion of remitters at 8 weeks (Table 52, page 130 of the ERG report)

Treatment	Probability of remission			
	<i>Company submission [from ITC]</i>	<i>ERG scenario 1 [Llorca]</i>	<i>ERG scenario 2 [Pae]</i>	<i>ERG scenario 3 [equal effectiveness]</i>
Vortioxetine	40.50%	40.50%	40.50%	40.50%
Agomelatine	29.50%	35.81%	26.48%	40.50%
Sertraline	26.10%	--	--	--
Venlafaxine (XR)	33.30%	49.70%	42.52%	40.50%
Duloxetine	--	43.23%	49.30%	40.50%
Citalopram	23.70%	--	--	--
Escitalopram	--	40.74%	--	40.50%
ITC, indirect treatment comparison; XR, extended release.				

Table 13 ERG exploratory analysis 1 using STAR*D data [with up-titration] (Table 56, page 133 of the ERG report)

	Costs	QALYs	Incremental		ICER	
			Costs	QALYs	w SSRI	w/o SSRI
					(incremental analyses, in relation to next best)	
ERG scenario 1: Llorca et al. (2015)						
Venlafaxine (XR)	£885	0.736	ref	ref	ref	ref
Escitalopram	£887	0.729	£3	-0.007	Dominated	--
Vortioxetine	£971	0.733	£83	0.004	Dominated	Dominated
Duloxetine	£1,032	0.730	£61	-0.003	Dominated	Dominated

Agomelatine	£1,069	0.728	£36	-0.002	Dominated	Dominated
ERG scenario 2: Pae et al. (2014)						
Venlafaxine (XR)	£919	0.728	ref	ref	ref	NA
Vortioxetine	£971	0.733	£52	0.006	£9,191	NA
Duloxetine	£1,017	0.737	£46	0.003	£13,393	NA
Agomelatine	£1,088	0.717	£71	-0.020	Dominated	NA
ERG scenario 3: Equal effectiveness						
Escitalopram	£889	0.729	ref	ref	ref	--
Venlafaxine (XR)	£929	0.725	£40	-0.003	Dominated	ref
Vortioxetine	£971	0.733	£42	0.008	£18,188	£5,318
Duloxetine	£1,039	0.727	£68	-0.006	Dominated	Dominated
Agomelatine	£1,059	0.734	£20	0.007	£128,927	£128,927
ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year; SSRI, selective serotonin re-uptake inhibitor; XR, extended release; w, with; w/o, without.						

Table 14 ERG exploratory analysis 2 using STAR*D data [without up-titration]
(Table 57, page 134–35 of the ERG report)

	Costs	QALYs	Incremental		ICER	
			Costs	QALYs	w SSRI	w/o SSRI
					(incremental analyses, in relation to next best)	
ERG scenario 1: Llorca et al. (2015)						
Venlafaxine (XR)	£869	0.736	ref	ref	ref	ref
Escitalopram	£886	0.729	£17	-0.007	Dominated	--
Vortioxetine	£971	0.733	£85	0.004	Dominated	Dominated
Duloxetine	£972	0.730	£1	-0.003	Dominated	Dominated
Agomelatine	£1,026	0.728	£54	-0.002	Dominated	Dominated
ERG scenario 2: Pae et al. (2014)						
Venlafaxine (XR)	£906	0.728	ref	ref	ref	NA
Duloxetine	£949	0.737	£42	0.009	£4,676	NA
Vortioxetine	£971	0.733	£22	-0.003	Dominated	NA
Agomelatine	£1,057	0.717	£86	-0.017	Dominated	NA
ERG scenario 3: Equal effectiveness						
Escitalopram	£887	0.729	ref	ref	ref	--
Venlafaxine (XR)	£917	0.725	£29	-0.003	Dominated	ref
Vortioxetine	£971	0.733	£54	0.008	£18,535	£6,899
Duloxetine	£983	0.727	£12	-0.006	Dominated	Dominated
Agomelatine	£1,010	0.734	£28	0.007	£57,955	£57,955
ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year; SSRI, selective serotonin re-uptake inhibitor; XR, extended release; w, with; w/o, without.						

Table 15 ERG exploratory analysis 3 assuming same relapse rate and average remission rate of 2nd line treatments [with up-titration] (Table 58, page 137 of the ERG report)

	Costs	QALYs	Incremental		ICER	
			Costs	QALYs	w SSRI	w/o SSRI
					(incremental analyses, in relation to next best)	
ERG scenario 1: Llorca et al. (2015)						
Escitalopram	£706	0.777	ref	ref	ref	--
Venlafaxine (XR)	£724	0.778	£17	0.001	£15,778	ref
Vortioxetine	£796	0.780	£72	0.002	£36,434	£36,434
Duloxetine	£856	0.777	£60	-0.003	Dominated	Dominated
Agomelatine	£882	0.778	£27	0.001	Dominated	Dominated
ERG scenario 2: Pae et al. (2014)						
Venlafaxine (XR)	£751	0.772	ref	ref	ref	NA
Vortioxetine	£806	0.778	£55	0.005	£10,394	NA
Duloxetine	£864	0.777	£58	-0.000	Dominated	NA
Agomelatine	£889	0.770	£25	-0.007	Dominated	NA
ERG scenario 3: Equal effectiveness						
Escitalopram	£713	0.775	ref	ref	ref	--
Venlafaxine (XR)	£752	0.772	£39	-0.003	Dominated	ref
Vortioxetine	£802	0.779	£50	0.006	£27,752	£7,882
Duloxetine	£862	0.774	£60	-0.005	Dominated	Dominated
Agomelatine	£891	0.779	£29	0.005	£196,655	£196,655
ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year; SSRI, selective serotonin re-uptake inhibitor; XR, extended release; w, with; w/o, without.						

Table 17 ERG exploratory analysis 4 assuming same relapse rate and average remission rate of 2nd line with proportionate reduction based on STAR*D [with up-titration] (Table 59, page 138 of the ERG report)

	Costs	QALYs	Incremental		ICER	
			Costs	QALYs	w SSRI	w/o SSRI
					(incremental analyses, in relation to next best)	
ERG scenario 1: Llorca et al. (2015)						
Escitalopram	£809	0.751	ref	ref	ref	--
Venlafaxine (XR)	£813	0.755	£3	0.005	£766	ref
Vortioxetine	£899	0.754	£86	-0.002	Dominated	Dominated
Duloxetine	£955	0.751	£56	-0.002	Dominated	Dominated
Agomelatine	£993	0.750	£38	-0.002	Dominated	Dominated
ERG scenario 2: Pae et al. (2014)						
Venlafaxine (XR)	£848	0.747	ref	ref	ref	NA
Vortioxetine	£906	0.752	£58	0.004	£13,068	NA

Duloxetine	£951	0.755	£45	0.003	£14,583	NA
Agomelatine	£1011	0.739	£60	-0.016	Dominated	NA
ERG scenario 3: Equal effectiveness						
Escitalopram	£815	0.749	ref	ref	ref	--
Venlafaxine (XR)	£854	0.746	£39	-0.003	Dominated	ref
Vortioxetine	£904	0.752	£50	0.006	£28,270	£7,992
Duloxetine	£964	0.748	£60	-0.005	Dominated	Dominated
Agomelatine	£993	0.753	£29	0.005	£200,797	£200,797
ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year; SSRI, selective serotonin re-uptake inhibitor; XR, extended release; w, with; w/o, without.						

Innovation

5.20 The company considered vortioxetine to be innovative because:

- it reduces cognitive dysfunction independent of its effect on MADRS (see section 5.1 of vortioxetine's SmPC)
- it has potential to minimise impact on social relationships (that is, strained family functioning through poorer communication, increased conflicts)
- it has potential to reduce symptoms associated with stopping treatment
- the health-related quality of life benefits may be underestimated (the EQ-5D instrument may not capture the impact of mental health conditions adequately compared with other diseases and conditions).

6 Equality issues

6.1 During the scoping workshop attendees indicated that there are equality issues with selective serotonin reuptake inhibitors for postmenopausal and elderly women, and discussed whether these subgroups would be affected by an appraisal of vortioxetine for major depressive disorder. The company indicated that vortioxetine is classed under 'other antidepressants', which makes it a "non-selective serotonin reuptake inhibitor". In addition, the clinical trials included adult men and women.

This issue relates to implementation and cannot be addressed through technology appraisal recommendations.

- 6.2 The company highlighted a report by the Royal College of Psychiatrists in its submission that noted “people with intellectual disability find it difficult to navigate through services and to negotiate the care they need. Therefore, it is essential that providers of services do not present barriers to their gaining access because of intellectual disability”.

This issue relates to implementation and cannot be addressed through technology appraisal recommendations.

7 Authors

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Appendix A: Clinical efficacy section of the European public assessment report

European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002717/WC500159447.pdf

“To summarise:

- Vortioxetine 1 mg/day was efficacious in the one study in which it was investigated.
- Vortioxetine 2.5 mg/day was not efficacious in either of the two studies in which it was investigated.
- Vortioxetine 5 mg/day was efficacious in five of the eight studies: the results were positive in four studies (two short-term studies in adult patients, the dedicated study in the elderly, and the relapse-prevention study) and supportive in a fifth study as reflected by additional sensitivity analyses in adult patients; no effect was observed in three short-term studies in adult patients.
- Vortioxetine 10 mg/day was efficacious in seven of the eight studies in which it was investigated: the results were positive in four studies (three short-term studies and the relapse-prevention study) and supportive in the remaining three studies as reflected by additional sensitivity analyses.
- Vortioxetine 15 mg/day was efficacious in one of the three studies in which it was investigated.
- Vortioxetine 20 mg/day was efficacious in all five studies in which it was investigated; the results were positive in four studies and supportive in one study.

It can therefore be concluded that the efficacy of vortioxetine was demonstrated with at least one dosage group across 9 of the 12 studies, showing at least a 2-point difference to placebo in the Montgomery and Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale 24-item (HAM-D24) total score. The clinical relevance of the effects were supported by the proportions of responders and remitters and the improvement in the Clinical Global Impression – Global Improvement (CGI-I) score. The efficacy of vortioxetine increased with increasing dose.”

- *Conclusions on clinical efficacy, pages 122–23 of the EPAR*

Vortioxetine for the treatment of major depressive disorder [ID583]

Manufacturer submission to National Institute for Health and Care Excellence for a Single Technology Appraisal

Submitted: February 2015

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Contents

Contents	2
List of tables and figures	8
Glossary	11
Executive summary	14
Section A – Decision problem	20
1 Description of technology under assessment.....	21
1.1 Name and therapeutic class.....	21
1.2 Principal mechanism of action	21
1.3 UK marketing authorisation.....	22
1.4 Main regulatory issues	22
1.4.1 Active reference arms do not allow valid head-to-head comparison....	23
1.4.2 Switch study: ensuring enrolment of inadequate responders.....	23
1.4.3 Effect of vortioxetine on cognitive dysfunction	23
1.4.4 US vs. non-US clinical trials.....	24
1.4.5 Dosage in the elderly	24
1.4.6 Negative/failed studies.....	24
1.4.7 Mechanism of action.....	24
1.4.8 Conclusions	25
1.5 Indication.....	25
1.6 Completed and ongoing studies.....	25
1.7 Expected date of availability in the UK.....	26
1.8 Regulatory approvals outside the UK.....	26
1.9 Other health technology assessment in the UK	26
1.10 Cost of vortioxetine to the NHS.....	27
1.11 Use of concomitant therapies.....	27
2 Context.....	29
2.1 Overview of major depressive disorder and its course.....	29
2.1.1 Summary	29
2.1.2 Terminology	29
2.1.3 Aetiology and natural history.....	30
2.1.4 Treatment objectives.....	30
2.1.5 The burden of treatment failure.....	31
2.1.6 Health-related quality of life impact of depression	32
2.1.7 Family impact of depression	33
2.1.8 Cost of depression to the NHS	33
2.1.9 Impact of depression in the workplace and on the wider economy.....	34
2.2 Numbers of patients.....	34
2.3 Life expectancy of people with depression	34
2.4 NICE guidance concerning depression.....	35
2.5 Clinical pathway of care and the impact of vortioxetine	35
2.5.1 Clinical pathway.....	35

2.5.2	Positioning of vortioxetine with the pathway	38
2.6	Issues relating to current clinical practice	39
2.6.1	Patient heterogeneity and treatment choice.....	39
2.6.2	Inadequate outcomes from antidepressant therapy	40
2.6.2.1	Low rates of response and remission.....	40
2.6.2.2	Antidepressant side-effects	40
2.6.2.3	Treatment adherence	43
2.6.3	High rates of switching.....	44
2.6.4	Choice of antidepressants when switching	45
2.7	Main comparators and justification for their selection	45
2.8	Issues concerning trials of antidepressants in MDD	48
2.8.1	High rates of trial failures	48
2.8.2	The use of active references.....	48
2.9	Therapy to manage adverse reactions.....	49
2.10	Resource implications for the NHS	49
3	Equality	50
3.1	Identification of and response to equality issues.....	50
4	Innovation	51
4.1	Appraisal of level of innovation provided by vortioxetine.....	51
4.1.1	Commitment to invest	51
4.1.2	Addressing unmet needs	51
4.1.3	Health-related benefits excluded from QALY calculation.....	52
4.1.4	Supporting data on innovation	53
5	Statement of the decision problem.....	54
	Section B – Clinical and cost effectiveness	56
6	Clinical evidence for vortioxetine.....	57
6.1	Identification of studies	57
6.1.1	Search strategy.....	57
6.2	Study selection.....	59
6.2.1	Eligibility criteria	59
6.2.2	Flow diagram	60
6.2.3	Source references to RCTs	63
6.2.4	List of relevant RCTs	64
6.2.5	Direct comparators	65
6.2.6	Excluded studies.....	66
6.2.7	Relevant non-RCTs	66
6.3	Summary of methodology of relevant RCTs	66
6.3.1	(Instruction from NICE)	66
6.3.2	Methods.....	66
6.3.2.1	Study 14178A (REVIVE)	66
6.3.2.2	Study TAK318	67
6.3.3	Participants.....	70
6.3.4	Patient characteristics at baseline	75
6.3.4.1	Study 14178A (REVIVE)	75
6.3.4.2	Study TAK318	75
6.3.5	Outcomes	76

6.3.6	Statistical analysis and definition of study groups	77
6.3.6.1	Study 14178A (REVIVE) ^{27,180}	77
6.3.6.2	Study TAK318 ^{30,182}	79
6.3.7	Subgroup analyses	80
6.3.7.1	Study 14178A (REVIVE) ²⁷	80
6.3.7.2	Study TAK318 ³⁰	80
6.3.8	Participant flow	80
6.3.8.1	Study 14178A (REVIVE) ²⁷	80
6.3.8.2	Study TAK318 ³⁰	82
6.4	Critical appraisal of relevant RCTs	82
6.4.1.1	Study 14178A (REVIVE)	82
6.4.1.2	Study TAK318	85
6.5	Results	87
6.5.1	Presentation of data	87
6.5.2	Study 14178A (REVIVE): results ²⁷	87
6.5.2.1	Dosage	87
6.5.2.2	Efficacy	87
6.5.2.3	EQ-5D and other PROs	89
6.5.2.4	Subgroup analyses	92
6.5.2.5	Safety and tolerability ²⁷	93
6.5.2.6	Conclusions	95
6.5.3	Study TAK318 ³⁰	95
6.5.3.1	Dosage	95
6.5.3.2	Study TAK318: primary endpoint	96
6.5.3.3	Study TAK318: secondary endpoints ³⁰	97
6.5.3.4	Study TAK318: adverse events ³⁰	99
6.5.3.5	Conclusions ³⁰	99
6.6	Meta-analysis	99
6.7	Indirect and mixed treatment comparisons	100
6.7.1	Strategies to retrieve relevant clinical data on comparators	100
6.7.2	Study identification, selection and methodology	100
6.7.2.1	Databases and registries searched	100
6.7.2.2	Study identification	101
6.7.2.3	Data extraction	103
6.7.2.4	Flow diagram	104
6.7.2.5	Study selection	105
6.7.2.6	Quality assessment of retained studies	106
6.7.2.7	Study characteristics	108
6.7.3	Trials included in indirect comparison	115
6.7.3.1	Limitations of potential evidence network in light of relevant comparators	115
6.7.4	Study selection for the indirect treatment comparison	115
6.7.4.1	Study selection	115
6.7.4.2	Data used in the ITC	119
6.7.4.3	Remission rates	119
6.7.4.4	Withdrawal rates due to adverse events	120
6.7.5	Methodology of the indirect comparisons	120
6.7.5.1	Frequentist framework	121
6.7.6	Results of the ITC	121
6.7.6.1	Remission	121
6.7.6.2	Withdrawal due to adverse events	122
6.7.7	Statistical assessment of heterogeneity	123
6.7.8	Inconsistencies	123
6.7.9	Similarity assumption	123

6.7.10	Sensitivity analyses	125
6.7.11	Conclusions	125
6.8	Non-RCT evidence	125
6.8.1	Study selection	125
6.9	Adverse events	128
6.9.1	Identification of studies	128
6.9.1.1	Study selection	128
6.9.1.2	Broadened population scope	130
6.9.2	Details of adverse events	132
6.9.2.1	Open-label, long-term studies	132
6.9.3	Overview of safety in relation to the decision problem	133
6.10	Interpretation of clinical evidence	134
6.10.1	Principal findings	134
6.10.2	Strengths and limitations of the evidence base	135
6.10.2.1	REVIVE	135
6.10.2.2	TAK318	136
6.10.2.3	Indirect treatment comparison	137
6.10.3	Relevance of evidence base to decision problem	138
6.10.4	Factors influencing external validity of evidence base	139
7	Cost effectiveness	141
7.1	Published cost-effectiveness evaluations	141
7.1.1	Identification of studies	141
7.1.2	Description of identified studies	141
7.1.3	Quality assessment	142
7.2	<i>De novo</i> analysis	142
7.2.1	Patient groups	142
7.2.2	Diagrammatical representation	144
7.2.3	Correspondence to clinical pathway	145
7.2.4	Events, health states and transitions	147
7.2.4.1	Clinical starting point	147
7.2.4.2	Side-effects and tolerability	147
7.2.4.3	Effectiveness	147
7.2.5	Context of the model	148
7.2.6	Key features and assumptions	149
7.2.7	Concordance of modelled interventions with marketing authorisation	150
7.2.8	Clinical continuation rules	151
7.3	Clinical parameters and variables	151
7.3.1	Clinical data sources	151
7.3.1.1	Effectiveness outcome: remission	152
7.3.1.2	Tolerability	152
7.3.2	Transition probabilities	153
7.3.3	Variability of transition probabilities over time	153
7.3.4	Intermediate outcomes	154
7.3.5	Clinical expert assessment of values	154
7.3.5.1	Approach used	154
7.3.5.2	Modelling of effectiveness	155
7.3.5.3	Modelling of adverse events	155
7.3.5.4	Model structural assumptions	156
7.3.6	Summary of selected values	156
7.3.7	Extrapolation	159

7.3.8	List of assumptions	159
7.4	Measurement and valuation of health effects.....	159
7.4.1	Impact of MDD/MDEs on patients' health-related quality of life.	159
7.4.2	HRQoL change over the course of an MDE.....	160
7.4.3	HRQoL data derived from clinical trials.....	160
7.4.4	Mapping.....	161
7.4.5	Systematic search for HRQoL data	161
7.4.5.1	Study identification	161
7.4.5.2	Study selection	162
7.4.6	Description of identified studies	163
7.4.6.1	Health state utilities	163
7.4.6.2	Disutilities associated with side-effects	165
7.4.7	Differences between the values reported in literature and from REVIVE. 165	
7.4.8	Impact of side-effects on HRQoL.....	165
7.4.9	Quality-of-life data used in cost-effectiveness analysis.....	166
7.4.9.1	Acute phase.....	166
7.4.9.2	Maintenance phase	166
7.4.9.3	Disutilities associated with adverse events	166
7.4.9.4	Summary of utility values used in model	167
7.4.10	Clinical expert assessment	168
7.4.11	Patient experience in terms of HRQoL.....	168
7.4.12	Excluded health effects.....	168
7.4.13	Baseline quality of life	168
7.4.14	HRQoL trajectory	169
7.4.15	Amendments to HRQoL data.....	169
7.5	Resource identification, measurement and valuation.....	169
7.5.1	NHS costs.....	169
7.5.2	Costing conventions	169
7.5.3	Resource identification, measurement and valuation studies	169
7.5.4	Clinical expert assessment	172
7.5.5	Cost of each treatment.....	172
7.5.6	Health state costs	173
7.5.7	Adverse event costs.....	174
7.5.8	Productivity costs.....	175
7.6	Sensitivity analysis.....	176
7.6.1	Structural assumptions	176
7.6.2	Deterministic sensitivity analysis.....	178
7.6.3	Probabilistic sensitivity analyses.....	183
7.7	Results.....	183
7.7.1	Clinical outcomes from the model.....	183
7.7.2	Markov traces	183
7.7.3	Accrual of QALYs over time.....	183
7.7.4	Accrual of QALYs for each clinical outcome.	184
7.7.5	Disaggregation of QALYs and costs by health state.....	184
7.7.6	Base-case analysis	188
7.7.7	Sensitivity analyses	188
7.7.8	Probabilistic sensitivity analysis	193
7.7.9	Scenario and structural sensitivity analyses	196
7.7.10	Sensitivity analysis findings	199
7.7.10.1	Deterministic sensitivity analyses	199

7.7.10.2	Probabilistic sensitivity analyses	200
7.7.10.3	Structural and scenario analyses	201
7.7.11	Key drivers of the cost-effectiveness results	201
7.8	Validation	202
7.8.1	Methods used	202
7.9	Subgroup analysis	202
7.9.1	Approach	202
7.9.2	Patient characteristics.....	202
7.9.3	Statistical analysis	202
7.9.4	Results.....	202
7.9.5	Subgroups not considered	202
7.10	Interpretation of economic evidence	203
7.10.1	Consistency with literature	203
7.10.2	Relevance to entire decision problem population	203
7.10.3	Strengths and weaknesses of the evaluation.....	203
7.10.3.1	Strengths	203
7.10.3.2	Weaknesses and other considerations.....	204
7.10.3.3	Conclusion.....	205
7.10.4	Further potential analyses to enhance robustness and completeness.....	205
Section C – Implementation		206
8	Assessment of factors relevant to the NHS and other parties	207
8.1	Patients eligible for treatment in England and Wales.....	207
8.2	Assumption(s) about current treatment options and uptake of technologies.....	207
8.3	Market share assumptions	208
8.4	Other significant costs associated with treatment	209
8.5	Measurement of unit costs	209
8.6	Estimates of resource savings	210
8.7	Annual budget impact for the NHS in England and Wales	210
8.8	Other opportunities for resource savings	211
9	References.....	212

List of tables and figures

Figure A1. Targets of SSRIs, SNRIs and vortioxetine	22
Figure A2. Overview of clinical evidence for vortioxetine in adults with MDD	26
Table A1. Unit costs of vortioxetine	28
Figure A3. Diagrammatic representation of the course of an MDD episode (after Bakish 2001 ⁶⁰ and Zimovetz 2012 ³⁴)	30
Figure A4. Proportions of patient cohort with MDD reporting problems on EQ-5D dimensions (after Sapin 2004 ¹⁸)	32
Table A2. Guidance issued by NICE on depression and subgroups considered	35
Figure A5. Interpretation of NICE CG90 recommended management and treatment pathway (after Reid 2014 ⁸³)	36
Figure A6. NICE Pathways diagram for antidepressant treatment in adults, showing the algorithm leading to sequencing treatments after an inadequate response	37
Figure A7. Treatment pathway for patients who experience an inadequate response to pharmacological therapy: diagrammatic representation of CG90 guidance	38
Figure A8. Modified treatment pathway for patients who experience an inadequate response to pharmacological therapy, showing proposed positioning of vortioxetine	39
Table A4. Relative side-effects of antidepressants (after Maudsley Prescribing Guideline, Taylor ⁸⁸)	43
Figure A9. Outcomes in outpatients with depression over successive steps of antidepressant treatment (after Rush 2006 ¹¹)	45
Figure A10. Pharmacological treatments prescribed for patients ever diagnosed with depression, by line of therapy ⁹⁹	46
Table A5. Comparison of scope for the STA with decision problem addressed by this submission ..	54
Table B1. Eligibility criteria for selection of RCTs	60
Figure B1. PRISMA flow diagram of the selection process for clinical studies of vortioxetine	62
Table B2. Bibliographic details of studies in the switch population for NCT01488071 (REVIVE)	63
Table B3. Bibliographic details of studies in the switch population for NCT01364649	63
Table B4. Clinical trials featuring the intervention of interest but excluded due to population	64
Table B5. List of relevant RCTs for switch population	65
Figure B2. Design of Study 14178A (REVIVE) ²⁷	67
Figure B3. Design of Study TAK318 ²⁸⁻³⁰	68
Table B6. Comparative summary of methodology of the relevant RCTs	69
Table B7. Eligibility criteria for recruitment into the relevant RCTs	70
Table B8. Study 14178A (REVIVE). Baseline characteristics of participants ²⁷	75
Table B9. Study TAK318. Baseline characteristics of participants ³⁰	76
Table B10. Primary and secondary outcomes of the RCTs	76
Figure B4. Study 14178A (REVIVE) ²⁷ . Modified CONSORT flow diagram of patient disposition	81
Figure B5. Study 14178A (REVIVE). Kaplan-Meier analysis of time to withdrawal (APTS) ²⁷	81
Figure B6. Study TAK318 ³⁰ . Modified CONSORT flow diagram of patient disposition	82
Table B11. Critical appraisal of Study 14178A (REVIVE)	83
Table B12. Critical appraisal of Study TAK318	85
Figure B7. Study 14178A (REVIVE). Estimated change from baseline in MADRS total scores from baseline to Week 12 (FAS, MMRM) and LOCF (FAS, ANCOVA) at Week 12 ²⁷	88
Table B13. Study 14178A (REVIVE). Primary and secondary efficacy outcomes: scale score differences ²⁷	88
Table B14. Study 14178A (REVIVE). Proportion of responders and remitters (FAS, LOCF, LREG) ²⁷	89
Figure B8. Study 14178A (REVIVE). EQ-5D profile: proportions of patients reporting problems, by treatment and assessment point (FAS, OC)	90
Table B15. Study 14178A (REVIVE). EQ-5D summary index scores (FAS, OC) ²⁷	91
Figure B9. Study 14178A (REVIVE). Mean changes from baseline in EQ-5D summary index and mean treatment differences to agomelatine (FAS, MMRM) ²⁷	91
Table B16. Study 14178A (REVIVE). Secondary efficacy outcomes: socioeconomic PROs (FAS) ²⁷ ..	92
Figure B10. Study 14178A (REVIVE). Subgroup analysis of primary efficacy endpoint by previous class of treatment ^{135,137}	93
Table B17. Study 14178A (REVIVE): summary of adverse events reported over 12-week treatment period ²⁷	94

Table B18. Study 14178A (REVIVE): sleep-related adverse events ²⁷	95
Table B19. Study TAK318 ³⁰ . Analysis of primary endpoint: change from Baseline in the CSFQ-14 total score after 8 weeks of treatment (FAS, MMRM).....	96
Figure B11. Study TAK318 ³⁰ . Change from baseline in CSFQ-14 total score by visit (MMRM, LS means)	96
Figure B12. Study TAK318 ³⁰ . Comparative effect of vortioxetine and escitalopram treatment in patient subgroups on CSFQ-14 total score at Week 8 (MMRM, FAS, LS means).....	97
Figure B13. Study TAK318 ³⁰ . Difference between vortioxetine and escitalopram on CSFQ-14 subscales at Week 8 (MMRM, FAS, LS Means).....	98
Figure B14. Study TAK318. Changes in clinical measures of depressive symptoms over 8 weeks of treatment with vortioxetine and escitalopram (FAS, MMRM) ³⁰	98
Table B20. Study TAK318. Treatment-emergent adverse events (Safety Set) ³⁰	99
Table B21. Databases examined for the literature search.....	100
Table B22. Eligibility criteria for studies to be included in the systematic review	102
Table B23. Study design criteria for eligibility into the network for the indirect treatment comparison	103
Figure B15. Flow diagram of the search for eligible studies for the indirect treatment comparison ..	105
Table B24. List of studies retained from the systematic review for potential inclusion in the indirect treatment comparison	106
Table B25. Overview of quality of retained studies (NICE checklist).....	107
Table B26. Summary of trials assessed for inclusion in the mixed treatment comparison: methodological characteristics	110
Table B27. Summary of trials assessed for inclusion in the indirect treatment comparison: primary and secondary outcomes	111
Table B28. Summary of trials included in the mixed treatment comparison: participant characteristics	112
Table B29. Summary of trials assessed for inclusion in the indirect treatment comparison: prior therapy status.....	113
Table B30. Indirect treatment comparison: summary basis of study inclusion/exclusion decisions..	115
Table B31. Trials included in the indirect treatment comparison	116
Figure B16. Base-case network for the indirect treatment comparison	116
Table B32. Indirect treatment comparison: summary of study characteristics	118
Table B33. Indirect treatment comparison: baseline characteristics of participants in included studies	118
Table B34. Remission rates from studies included in the indirect treatment comparison	120
Table B35. Withdrawal rates due to AEs from studies included in the indirect treatment comparison	120
Table B36. Remission rates estimated by the indirect treatment comparison.....	122
Table B37. Rates of withdrawal due to AEs estimated by the indirect treatment comparison	123
Table B38. Comparison of ITC estimates with inputs: remission rates	124
Table B39. Comparison of ITC estimates with inputs: withdrawal rates due to AEs	124
Table B40. Eligibility criteria for selection of non-RCTs	126
Figure B17. PRISMA flow diagram of the selection process for non-RCTs	127
Table B41. Eligibility criteria for selection of safety studies	128
Figure B18. PRISMA flow diagram of the selection process for safety studies.....	129
Table B42. Revised eligibility criteria used in the search for safety studies	130
Figure B19. PRISMA flow diagram of the revised selection process for safety studies	131
Table B43. Bibliographic details of primary safety studies in adult MDD population.....	132
Table B44. Incidence of TEAEs of $\geq 5\%$ in the open-label, long-term pool ²¹⁴	133
Table B45. Cost-effectiveness articles excluded following initial screening	142
Figure B20. PRISMA flow diagram of the selection process for cost-effectiveness studies	142
Figure B21. Decision tree for modelled events before possible switch to third line.....	144
Figure B22. Markov state transition diagram for modelled events following switch to third line.....	145
Table B46. Rationale for differences between submission model and CG90 model	146
Table B47. Disposition of 12-month time horizon according to events in the acute stage of the model	148
Table B48. Key features of the cost-effectiveness analysis	149
Table B49. Summary of primary sources of model parameters	153
Table B50. Probability assumptions for remission rates after switching to third- and fourth-line treatment	154

Table B51. Participation of experts in advisory board meetings.....	154
Table B52. Model parameter inputs: effectiveness.....	157
Table B53. Model parameter inputs: withdrawal due to side-effects	157
Table B54. Model parameter inputs: short-term side-effects (acute phase).....	158
Table B55. Model parameter inputs: long-term side-effects (maintenance phase).....	159
Table B56. Definition and results of analyses of REVIVE to generate utility values for model	161
Figure B23. PRISMA flow diagram of the selection process for HRQoL studies	163
Table B57. Comparison of utility values between potential sources	165
Table B58. Calculation of disutility value for weight gain.....	167
Table B59. Model parameter inputs: utility values	168
Table B60. Model parameter inputs: healthcare resource utilisation.....	171
Table B61. Model parameter inputs: absenteeism effects.....	171
Table B62. Model parameter inputs: unit costs of vortioxetine and other antidepressants	173
Table B63. Model parameter inputs: health state contingent costs	173
Table B64. Model parameter inputs: adverse event contingent costs.....	175
Table B65. Model parameter inputs: costs of absenteeism.....	176
Table B66. Structural and other assumptions tested in scenario analyses	177
Table B67. Deterministic sensitivity analysis: efficacy parameters.....	179
Table B68. Deterministic sensitivity analysis: short-term side-effects parameters (acute phase).....	179
Table B69. Deterministic sensitivity analysis: long-term side-effects parameters (maintenance phase)	180
Table B70. Deterministic sensitivity analysis: resource use parameters.....	181
Table B71. Deterministic sensitivity analysis: absenteeism parameters	182
Table B72. Deterministic sensitivity analysis: health state utility values.....	183
Table B73. Model outputs by clinical outcomes, for each comparator	184
Table B74. Breakdown of QALYs accrued by health state: vortioxetine vs. agomelatine	185
Table B75. Breakdown of QALYs accrued by health state: vortioxetine vs. sertraline.....	185
Table B76. Breakdown of QALYs accrued by health state: vortioxetine vs. venlafaxine	185
Table B77. Breakdown of QALYs accrued by health state: vortioxetine vs. citalopram	186
Table B78. Breakdown of costs accrued by category: vortioxetine vs. agomelatine.....	186
Table B79. Breakdown of costs accrued by category: vortioxetine vs. sertraline.....	186
Table B80. Breakdown of costs accrued by category: vortioxetine vs. venlafaxine	187
Table B81. Breakdown of costs accrued by category: vortioxetine vs. citalopram.....	187
Table B82. Results of the base-case analysis	188
Figure B24. Sensitivity analysis of incremental costs: vortioxetine vs. venlafaxine.....	189
Figure B25. Sensitivity analysis of incremental QALYs: vortioxetine vs. venlafaxine.....	189
Figure B26. Sensitivity analysis of incremental costs: vortioxetine vs. citalopram	190
Figure B27. Sensitivity analysis of incremental QALYs: vortioxetine vs. citalopram	190
Figure B28. Sensitivity analysis of incremental costs: vortioxetine vs. sertraline	191
Figure B29. Sensitivity analysis of incremental QALYs: vortioxetine vs. sertraline	191
Figure B30. Sensitivity analysis of incremental costs: vortioxetine vs. agomelatine	192
Figure B31. Sensitivity analysis of incremental QALYs: vortioxetine vs. agomelatine	192
Figure B32. Scatter plot of PSA: vortioxetine vs. venlafaxine.....	193
Figure B33. Cost-effectiveness acceptability curve: vortioxetine vs. venlafaxine.....	193
Figure B34. Scatter plot of PSA: vortioxetine vs. citalopram	194
Figure B35. Cost-effectiveness acceptability curve: vortioxetine vs. citalopram	194
Figure B36. Scatter plot of PSA: vortioxetine vs. sertraline	194
Figure B37. Cost-effectiveness acceptability curve: vortioxetine vs. sertraline	194
Figure B38. Scatter plot of PSA: vortioxetine vs. agomelatine	195
Figure B39. Cost-effectiveness acceptability curve: vortioxetine vs. agomelatine	195
Figure B40. Multiple cost-effectiveness acceptability curves: all comparators.....	195
Table B83. Scenario and structural sensitivity analyses: results vs. base case.....	197
Table B84. Threshold analysis of remission rates of vortioxetine.....	200
Table C1. Number of patients eligible for treatment over five years.....	207
Table C2. Market share forecasts: scenario without vortioxetine	208
Table C3. Market share forecasts: scenario with vortioxetine	209
Table C4. Drug unit costs.....	210
Table C5. Estimated budget impact to the NHS over the next five years.....	211
Figure C1. Estimated budget impact to the NHS over the next five years	211

Glossary

AC	Active comparator
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APRS	All patients randomised set
APTS	All patients treated set
ATC	Anatomical Therapeutic Chemical (classification system)
AWMSG	All Wales Medicines Strategy Group
BD (or BID)	Twice daily
BMI	Body mass index
CBT	Cognitive behavioural therapy
CG90	National Clinical Guideline 90. Depression: The Treatment and Management of Depression in Adults
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CSFQ-14	Changes in Sexual Functioning Questionnaire Short-Form
CUA	Cost-utility analysis
CGI-I	Clinical Global Impression - Improvement Scale
CGI-S	Clinical Global Impression - Severity Scale
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRA	Clinical Research Associate
CRF	Case record form
CPRD	Clinical Practice Research Datalink, formerly General Practice Research Database (GPRD)
CSFQ-14	Changes in Sexual Functioning Questionnaire short-form
DC-LD	Diagnostic Criteria-Learning Disabilities
DDD	Defined daily dose
DFFS	Depression and Family Functioning Scale
DSA	Deterministic sensitivity analysis
DSM	Diagnostic and Statistical Manual of Mental Disorders. Edition 4 (DSM-IV-TR) is in common use, e.g. in CG90, but was superseded by edition 5 (DSM-5) in 2013
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
eCRF	Electronic case record form
EE	Economic evaluation
EEG	Electroencephalograph
EMA	European Medicines Agency. Formerly abbreviated as "EMEA".
EPAR	European Public Assessment Report
EQ-5D	EuroQoL Questionnaire 5-Dimension
FAS	Full analysis set
FDA	Food and Drug Administration
FIBSER	Frequency, Intensity, and Burden of Side Effects Ratings

GHQ-12	General Health Questionnaire
GPRD	General Practice Research Database (see CPRD)
HAM-A	Hamilton Anxiety Rating Scale
HAM-D ₁₇	Hamilton Depression Rating Scale 17-item
HAM-D ₂₄	Hamilton Depression Rating Scale 24-item
HES	Hospital Episode Statistics
HRQoL	Health-related quality of life
HR	Hazard ratio
ICD-10	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
IMP	Investigational medicinal product
ITC	Indirect treatment comparison
ITT	Intention to treat
IVRS/IWRS	Interactive Voice/Web Response System
LOCF	Last observation carried forward
LREG	Logistic regression
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
MDE	Major depressive episode
MMRM	Mixed model for repeated measures
MTC	Mixed treatment comparison
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
OC	Observed cases
ONS	Office for National Statistics
OR	Odds ratio
PASS	Post-authorisation safety study
PBO	Placebo
PHQ-9	Patient Health Questionnaire
PMS	Psychiatric Morbidity Survey
PPS	Per protocol set
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QIDS-SR ₁₆	Quick Inventory for Depressive Symptomatology
QD	Once daily
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDS	Sheehan Disability Scale
SLAM	South London and Maudsley NHS Foundation Trust
SMC	Scottish Medicines Consortium

SmPC	Summary of Product Characteristics
SNRI	Serotonin-noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TEAE	Treatment-emergent adverse event
TESD	Treatment-emergent sexual dysfunction
TLV	Swedish Dental and Pharmaceutical Benefits Agency
WFSBP	World Federation of Societies of Biological Psychiatry
WHO	World Health Organisation
WHOQOL-BREF	World Health Organization Quality of Life-BREF: a 26-item brief version of the WHOQOL-100 instrument for measuring physical health, psychological health, social relationships, and environment
WLQ	Work Limitations Questionnaire

Executive summary

Registration status, licensed indication and target population

On 18th December 2013, vortioxetine (Brintellix[®]) was granted a European marketing authorisation for the following indication within major depressive disorder (MDD)¹:

“The treatment of major depressive episodes in adults”.

The decision problem addressed within this submission is concerned with a subset of the licensed patient population as follows:

Decision problem patient population¹

“Adult patients with moderate-to-severe MDD who are experiencing an MDE, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to alternative antidepressant”

Formulation, dosing, and mechanism of action

Vortioxetine is formulated as film-coated tablets available in packs of 28 in 5, 10 and 20mg strengths. The NHS acquisition cost is £27.72 per pack for all strengths of tablets.

Vortioxetine should be taken once daily. The starting dose for adults under 65 years of age is 10mg. Depending on individual patient response, the daily dose may be increased to a maximum of 20mg or decreased to a minimum of 5mg. The lowest effective dose of 5mg should be used as the starting dose in patients aged 65 years or over. As with other antidepressants, treatment for at least a further 6 months after the depressive symptoms resolve is recommended for consolidation of the response¹.

The mechanism of action of vortioxetine differs from all other antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs). Nonclinical data indicate that vortioxetine is an inhibitor of the 5-HT transporter, a property it has in common with other antidepressants, but it is also a 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, and 5-HT_{1A} receptor agonist. This multiple receptor profile has been shown to modulate neurotransmission in multiple systems, including predominantly the serotonin, but possibly also the noradrenaline, dopamine, histamine, acetylcholine, gamma-aminobutyric acid (GABA) and glutamate systems².

The burden of MDD and limitations of current treatment

Major depressive disorder (MDD) is a serious, episodic disorder characterised by a pervasive and persistent low mood. MDD affects 8-12% of the UK population³. The presentation of MDD is multifactorial⁴ and the DSM-5 criteria⁵ for diagnosis of an episode include a history for at least 2 weeks of sadness or loss of interest or pleasure in most activities (anhedonia), plus at least four of the following symptoms: irritability, sleep disturbances, loss of appetite, loss of sexual desire; lack of concentration; psychomotor retardation; suicidal thoughts. In addition to the diagnostic symptoms, MDD also impairs

¹ Herein referred to as the “switch population”.

work performance or education, social functioning and general health. It may also harm the wellbeing of the family⁶, including children⁷.

The course of an MDE varies between individuals depending on a range of factors.⁸ If left untreated, an episode may last from two months to several years, with an average duration of 5-6 months, but appropriate treatment of episodes can greatly reduce their duration and decrease mortality and morbidity rates⁹.

For moderate-to-severe MDEs, NICE Clinical Guideline 90¹⁰ recommends pharmacological and psychological therapy as options. If a pharmacological treatment is prescribed, a generic SSRI is recommended as initial treatment. While antidepressants are a mainstay of MDE treatment, the effectiveness of current treatments is modest and side-effects can be troublesome. In the landmark STAR*D study, less than half of patients with MDD responded to initial treatment with citalopram, the most commonly prescribed SSRI in the UK, and only 28% achieved remission¹¹. Other studies report comparably disappointing statistics for the effectiveness of initial therapy¹²⁻¹⁴. Intolerability to side-effects of antidepressant therapy is a further problem that may force patients to switch treatment¹⁵. As a result, as many as half of all patients may discontinue treatment within the first six months, with efficacy and tolerability concerns being the most frequently cited reasons¹⁶.

The magnitude of the individual burden of MDD is evident from utility estimates. In the UK Psychiatric Morbidity Survey, people with depression scored a mean EQ-5D utility of 0.57, the lowest of all mental and physical health problems¹⁷. The source of utility data used in NICE CG90, reported a mean EQ-5D utility of 0.33 for untreated patients experiencing an MDE. Eight percent of patients rated their health state as worse than death¹⁸. The same study reported that if remission could be achieved, a patients' EQ-5D score increased dramatically to 0.81. A Prospective Epidemiological Research on Functioning Outcomes Related to Major depressive disorder (PERFORM) study found that patients experiencing an episode and requiring a switch treatment suffered from graver effects on their HRQoL compared to those receiving initial treatment (EQ-5D: 0.45 vs 0.57 respectively)^{19,20}.

Failure of initial treatment imposes additional burden on switching patients, on the health service and on wider society. Patients who have encountered multiple episodes or multiple lines of treatment are at greater risk of suicide attempts²¹, hospital admissions,²² and impaired work productivity²³. Switch patients were likelier than those starting initial treatment to be admitted to hospital (4.6% vs. 2.7%, $p=0.134$) in the initial 12 weeks on treatment^{19,20}. They were also likelier to take time off work (35.1% vs. 21.8%, $p=0.001$) and those who did were absent for longer (47.3 vs. 27.9 days, $p=0.002$).

The impact of depression goes far beyond the individual patient. In 2007 in England alone, depression was estimated to account for £1.7 billion in direct healthcare costs annually, rising to a total cost of £7.5 billion when lost employment is included²⁴.

Rationale for the decision problem definition: vortioxetine for patients switching following inadequate response to initial treatment

The extent and undesirable consequences of initial treatment failure illustrate the unmet clinical and economic need for more effective and better-tolerated options for patients requiring a switch of treatment where such initial treatment has failed. Vortioxetine, by virtue of its distinct pharmacological profile, may be particularly suitable in the switch population.

The clinical evidence supports this as both direct and indirect evidence indicate that switch patients treated with vortioxetine achieve greater remission rates than agomelatine, sertraline, citalopram and venlafaxine, the latter 3 products being the most commonly used SSRIs and SNRI prescribed in the UK overall and within the switch population. In addition, these direct and indirect data show vortioxetine to have a favourable tolerability profile

leading to lower rates of withdrawals due to adverse events compared to the same basket of agents. Avoidance of a second treatment failure is an important clinical objective, and a switch antidepressant should promote adherence over the duration of acute and maintenance treatment.

The proposed positioning of vortioxetine is consistent with NICE's recommendation of "*an alternative SSRI or a newer-generation better tolerated antidepressant*" for patients making their first switch¹⁰.

Direct clinical evidence for vortioxetine

Vortioxetine has been studied in an extensive clinical development programme amounting to 24 completed trials involving over 7,000 patients. The submission focuses on the portion of clinical evidence and the outcomes that are relevant to the decision problem.

The relative efficacy of antidepressants cannot be assumed to be constant between initial and switch usage²⁵, and therefore only studies in populations switching after initial treatment were considered appropriate evidence sources. Two studies of vortioxetine, Study 14178A, (REVIVE) and TAK318 provided short-term efficacy and/or tolerability data relevant to the decision problem. UK clinical experts advised that tolerability and safety data are however likely to be transferable to a switch population. Therefore the long-term safety studies are pooled and presented.

Short-term switch data

REVIVE (Study 14178A)^{26,27}

REVIVE was a 12-week, international phase IIIb, double-blind, parallel group, randomised controlled trial. The primary objective of REVIVE was to compare the efficacy of flexible doses of vortioxetine (10–20 mg/day) with agomelatine (25–50 mg/day), after 8 weeks of treatment, on depressive symptoms in patients with MDD (≥ 18 and ≤ 75 years) who had a suboptimal efficacy response to SSRI/SNRI antidepressant monotherapy. A significant and clinically relevant improvement for vortioxetine versus agomelatine was observed on the MADRS total score at week 8 (MMRM estimates mean change from baseline: -16.5 and -14.4 respectively; mean difference -2.16; (95% CI: -3.51 to -0.81; $p = 0.002$)), with significance observed from week 4 and continued through the study. Rates of remission, as defined by a MADRS score of ≤ 10 , were also significantly higher for vortioxetine compared to agomelatine at weeks 8 and 12. The mean change in total scores was statistically in favour of vortioxetine on other scales as follows: MMRM: HAM-A total score: -1.9; CGI-S score: -0.3; CGI-I: -0.25. When comparing changes in EQ-5D summary index scores from baseline between the two groups, significant improvements were seen in the vortioxetine group compared to the agomelatine group from week 4 onwards. As early as week 4, the changes from baseline EQ-5D scores separated (0.16 and 0.08 for vortioxetine and agomelatine respectively, ($p < 0.001$); at week 8, 0.20 and 0.16 ($p = 0.03$) and at week 12, 0.25 and 0.20 ($p = 0.01$) (FAS, MMRM)). Along with HRQoL scores, vortioxetine was also observed to reduce disability and increase family functioning (as measured by the Sheehan Disability Score and Depression Family Functioning Scale respectively) compared to agomelatine (FAS, MMRM: -2.22 ($P < 0.01$) and -2.92 ($p < 0.01$) respectively).

Vortioxetine was generally well tolerated with fewer patients withdrawing over the study period than with agomelatine, a product which is often considered as the antidepressant with the most benign tolerability profile (5.9% versus 9.5% withdrawal rates in treatment groups at 12 weeks). Fewer patients in the vortioxetine group compared to the agomelatine group experienced SAEs (1.2% vs. 1.7%, respectively) over the 12-week period.

TAK 318²⁸⁻³⁰

TAK 318 was a phase IIIb, multicentre, randomised, double-blind, active-controlled, parallel-group, flexible-dose study comparing vortioxetine (10 to 20mg QD) with escitalopram (10 to 20mg QD) in subjects with well-treated MDD who were experiencing SSRI-induced sexual dysfunction.

The primary endpoint was change from Baseline in the CSFQ-14 total score after 8 weeks of treatment (FAS, MMRM). The least-squares mean difference of 2.2 points was statistically significant ($p=0.013$), indicating the improvement in sexual functioning for the vortioxetine group was superior to that in the escitalopram group.

Both treatments were also seen to maintain, and slightly improve, the depressive symptoms seen with the prior SSRI treatment as assessed by MADRS, CGI-S and CGI-I scores. Vortioxetine, again, was generally well tolerated with slightly higher rates of withdrawals due to AEs than escitalopram (9.4% vs 6.2%).

Long-term safety and tolerability

Long-term AE data were drawn from pooling five 12-month open-label extension safety studies (11492C, 11984B, 301, 13267B, 314). These studies permitted flexible doses of vortioxetine of 2.5 to 20mg/day, and included a total of 2,597 patients. Of these, 1,391 patients were exposed ≥ 52 weeks of treatment.

The incidence of TEAEs was 75% in the vortioxetine total group. The system organ classes (SOCs) with an incidence $\geq 20\%$ were gastrointestinal disorders, infections and infestations, and nervous system disorders. The incidence of TEAEs in the vortioxetine 15-20mg group was higher (79%) than that in the vortioxetine 2.5-10mg group (71%); the SOC with the highest incidence in both dose groups was gastrointestinal disorders (33% in the vortioxetine 2.5-10mg group and 42% in the vortioxetine 15-20mg group).

Generally, as recognised within the EPAR, TEAEs were mild-moderate and transient and did not usually lead to treatment discontinuation.

Indirect comparative clinical evidence

Relevant comparators

The relevant comparators, i.e. those frequently used in England in the switch population or/and recommended in NICE clinical guidance, were validated by clinical experts as the following: agomelatine, citalopram, fluoxetine, mirtazapine, sertraline and venlafaxine.

As the only head-to-head study of switch treatment with vortioxetine compared it with agomelatine, comparison with the remaining antidepressants required indirect methods. Despite a clear unmet need, research into the profile of antidepressants in the switch population has been limited. Therefore the systematic review undertaken to inform an ITC expanding the comparative data for vortioxetine identified studies to permit some, but not all, desired comparisons in spite of attempts to relax the eligibility criteria. Ultimately, a network was devised to support an ITC. The ITC compared vortioxetine with sertraline and citalopram, the most widely used SSRIs in the switch population; venlafaxine, the most widely used SNRI and agomelatine which, though not widely used in the UK, is effective^{31,32} and well-tolerated³³.

Indirect treatment comparison results

Using the analysis providing the most conservative relative results with respect to vortioxetine, the ITC estimated remission rates of: vortioxetine: 40.5%; agomelatine: 29.5%; sertraline: 26.1%; venlafaxine: XR 33.3% and citalopram: 23.7%. The estimated rates of

withdrawal due to adverse events were: vortioxetine: 5.9%; agomelatine: 9.5%; sertraline: 18%; venlafaxine XR: 18.2% and citalopram: 18%.

These results indicate that within the switch population vortioxetine is more efficacious and better tolerated than commonly used antidepressants in the UK.

Economic evaluation

Methods

The economic evaluation was model-based and incorporated a decision tree with a Markov component to model subsequent switches to third and later lines. The analytic horizon is 12 months. This reflects previously published models³⁴ including that of CG90 and is adequate to capture a single MDE. The clinical starting point is a cohort of adult patients with MDEs who are switching to a new treatment following inadequate response in terms of efficacy and/or tolerability to initial treatment. Remission is the efficacy endpoint, as this is the treatment goal for most patients and the most frequently used efficacy outcome in other CEAs³⁴⁻³⁶.

A limitation acknowledged in the discussion of the CG90 model was that the tolerability profiles of the treatments were not considered. Within the economic evaluation presented here, the impact of AEs is modelled as: i) withdrawal due to AEs in the acute phase, ii) occurrence of short-term adverse events in the acute phase and the occurrence of long-term adverse events in the maintenance phase.

Results

The base-case results of the cost-effectiveness analysis are presented below:

Executive Summary Table 1. Base-case cost-effectiveness results

Comparators	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Venlafaxine	£964	0.675	-	-	-
Vortioxetine	£971	0.694	£7	0.019	£378
Citalopram	£976	0.664	£5	-0.030	Dominated
Sertraline	£977	0.664	£0	-0.001	Dominated
Agomelatine	£1,082	0.676	£105	0.012	Dominated (ext)

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Costs are at 2014 levels. Dominated ext: Dominated by extended dominance.

In deterministic sensitivity analyses, the most influential driver of the results was the difference in 8-week remission rate between the comparators. Various scenarios and structural sensitivity analyses were conducted, in which vortioxetine was either dominant or had an ICER of no greater than £1,561 per QALY gained. Given the impact of depression on workplace performance, the impact of absenteeism was assessed in a partial societal analysis, in which vortioxetine dominated all four comparators. In probabilistic sensitivity analysis, vortioxetine had a probability of 78% of being the cost-effective option of the five comparators, given a willingness-to-pay of £20,000 per QALY gained.

Benefits not captured within the analysis

The base-case results indicate that vortioxetine is a cost-effective treatment option for switch patients in England and Wales. The analysis did not account, however, for the full array of benefits associated with vortioxetine as certain aspects were not modelled.

Firstly, in REVIVE, vortioxetine showed benefits over agomelatine on a range of functioning outcomes other than EQ-5D, including improvements in work, social and family functioning, as measured on validated scales. These benefits are unlikely to have also been captured fully by the EQ-5D, particularly the extrapersonal benefits accruing to spouses and children.

Furthermore, there is preliminary evidence for beneficial effects of vortioxetine on symptoms of cognitive dysfunction within MDE, which are thought to be mediated through the agent's distinct mechanism of action^{37,38}. Vortioxetine's effect on cognitive dysfunction in MDD has been shown to be independent from its effect on the MADRS score^{37,38}. Difficulties in thinking and concentrating are well-known symptoms of the acute phase of an MDE, but recent studies indicate cognitive dysfunction may also be an enduring component of MDD, associated with residual symptoms, delayed functional recovery or relapse³⁹.

In addition to these points, a broader consideration is whether the societal preference-based measurement of HRQoL is able to capture the full impact of mental health conditions on quality of life. Due to the limitations of current methods, Fujiwara and Dolan claim that "traditional valuation methods have understated the value of mental health (in relation to physical health) and, as a result, the value and social benefit of mental health interventions too"⁴⁰. Such shortcomings of utility measurement based on societal preferences may hinder progress towards "parity of esteem" between mental and physical health⁴¹, which has become a statutory requirement of the Health and Social Care Act.

Overall conclusions

This submission has considered the clinical and cost-effectiveness of vortioxetine as switch therapy in patients with MDEs who wish to switch antidepressant therapy following inadequate response in terms of efficacy or tolerability to initial treatment with an SSRI or SNRI. Within this population, vortioxetine has demonstrated a favourable effectiveness and tolerability profile compared with other widely-used antidepressants in England and Wales, and provides a valuable new treatment option.

The analyses presented in the submission show that the use of vortioxetine in this application is likely to be a clinically and cost-effective allocation of healthcare resources in the National Health Service in England and Wales.

Section A – Decision problem

1 Description of technology under assessment

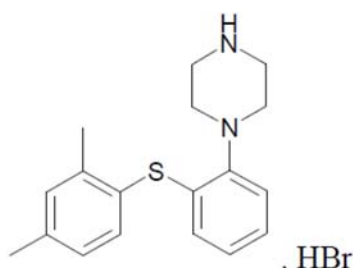
1.1 Name and therapeutic class

Brand name: Brintellix®

Approved name: Vortioxetine (formulated as vortioxetine hydrobromide)

Lundbeck research compound name: Lu AA21004

Chemical name and structure: 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide

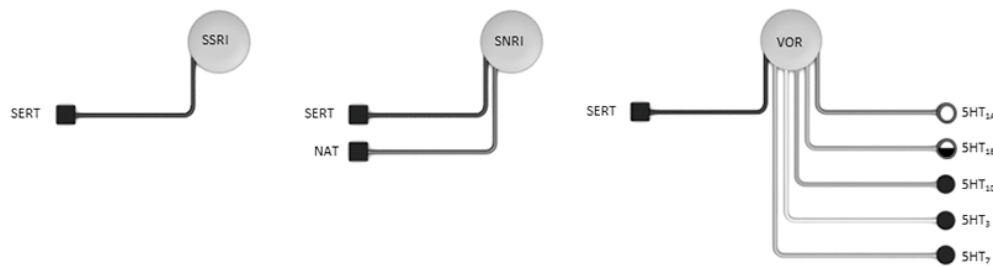


Therapeutic class: Other antidepressants (ATC-code: N06AX26)

1.2 Principal mechanism of action

The mechanism of action of vortioxetine differs from all other antidepressants (ADs), including specific serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs). The antidepressant effects of SSRIs are attributed to the elevation of serotonin (5-hydroxytryptophan, (5-HT)), mediated via blockade of the serotonin transporter (SERT). SNRIs mediate their antidepressant effects via elevations of serotonin and – at higher doses – noradrenaline via blockade of SERT and the norepinephrine transporter (NAT), respectively. Nonclinical data indicate that vortioxetine is an inhibitor of the 5-HT transporter, which property it has in common with other antidepressants, as well as being a 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, and 5-HT_{1A} receptor agonist. This multiple receptor profile has been shown to modulate neurotransmission in multiple systems, including predominantly the serotonin, but possibly also the noradrenaline, dopamine, histamine, acetylcholine, gamma-aminobutyric acid (GABA) and glutamate systems². This multimodal activity, as shown in Figure A1, is considered responsible for the improvement of cognitive function, learning and memory observed with vortioxetine in animal studies, in addition to the existing antidepressant and anxiolytic-like effects².

This activity in several transmitter systems is assumed to be important for the broad antidepressant activity and favourable tolerability profile of vortioxetine. Its multimodal mechanism may make vortioxetine particularly suitable for patients who do not respond adequately to SSRIs or SNRIs or patients who cannot tolerate these types of antidepressants. In addition, improvements in cognitive dysfunction in patients with major depressive disorder (MDD) have been demonstrated in studies 202 (CONNECT), 14122A (FOCUS)⁴², 12541A (elderly)⁴³, and 316⁴⁴.

Figure A1. Targets of SSRIs, SNRIs and vortioxetine

1.3 UK marketing authorisation

The European Medicines Agency (EMA) granted the marketing authorisation on 18 December 2013, following positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 24 October 2013 (EMA/CHMP/630715/2013).

The marketing authorisation for vortioxetine is licensed for the treatment of major depressive episodes (MDE) in adults. The marketing authorisation only covers MDEs that are associated with major depressive disorder (MDD), but not with other distinct indications such as bipolar disorder. Please see section 2.1 for additional information regarding MDE as the characterising feature of MDD.

As will be explained in section 2.5.2, the decision problem will address a subset of the patient population included in the marketing authorisation and the scope. **Lundbeck will present evidence for the clinical and cost-effectiveness of vortioxetine as a switch treatment for adults experiencing an MDE, after inadequate response (in terms of efficacy and/or tolerability) to initial antidepressant treatment with an SSRI or SNRI.**

1.4 Main regulatory issues

The EMA concluded in the European Public Assessment Report (EPAR): *“Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Brintellix in the treatment of major depressive episodes in adults is favourable and therefore recommends the granting of the marketing authorisation”*. The EMA has accepted a risk management plan, which includes a non-interventional post-authorisation safety study (PASS) of vortioxetine in Europe. However, as with any submission to the EMA, comments and questions were raised through the regulatory process. The key discussion points were as follows and will be briefly outlined in this section:

- Active reference arms do not allow valid head-to-head comparison
- Switch study (14178A, REVIVE): ensuring enrolment of inadequate responders to initial treatment
- Effect of vortioxetine on cognitive dysfunction
- US vs. non-US clinical trials
- Dosage in the elderly
- Negative/failed studies
- Mechanism of action

1.4.1 Active reference arms do not allow valid head-to-head comparison

In some of the placebo-controlled studies (see Appendix 14), an active reference was included as an internal control: duloxetine was the active reference in 5 studies and venlafaxine in one study. The EPAR noted: *“although no formal comparison was conducted, numerically larger effect sizes were observed for the active reference than for vortioxetine, except in studies 11492A and 11984A. The exclusion of non-responders and the inclusion of previous responders in the active reference arm could have introduced a bias in favour of the efficacy of the active reference, so differences in the efficacy of vortioxetine versus the active reference cannot be inferred on the basis of these studies.”* This issue is discussed further in section 2.8.

1.4.2 Switch study: ensuring enrolment of inadequate responders

In a European Phase IIIb Study 14178A (REVIVE), vortioxetine was compared to agomelatine in adults who had depressive symptoms and who were non or partially responsive to no more than one adequate course of SSRI/SNRI monotherapy by the following *a priori* definition. Patients had to be considered by investigators to be non- or partial responders, which is consistent with the use of clinical judgement to assess treatment response in routine practice.

The CHMP asserted that fully responsive patients could have been included in the study since the severity of depression was not assessed prospectively at the onset of the first monotherapy during the lead-in period. Lundbeck has responded to the EMA that it considers that the absence of a baseline score prior to the initial treatment phase does not invalidate the population definition. The requirement of a baseline MADRS total score at study entry ≥ 22 implies that patients fully responsive to previous treatment would need to have a total score ≥ 44 prior to the initiation of the previous treatment. Patients with a MADRS total score ≥ 44 points are very rare: only 0.6% of the patients included in all the short term placebo-controlled studies in the clinical programme in MDD with vortioxetine had such a high MADRS total score.

1.4.3 Effect of vortioxetine on cognitive dysfunction

The EPAR states² that *“Cognitive impairment is recognised as an important characteristic during the acute phase of MDD”,* and that *“additional nonclinical data have been generated that strengthen that vortioxetine has the potential to enhance cognitive function”*. (Please note: cognitive impairment is considered synonymous with, and within this submission will be referred to as, cognitive dysfunction). The CHMP acknowledged the specific cognitive symptoms evaluated in four placebo-controlled, short-term studies (Studies 14122A, 12541A, 316, and 317) that were included in the Marketing Authorisation Application (MAA). The CHMP also recognised that cognitive dysfunction in MDD is even more pronounced in the elderly. Furthermore, the efforts already undertaken in Study 14122A, where cognitive dysfunction was the primary endpoint, were acknowledged. However, the CHMP considered these data *“not to be sufficient to support the claim of an independent effect on cognition”* in the overall population, and that an active reference, for example, duloxetine, should be included for internal validity (assay sensitivity). Since Brintellix® (vortioxetine) was granted marketing authorisation for the treatment of MDE, Study 202 has been completed. Study 202 was a short-term, placebo-controlled, active-reference (duloxetine) study with vortioxetine (10-20mg/day flexible dosing) in which cognitive dysfunction was the primary endpoint. With the completion of Study 202, the effects on cognitive dysfunction shown in the study in the elderly (Study 12541A) have been supported in the adult population, (in addition to Study 14122A), adding to the evidence for an independent and distinct effect of vortioxetine on cognitive dysfunction. With this strengthened evidence base, Lundbeck has

applied for a licence variation, with the benefits of vortioxetine on cognitive dysfunction being added to section 5.1 of the licence. A decision from the EMA is expected in Q1 2015.

1.4.4 US vs. non-US clinical trials

Over the last two or three decades there has been a steady decline worldwide in the antidepressant-placebo difference reported in clinical studies⁴⁵⁻⁴⁹. In recent years this decline appears to be particularly pronounced in studies conducted in the US⁵⁰, although the reasons for this remain elusive. No single causative factor can be isolated to explain the differences between studies conducted inside and outside the US. It does seem, however, that issues around study conduct, including patient selection and adherence to the protocol and study regimen are critical. For these reasons it was relevant to analyse the effect of vortioxetine in studies conducted outside the US.

The EPAR notes that when the results from the non-US trials of vortioxetine were meta-analysed, both the effect sizes and the increased effect with increasing dose were more pronounced. It was noted that the lower efficacy observed in the US studies, which drives this difference, is hard to explain.

1.4.5 Dosage in the elderly

It is noted in the EPAR that data available in the elderly population are limited. Of the short-term studies roughly 13% of patients were aged 65 years and over. The EPAR also notes that in the pool of elderly patients receiving vortioxetine the 15mg dose had no effect and the 20mg dose failed to separate from placebo but based on the number of elderly patients on these doses no conclusion could be drawn from these findings.

With respect to the 5mg dose, the EPAR also states that in the elderly *“the safety profile was not different from that in patients aged <65”*.

The SmPC has recognised that the evidence base is limited for doses over 10mg within the elderly, and recommends a 5mg start dose in these patients and caution when prescribing dosages of over 10mg. Despite the limited evidence it should be highlighted that according to the licence, age does not preclude the use of higher dosages in the elderly population if it is clinically suitable.

1.4.6 Negative/failed studies

Three studies (all of which were short-term studies conducted in the US) of the 13 completed phase II/III studies (12 short-term studies and 1 relapse-prevention study) with vortioxetine in MDD did not support efficacy. This is not uncommon in depression; of the randomised, placebo-controlled studies conducted in support of an antidepressant claim, approximately 50% have failed⁵¹. Considering this, the success rate for the clinical studies with vortioxetine is high. Furthermore, among the positive studies with vortioxetine was a positive study in the elderly, a population in which most antidepressants have failed to show efficacy⁴³. The EPAR comments that *“negative studies are not uncommon in MDD due to the lack of sensitivity”*. This phenomenon is discussed further in section 2.8.

1.4.7 Mechanism of action

The unique mechanism of action of vortioxetine was challenged within the EPAR with statements such as *“Vortioxetine exerts its antidepressive mechanism solely by serotonergic regulation, similar to duloxetine, escitalopram, fluoxetine, and sertraline”* and *“the mode of action of vortioxetine remains largely elusive”*.

Lundbeck refuted arguments that the mechanism of action of vortioxetine is similar to other antidepressants, as it has been demonstrated that its effect is mediated through multiple mechanisms. In addition to raising serotonin in relevant brain areas, vortioxetine also increases noradrenergic, dopaminergic, cholinergic, histaminergic and glutaminergic neurotransmission in brain structures associated with MDD⁵². Studies of occupancy of the serotonin transporter^{52,53} suggest that vortioxetine does not act purely through this mechanism.

The exact mode of action of many psychoactive medicines cannot be definitively identified. The World Health Organisation (WHO) categorisation of vortioxetine into the “others” Anatomical Therapeutic Chemical (ATC) classification system is consistent with the evidence that vortioxetine acts through multiple mechanisms of action and is distinct from all other available antidepressants.

1.4.8 Conclusions

Despite the above questions which were raised, the EMA was satisfied that the short and long-term efficacy of vortioxetine for the treatment of MDEs in adult patients had been established. Based on the regulatory package submitted, vortioxetine was granted a licence for the treatment of major depressive episodes in adults.

1.5 Indication

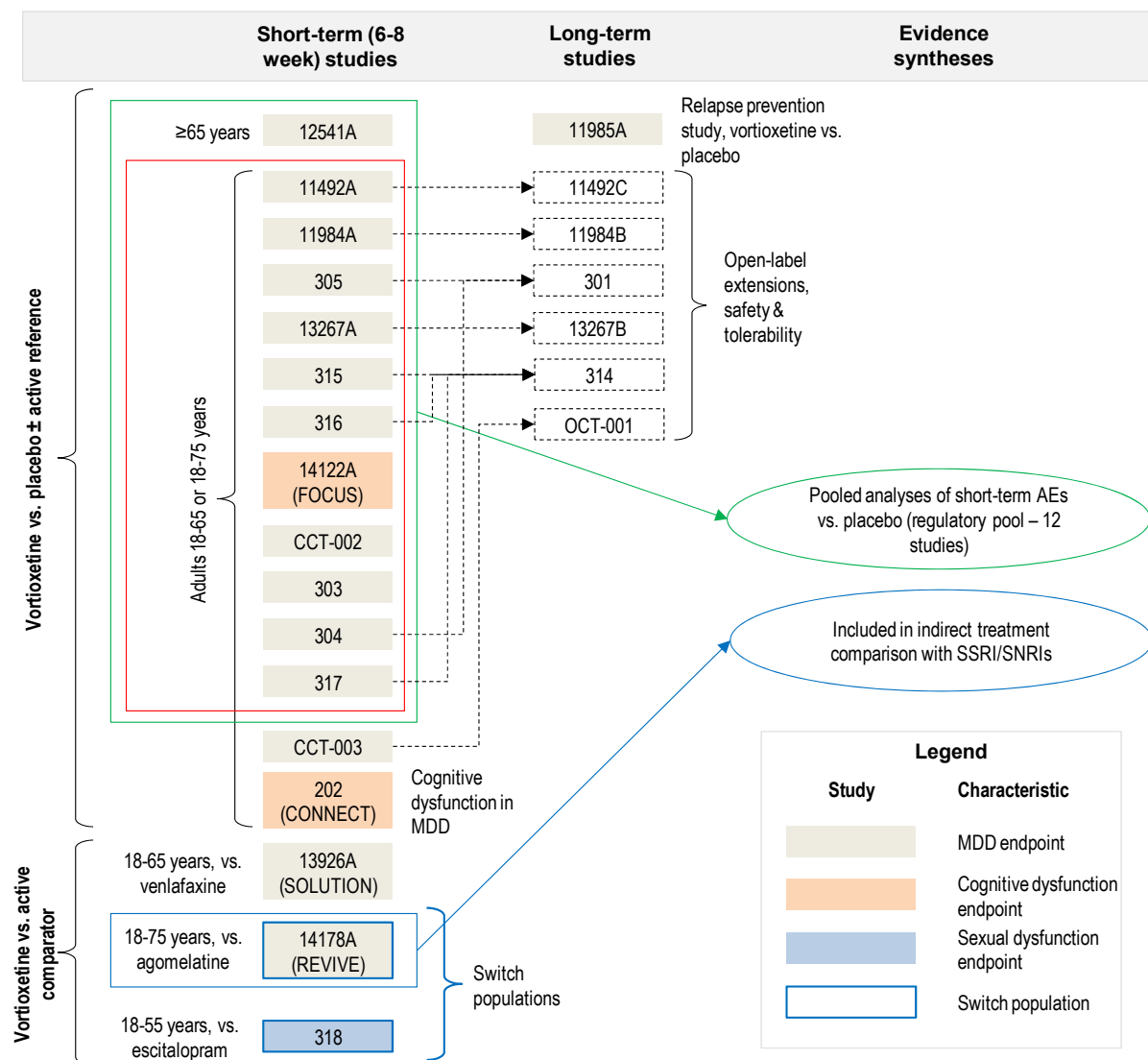
The SmPC states “*Brintellix is indicated for the treatment of major depressive episodes in adults*”.

A major depressive episode (MDE) is not a disorder in itself, but rather is a clinical manifestation of major depressive disorder (MDD), as explained in section 2.1.2 below.

1.6 Completed and ongoing studies

Figure A2 provides an overview of the completed clinical trials of vortioxetine in adults with MDD to be presented later in this submission. The trials in switch populations (Study 14178A [REVIVE]) and Study TAK318), which are pivotal to the decision problem, are reported in section 6 below, while the remaining trials are reported in Appendix 14. This Appendix also contains tabulations of all these trials including study design summaries and cross-references between Lundbeck/Takeda study numbers, clinicaltrials.gov IDs and publications.

The ongoing vortioxetine development programme includes a paediatric programme, and four smaller scale clinical trials investigating the effect of vortioxetine on electroencephalograph (NCT02072278) in healthy volunteers and on cognitive dysfunction in patients in different stages of MDD in three phase III studies (NCT02272517, NCT02279953 and NCT02279966). These studies are not due to complete until 2016 and are beyond the scope of this application.

Figure A2. Overview of clinical evidence for vortioxetine in adults with MDD

1.7 Expected date of availability in the UK

The expected date of availability of vortioxetine in the UK is June 2015.

1.8 Regulatory approvals outside the UK

Vortioxetine was approved by the Food and Drug Administration (FDA) on 30 September 2013 and is co-marketed in the USA by Takeda Pharmaceuticals and Lundbeck. Vortioxetine is also approved in all 28 European Union member states plus Iceland, Liechtenstein and Australia.

1.9 Other health technology assessment in the UK

Vortioxetine is expected to be appraised by the Scottish Medicines Consortium (SMC), with submission scheduled for mid-2015. The All Wales Medicines Strategy Group (AWMSG) was unable to appraise the use of vortioxetine within NHS Wales due to non-submission (7 May 2014). Lundbeck did not submit to the AWMSG because the product was not expected

to be available in the UK until 2015. Vortioxetine was scheduled in the NICE STA programme, which covers both England and Wales.

1.10 Cost of vortioxetine to the NHS

The expected costs to the NHS associated with the therapeutic use of vortioxetine are shown in Table A1.

1.11 Use of concomitant therapies

As will be described in section 2.1, MDD can be categorised by severity: mild, moderate and severe. For people with moderate or severe MDD, NICE CG90¹⁰ recommends that antidepressant medication be combined with a high-intensity psychological intervention, usually cognitive behavioural therapy (CBT) or interpersonal therapy (IPT).

Table A1. Unit costs of vortioxetine

Pharmaceutical formulation	Film-coated tablets, 5mg, 10mg, 20mg. (Also approved but not available: 15mg tablets).
Pack sizes	5mg x 28 10mg x 28 20mg x 28
Acquisition cost (excluding VAT)	5mg x 28: £27.72 per pack 10mg x 28: £27.72 per pack 20mg x 28: £27.72 per pack
Method of administration	Oral
Posology	The starting and recommended dose is 10mg once daily in adults less than 65 years of age. The lowest effective dose of 5mg vortioxetine once daily should always be used as the starting dose in patients ≥65 years of age.
Average length of a course of treatment	After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response (see SmPC).
Average cost of a course of treatment	Approximately £220 for patients who achieve remission after an acute phase of treatment, assuming treatment is continued for 240 days or 8 months (assumed 8 weeks in acute phase and 6 months' consolidation) in total.
Expected average interval between courses of treatments	According to need, depending on whether remission is sustained through the recommended period of maintenance treatment or whether a MDE recurs. (See section 2.1 for additional information on the course of disease).
Expected number of repeat courses of treatments	According to need, depending on recurrence of MDEs. Recurrence of episodes is a feature of MDD, but the course of disease is highly variable (see section 2.1).
Dose adjustments	Depending on individual patient response, the dose may be increased to a maximum of 20mg once daily or decreased to a minimum of 5mg once daily. Adjustments are normally made early in treatment with assessment of response and tolerability at 2-4 weeks.
Special populations	The lowest effective dose of 5mg vortioxetine once daily should always be used as the starting dose in patients ≥65 years of age. Caution is advised when treating patients ≥65 years of age with doses higher than 10mg vortioxetine once daily for which data are limited. Dose adjustments may be considered in patients taking concomitant medications that induce or inhibit the P450 cytochrome system (see SmPC for details). The safety and efficacy of vortioxetine in children and adolescents aged less than 18 years has not been established.
Additional tests or investigations needed to identify suitable patients, or particular administration requirements	None.
Monitoring	Usual clinical practice for antidepressants (see Figure A5).
Other therapies likely to be administered at the same time as the intervention as part of a course of treatment	Antidepressant therapy may be provided in combination with a high-intensity psychological intervention, such as cognitive behavioural therapy or interpersonal therapy.
VAT: value-added tax; SmPC: Summary of Product Characteristics; MDE: major depressive episode; MDD: major depressive disorder	

2 Context

2.1 Overview of major depressive disorder and its course

2.1.1 Summary

Major depressive disorder (MDD) is a serious mental disorder characterised by a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities. MDD adversely affects a person's work or education, sleep, energy and motivation, ability to think or concentrate, social functioning and general health. It may also harm the wellbeing of family members, including children.

2.1.2 Terminology

As in other areas of mental health, the terminology used in the field of depressive illnesses is not straightforward. While formal diagnostic categories such as MDD and major depressive episode (MDE) are defined, terms and definitions have evolved over time. Less formal terms, such as “depression” also remain in professional as well as lay usage. It is therefore necessary to review the accepted terminology and to define the conventions used in this submission.

MDD and other types of depressive illnesses are specified in the standard classification of mental disorders used by mental health professionals in the United States, the Diagnostic and Statistical Manual of Mental Disorders (DSM)⁵⁴. The terminology and diagnostic criteria for depressive illnesses is complex and definitions have changed over the years. The term “major depressive episode” (MDE) is not in itself a diagnosis, but is the essential clinical characteristic if a diagnosis of MDD is to be made. An MDE is defined as the occurrence of one of: a depressed mood, or a loss of interest or pleasure in life activities for at least 2 weeks, and at least five of the following symptoms that cause clinically significant impairment in social, work, or other important areas of functioning almost every day:

1. Depressed mood most of the day.
2. Diminished interest or pleasure in all or most activities.
3. Significant unintentional weight loss or gain.
4. Insomnia or sleeping too much.
5. Agitation or psychomotor retardation noticed by others.
6. Fatigue or loss of energy.
7. Feelings of worthlessness or excessive guilt.
8. Diminished ability to think or concentrate, or indecisiveness.
9. Recurrent thoughts of death (not just fear of dying but recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide)

Depressive episodes also occur in the context of several other mood disorders, including bipolar disorder, persistent depressive disorder (sometimes known as dysthymia) and substance-induced mood disorder. An MDE, however, denotes a diagnosis of MDD. For the purposes of this submission, Lundbeck is concerned only with MDEs, as the precise regulatory indication for vortioxetine is “*treatment of major depressive episodes in adults*”.

The simple term “depression” is in common medical usage to refer to clinically diagnosed depressive illness. The convention within this submission is to use the term “depression” only when citing literature that does not use more specific diagnostic terms, for example the

health economics and outcomes research literature. Where possible, we use preferentially the specific terms MDD and MDE, such as when referring to the scope of the appraisal, clinical guidelines for MDD or citing clinical evidence in subjects with MDD. We use the terms “episode” and MDE interchangeably to refer to major depressive episodes in the context of MDD.

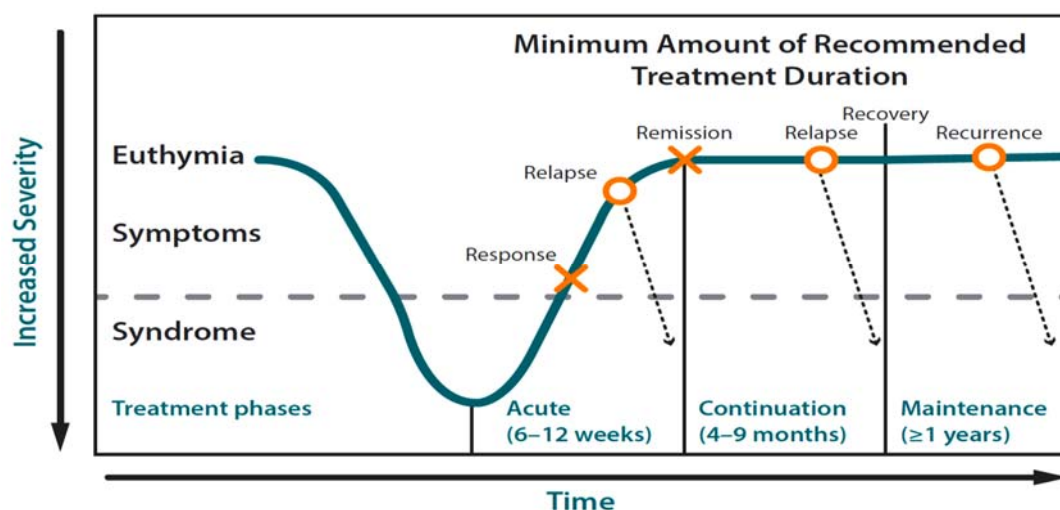
The diagnostic definitions used in NICE CG90 are based on the DSM-IV-TR⁵⁵. Although this edition of the DSM has recently been superseded by DSM-5⁵⁴, the changes with respect to depressive disorders do not materially affect the above definitions of MDD and MDE.

2.1.3 Aetiology and natural history

Many hypotheses have been proposed for the underlying mechanism of depressive disorders, but no unifying mechanism has been accepted as accounting for all manifestations of this heterogeneous cluster of disorders. In reviewing this topic, Belmaker and Agam⁵⁶ conclude: “*Avoidance of premature closure on any one scientific theory of the mechanism of depression will best serve the search for new, more effective treatments.*”

MDD is distinct from the symptoms precipitated by distressing events such as bereavement. In MDD, symptoms do not remit if an identifiable external cause dissipates, and such symptoms are disproportionate to their cause⁵⁶. Nevertheless, severe states of depression often have no external precipitating cause. The course of MDD varies across individuals depending on a range of factors⁸. If left untreated, an MDE may last from two months to several years, with an average duration of 5-6 months, but appropriate treatment can greatly reduce the duration of episodes and decrease mortality and morbidity rates⁹. There is consensus⁵⁷⁻⁵⁹ that five recognisable and measurable events characterise the potential course of an MDE: response, remission, recovery, relapse and recurrence, as illustrated in Figure A3.

Figure A3. Diagrammatic representation of the course of an MDD episode (after Bakish 2001⁶⁰ and Zimovetz 2012³⁴)



2.1.4 Treatment objectives

Recommended treatment of episodes of moderate-to-severe MDD includes offering patients pharmacological intervention with antidepressants and offering psychological therapy, such as cognitive behavioural therapy (CBT). While there is strong evidence for the effectiveness of both types of interventions in MDD as a whole, individual patient response is variable and the relative value of each type of intervention can be difficult to predict without adequate trial.

Response to treatment must be carefully monitored irrespective of the chosen treatment modality, and efficacy of antidepressant treatment is usually evaluated 2-4 weeks after the primary care provider starts treatment. Response is normally defined as a 50% or greater decrease in severity of symptoms compared with baseline⁶¹. However, contingent on achievement of response, remission at 6-12 weeks is considered the next treatment goal. Remission is the absence of core symptoms of depression (as described in the definition above), and is usually measured in terms of a cut-off point on one or more depression scales⁵⁹. Nevertheless, MDD is a chronic illness, and continuation of treatment up to the point of recovery (maintenance phase) following remission is a standard recommendation^{10,61}. In instances when symptoms recur after the recovery phase, such recurrence is considered to be a further episode of depression, to distinguish it from a relapse of the same episode. Though there is no consensus on exactly how long remission should be sustained in order to be able to declare recovery, it should be at least 4 and up to 9 months¹⁰. NICE Clinical Guideline 90 (CG90)¹⁰ recommends that after resolution of depression symptoms (i.e. remission), treatment should be continued for at least 6 months to consolidate response. Reflecting this accepted set of definitions, response and remission are conventional endpoints in short-term regulatory clinical trials of antidepressants while longer-term evidence for relapse prevention is also required for regulatory approval.

In clinical practice, the problem of partial or nonresponse to treatment is recognised as a problem¹⁰. Approximately one third to one half of patients treated for depression do not respond satisfactorily to initial antidepressant pharmacotherapy, which is usually an SSRI^{11,62}. Also, intolerable side-effects can lead to poor adherence or premature withdrawal, though the extent and types of side-effects tend to vary between different classes of antidepressants. Initial response may be apparent in as little as 2 to 4 weeks with continuing improvement thereafter, so there is little reason to persevere beyond approximately 8 weeks with a failing initial treatment when switching to one of the available alternative agents is easily possible. Consequently, switching between antidepressants is very common, and treatment of an MDE may involve multiple lines of treatment. Nevertheless, the goal is to achieve remission with as few steps as possible, and it is known that the probability of success diminishes with each additional switch¹¹, so the choice of a second-line treatment when switching from failed first-line treatment is an important question. The frequency of switching and clinical evidence to guide the choice of switch treatment are discussed in sections 2.6.3 and 0, respectively.

The 2010 NICE Guideline (CG90)¹⁰ notes that although depression has been thought of as a time-limited disorder, it is now clear that relapse and recurrence are common. The WHO study of mental disorders in 14 centres across the world found that 50% of patients still had a diagnosis of depression one year later⁶³ and at least 10% had persistent or chronic depression⁶⁴. This high rate of continuing morbidity can be attributed to failure to achieve durable control of symptoms, whether inadequate initial response to treatment, relapse within an episode or recurrence of episodes. At least 50% of patients, following their first MDE, will go on to have at least one more episode and, after the second and third episodes, the risk of further recurrence rises to 70 and 90%, respectively⁶⁵.

2.1.5 The burden of treatment failure

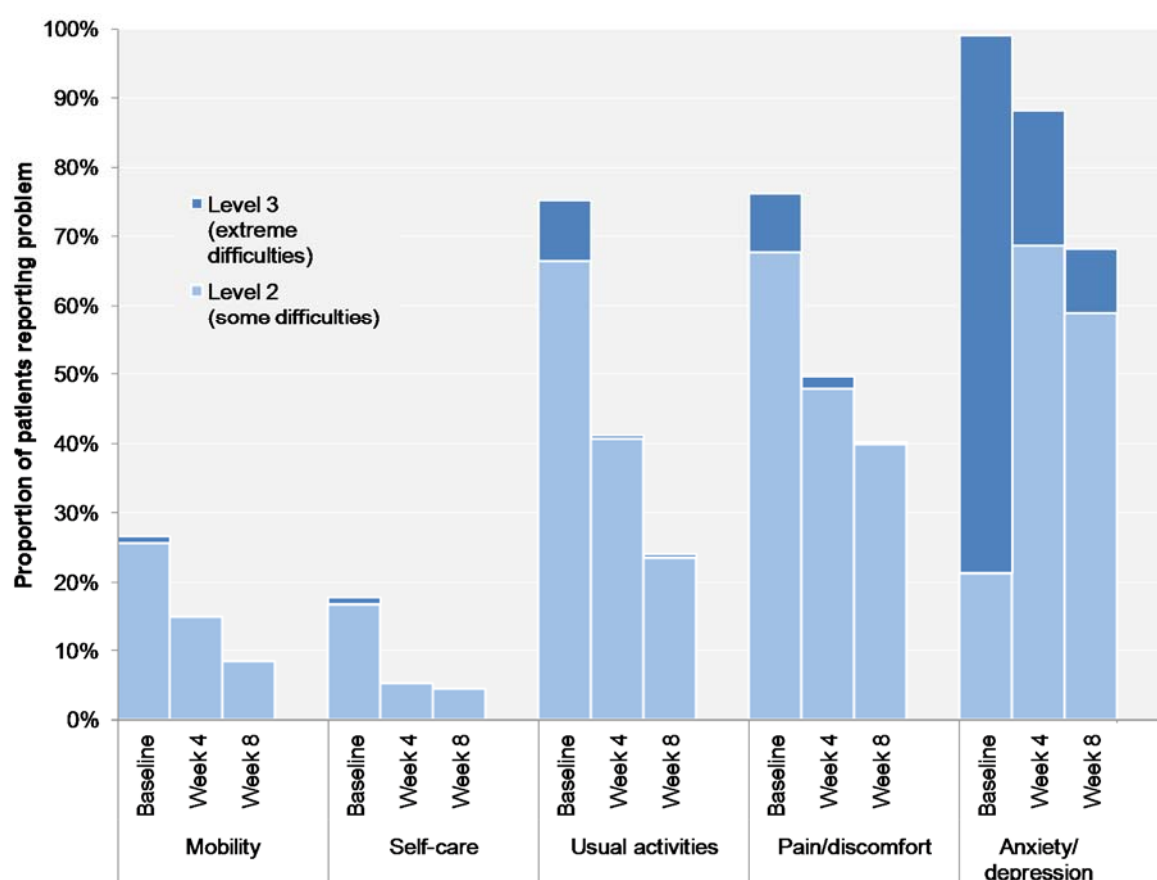
Among people with depression, those who have encountered multiple episodes or multiple lines of treatment are at greater risk of suicide attempts²¹, hospital admissions²², and impaired work productivity²³. Such undesirable consequences of failing to achieve control early in the course of MDD underline the importance of having effective and well-tolerated treatment options available at initial switch that patients will adhere to. The ideal treatment should support the clinical objectives of first achieving remission from the current MDE and then sustaining recovery.

2.1.6 Health-related quality of life impact of depression

MDD has a severe impact on patients' health-related quality of life (HRQoL). In an English study¹⁷ of the HRQoL impact of four mental health conditions (depression, anxiety, phobia and panic) using pooled data from the nationally representative adult Psychiatric Morbidity Surveys (PMS), the mean utility for depression was the lowest of all mental and physical health problems. Individuals with depression scored a mean utility of 0.57, as compared to those with generalised anxiety disorder (0.64), mixed anxiety depressive disorder (0.68) and no mental health problems (0.84). Depression scores also showed greater variability, reflecting heterogeneity in the impact of depression on patients' well-being.

A prospective cohort study¹⁸ of French primary care patients reported an even greater impact in patients with a DSM-IV diagnosis of MDD. The mean EQ-5D utility at baseline for an untreated patient with MDD experiencing a depressive episode was 0.33 (sd 0.25, range -0.59 – 0.85), and 8% of patients rated their health state as worse than death. The same study reported that if remission could be achieved, a patients' EQ-5D score increased to 0.81, demonstrating the substantial and achievable scope for improvement following appropriate care in general practice. As Figure A4 shows, the HRQoL burden encompassed not only anxiety/depression but also pain/discomfort and difficulties with usual activities for a majority of patients. The improvement that occurred over 8 weeks of treatment was manifest over all affected domains. This study was considered the most suitable source of utility data by the authors of the CG90 economic model.

Figure A4. Proportions of patient cohort with MDD reporting problems on EQ-5D dimensions (after Sapin 2004¹⁸)



Furthermore, there is evidence that the impact of MDD on HRQoL may be more pronounced in patients requiring switch from an initial inadequate treatment. In the PERFORM study¹⁹, patients starting switch treatment had a lower utility (0.449) at baseline than those starting initial treatment (0.567).

Aside from the utility impact of depression symptoms, the tolerability profiles of many leading antidepressants are poor, so side-effects may impose an additional HRQoL burden (see section 2.6.2). Better-tolerated antidepressants may lead to substantial improvement in quality-adjusted survival through two beneficial effects: first by decreasing the incidence of side-effects, particularly those that tend to be chronic and troublesome, and second by avoiding consequent premature withdrawal, leading to improved remission rates and prevention of relapse.

In conclusion, these studies show that the HRQoL impact of MDD is as profound or even more so than any other common physical or mental disorder, and particularly so in switch patients.

2.1.7 Family impact of depression

The impact of depression on family functioning has been relatively poorly studied compared to the impact of other mental disorders⁶⁶. It has been proposed that comprehensive management of unipolar major depression should include psychoeducational family intervention⁶⁷. Indeed, much of the literature on family impact concerns the role family members can play to understand the condition and improve outcomes rather than the reverse impact: the effect of mental disorders on family members. In a study on the latter question⁶, 133 spouses of people from Leipzig with mental disorders reported a significant reduction, as compared to the general population, in the domains of psychological well-being and social relationships as measured by the WHOQOL-BREF instrument. The quality of life reported by spouses of patients with depression was as poor as that of spouses of patients with anxiety or schizophrenia.

Unlike the difficulties experienced by adult relatives, those reported by children and adolescents living with patients with major depression have been explored in several studies⁷. Major depression influences parenting skills, especially in affected mothers⁶⁸, with a reduction in children's psychological wellbeing⁷. Epidemiological data show that children of parents with major depression have a fourfold greater risk of developing an affective episode, and that 64% of them go on to develop psychological problems⁶⁹. Moreover, school-aged children of mothers with severe depressive symptoms are more likely to experience emotional distress, depression and anxiety.

2.1.8 Cost of depression to the NHS

In a 2008 King's Fund study²⁴, McCrone and colleagues used UK PMS year 2000 data⁷⁰ for adults aged 16–74 years, which reported prevalence rates of 23 and 28 cases per 1,000 men and women, respectively, to estimate that 1.24 million people aged 15 years or over have depression in England. Total costs were £1.68 billion and average costs amounted to £2,085 per person for the 65% of people receiving treatment or in contact with services. These were composed of: other non-inpatient NHS (33%), non-psychiatric inpatient (17%), social services (15%), psychiatric inpatient (10%), residential care (10%), general practitioner (9%), other (5%) and medication (1%). It is clear that depression imposes a substantial burden on the NHS.

Incidence-based data that may allow calculation of the costs of episodes of MDEs in the context of MDD are provided by the observational PERFORM study^{19,20}, sponsored by Lundbeck. PERFORM provides information on per-patient healthcare resource utilisation

and outcomes for a period of up to one year following initiation of antidepressant treatment. A key finding is that patients who switched during the study period consumed more healthcare resources than those who did not. Switch patients were more likely than patients starting initial treatment to have been admitted to hospital (4.6% vs. 2.7%, $p=0.134$).

2.1.9 Impact of depression in the workplace and on the wider economy

The WHO has concluded that mental health problems are a leading cause of absenteeism and presenteeism and depression has already become a leading cause of disability worldwide. The extent of this workplace impact is shown by the Impact of Depression at Work European Audit (IDEA) survey⁷¹, conducted in 7 countries. Among the results for Great Britain ($n=1,007$) were the findings that:

- 26% had ever had a diagnosis of depression
- Of those ever diagnosed, 58% had taken time off for depression
- Of those who took time off for depression, the average absence was 41 days.

In the PERFORM study^{19,20} described above, patients starting switch treatment were more likely than those starting initial treatment to have taken sick leave in the 12 weeks following baseline (35.1% vs. 21.8%, $p=0.001$), and had a longer duration of absence (47.3 vs. 27.9 days, $p=0.002$).

The productivity impact of depression imposes costs on the wider economy that dwarf the cost to health and personal social services. In the King's Fund study²⁴ described in the previous section, the 2007 service costs attributable to depression of £1.68 billion were less than one third of the estimated £5.82 billion of lost earnings.

2.2 Numbers of patients

Based on Office for National Statistics (ONS) mid-2013 figures, the adult population in England and Wales is 44,811,567⁷². The diagnosed prevalence of depression is 10.9% in England and 7.9% in Wales. Based on a population weighted average, the 12-month diagnosed prevalence rate in England and Wales is 10.7%. Of these, 54% are estimated to be moderate or severe cases, of which 90% receive pharmacological therapy. Between 30 and 50% of these patients are likely to have experienced an inadequate response to initial pharmacological therapy for an MDE, and may require switch treatment. Hence, the number of adult patients experiencing a moderate-to-severe MDE and receiving switch antidepressant therapy is estimated at approximately 700,000 to 1.2 million per annum.

2.3 Life expectancy of people with depression

In an attempt to quantify the link between psychological distress and cause-specific mortality in a large scale, population-based sample, Russ and colleagues pooled individual participant data from the Health Survey for England, using 11 cross-sectional studies conducted from 1994-2004 and linking self-reported psychological status to National Health Service mortality data up to February 2008⁷³. Psychological distress was defined as a score of 4 or greater on the 12-item version of the General Health Questionnaire (GHQ-12), a widely used measure of distress in population studies⁷⁴ validated as a screening tool for anxiety and depression^{75,76}, consisting of items capturing symptoms of anxiety, depression, social dysfunction, and loss of confidence. The authors found increasing scores on GHQ-12, even from scores of 1-3 corresponding to subclinically asymptomatic, were associated with an increased hazard for total mortality, based on 8,365 deaths in 68,222 participants followed for a mean of 8 years. Each standard deviation disadvantage in GHQ-12 score was associated with a hazard ratio (HR) of 1.21 (95% CI: 1.15-1.27). Highly symptomatic

subjects (score 7-12) faced almost a twofold increase in hazard (mean HR: 1.94, 95% CI: 1.66 to 2.26) of death.

While this study did not attempt to quantify life expectancy, it follows from the HR statistics that life expectancy must be reduced for individuals with psychological distress. A 2011 study by Chang and colleagues⁷⁷ employed a life table method to estimate the life expectancy for people with serious mental illnesses using data from the South London and Maudsley NHS Foundation Trust (SLAM) and national mortality returns for 2007-09. Life expectancy at birth for males and females with depressive episode and recurrent depressive disorder (ICD-10 F32–F33) was estimated at 66.8 and 74.4 years, respectively, a loss of 10.6 and 7.2 years of life compared to the corresponding UK male and female population.

Some 70% of suicides are estimated to be related to depression⁷⁸. A recent meta-review⁷⁹ of 20 systematic reviews and meta-analyses on mortality in mental disorders, which drew upon a meta-analysis specific to depression⁸⁰, reported a relative risk of all-cause mortality among people with depression as 1.6 (95% CI: 1.6, 1.7), while the corresponding suicide risk was 19.7 (95% CI: 12.2-32.0), as compared to people without depression.

It can be concluded from these studies in a variety of settings and from the broader literature that MDD is associated with reduced life expectancy compared to the general UK population. Suicide is an important cause of death in MDD, though the proportional impact of suicide compared with other causes of death on years of life lost is unknown.

2.4 NICE guidance concerning depression

Table A2 lists all guidance issued by NICE relating to the diagnosis, treatment and management of depression.

Table A2. Guidance issued by NICE on depression and subgroups considered

Guideline	Issue date	Subgroups considered with respect to antidepressants
Clinical Guideline 90: The treatment and management of depression in adults ¹⁰ (CG90)	2010	Subthreshold depression; mild depression; moderate-to-severe depression; elderly; patients who have experienced an inadequate response to previous antidepressants; recurrent depression
Clinical Guideline 91: Depression in adults with a chronic physical health problem ⁸¹ (CG91)	October 2009	
Quality Standard 8: Depression in adults quality standard ⁸² (QS8)	March 2011	Persistent subthreshold depression; mild depression; moderate-to-severe depression; moderate depression with chronic physical health problem; severe depression with chronic physical health problem

CG90 includes sections on the use of antidepressants in such patients and is considered the most comprehensive of the documents in Table A2 to this submission.

2.5 Clinical pathway of care and the impact of vortioxetine

2.5.1 Clinical pathway

Throughout this submission we refer to the NICE collaborative clinical guideline CG90¹⁰ to define the care pathway into which vortioxetine will be introduced. Figure A5 presents an interpretation of the CG90 clinical guideline pathway⁸³. The portions enclosed by the red boxes concern switching an antidepressant after initial inadequate response, which represents the proposed position for vortioxetine within the decision problem being

addressed in this submission (section 5). The corresponding part of CG90 is entitled “*Sequencing treatments after an initial inadequate response*”, (section 1.8 of the guideline). A diagrammatic care pathway based on CG90 and entitled “*Antidepressant treatment in adults*” is available on the NICE *Pathways* web site⁸⁴, as shown in Figure A6.

Figure A5. Interpretation of NICE CG90 recommended management and treatment pathway (after Reid 2014⁸³).

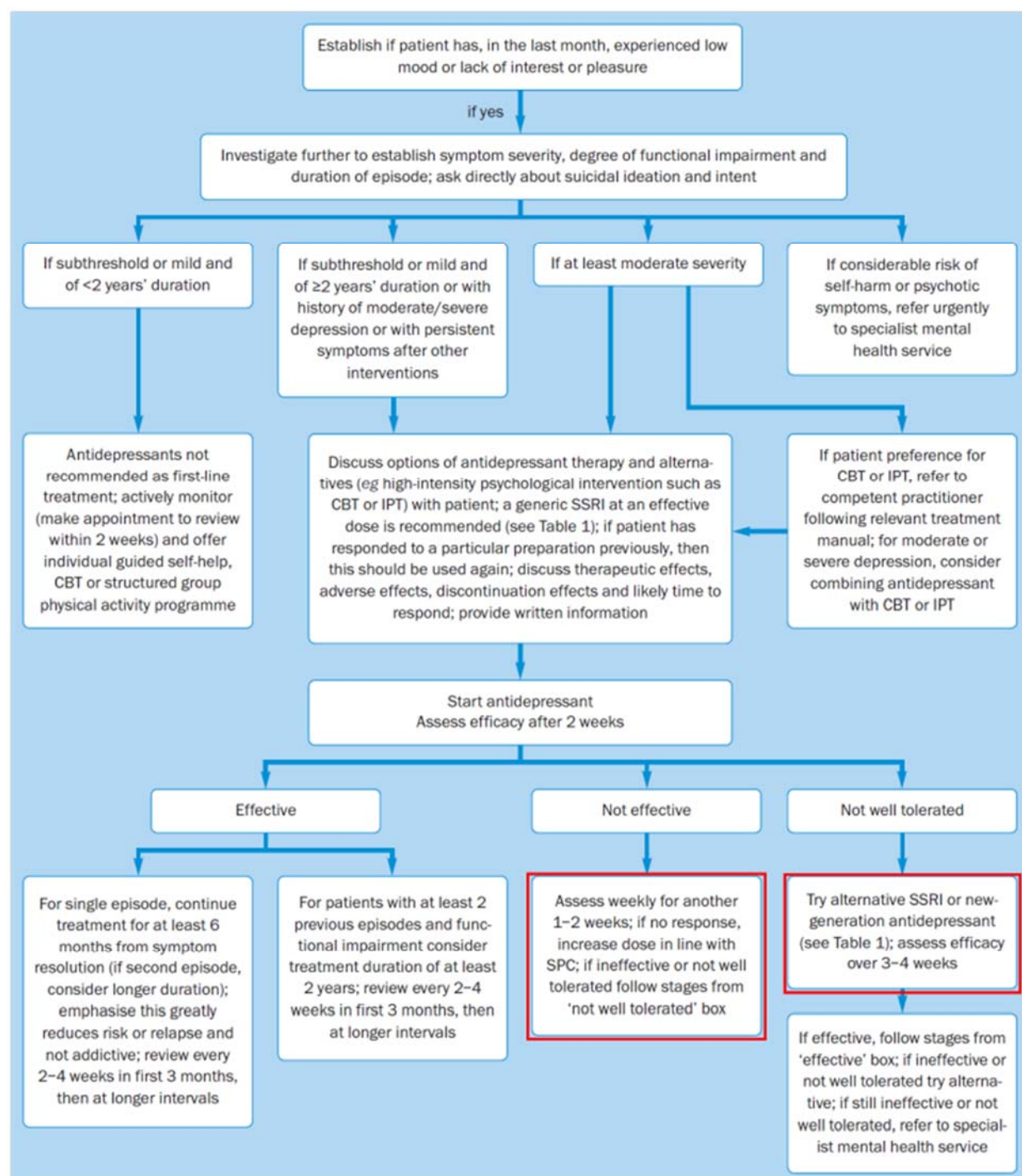
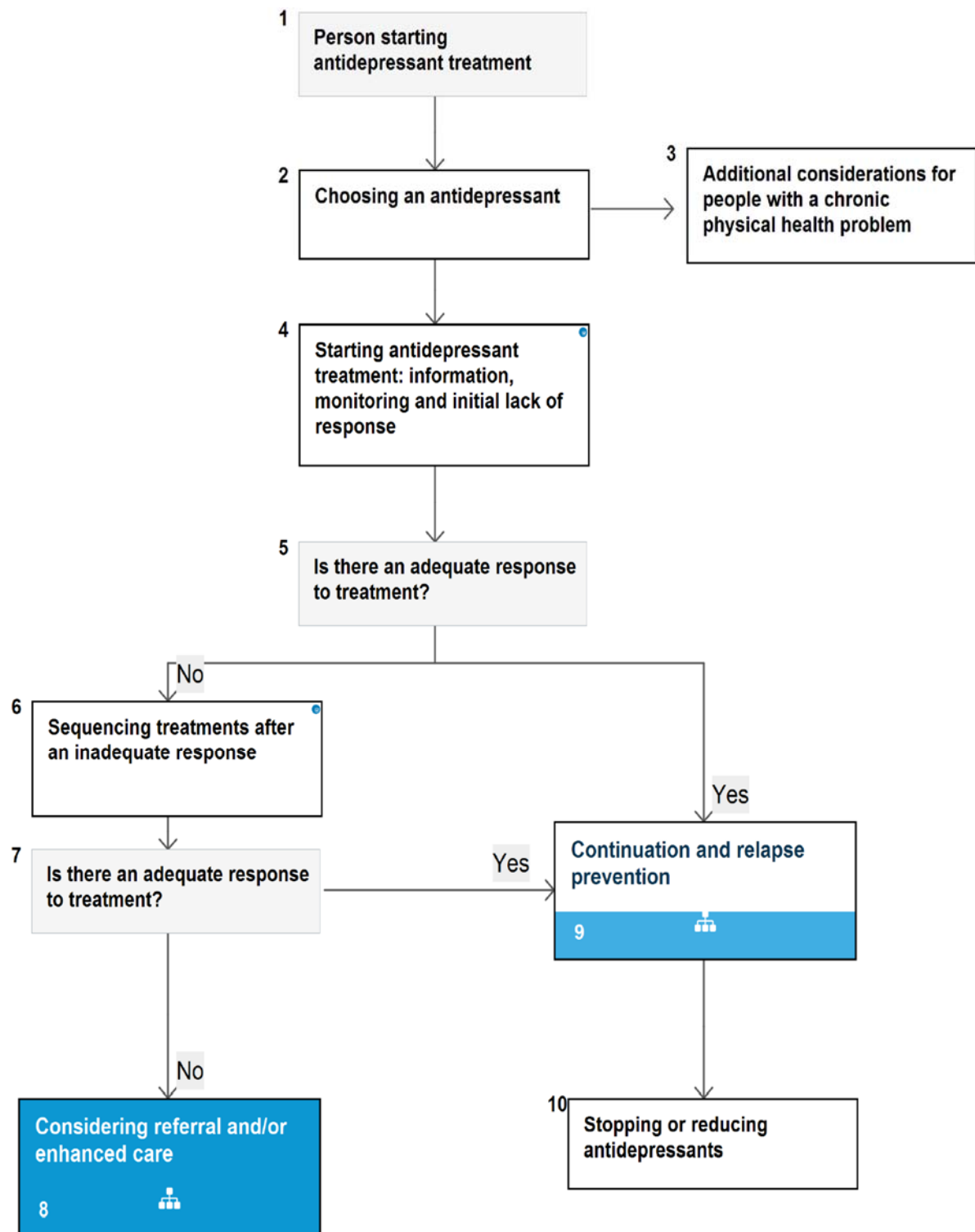


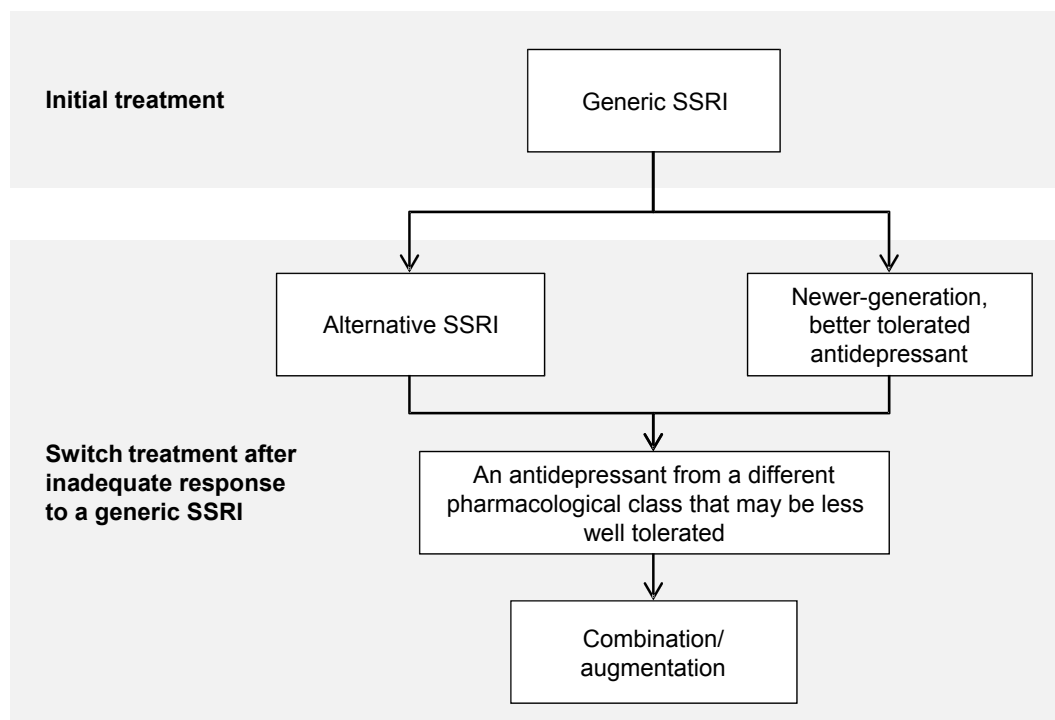
Figure A6. NICE Pathways diagram for antidepressant treatment in adults, showing the algorithm leading to sequencing treatments after an inadequate response



Antidepressants are normally recommended as first-line treatment in patients whose depression is of at least moderate severity. The guideline recommends that patients should be seen after 2 weeks of treatment and then every 2-4 weeks for the first 3 months. It describes the actions to be taken if side-effects develop or the depression does not respond adequately. After monitoring adherence and optimising dosage if necessary, switching to another antidepressant is recommended as an option in these circumstances if the patient

wishes to do so. With respect to switching, CG90 is not prescriptive, but recommends considering “initially a different SSRI or a better tolerated newer-generation antidepressant”, and “subsequently an antidepressant of a different pharmacological class that may be less well tolerated, for example venlafaxine, a tricyclic antidepressant (TCA) or a monoamine oxidase inhibitor (MAOI)”. A diagrammatic representation of this guidance is shown in Figure A7.

Figure A7. Treatment pathway for patients who experience an inadequate response to pharmacological therapy: diagrammatic representation of CG90 guidance



CG90 makes recommendations for continuation of antidepressant therapy beyond remission, with an emphasis on tailoring treatment to the patient’s history, circumstances and preferences. As a minimum, it recommends that a person who has benefited from taking an antidepressant should be encouraged to continue medication for at least 6 months after remission.

2.5.2 Positioning of vortioxetine with the pathway

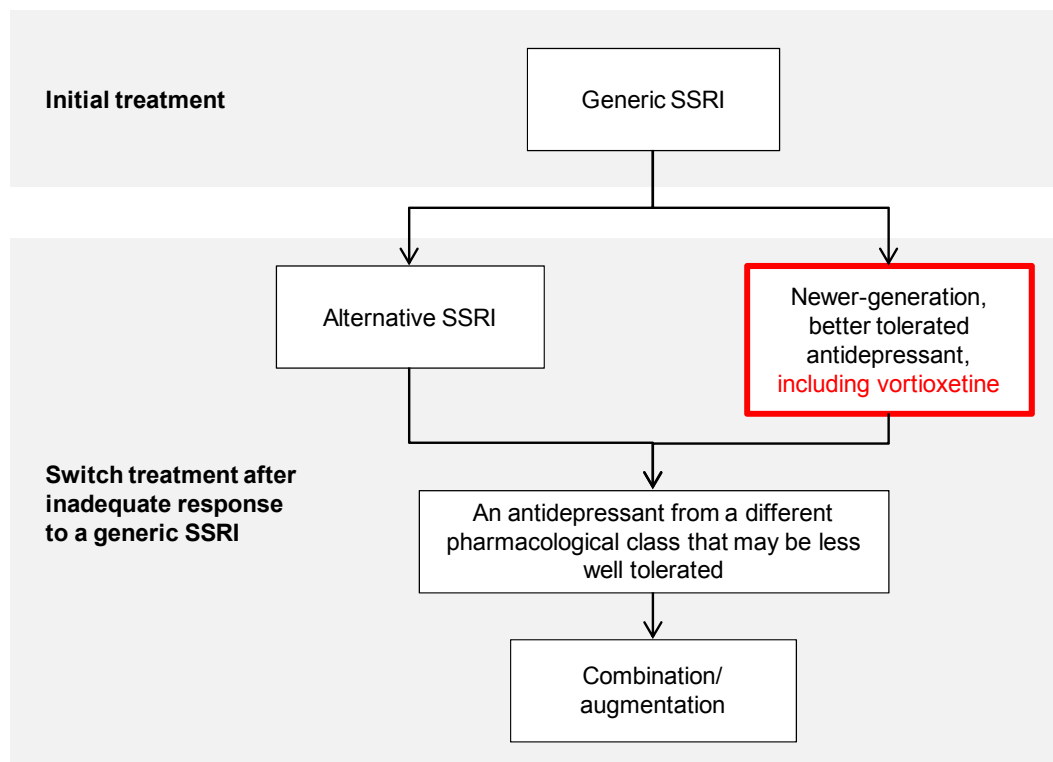
Vortioxetine has been granted a licence for the treatment of MDEs in adults. In this submission, Lundbeck is concerned with the use of vortioxetine in the following patient population, which is a subset of the licensed indication and scope of the STA:

- patients who are experiencing a moderate-to-severe MDE, and
- whose current episode has been treated initially with an SSRI or SNRI, and
- who are candidates for a switch in the clinician’s opinion, and
- who wish to change antidepressant treatment because of inadequate response or intolerability to the initial treatment.

For convenience, we refer to this population as the “**switch population**” elsewhere in the submission. Lundbeck believes that the tolerability profile of vortioxetine, supported by the clinical efficacy data available within this population, is consistent with positioning within the category described in CG90 as: “a better-tolerated newer-generation antidepressant” (see

Figure A8). The proposed positioning also reflects the common practice of switching to an agent with a differing mechanism of action.

Figure A8. Modified treatment pathway for patients who experience an inadequate response to pharmacological therapy, showing proposed positioning of vortioxetine



For the purposes of this submission, we equate MDE/MDD with the terminology “moderate-to-severe depression” used in CG90. This is justified on the basis that the patients included in the short-term phase III studies of vortioxetine had moderate-to-severe MDD, and the patients in a particularly relevant phase IIIb active-comparator switch study (Study 14178A, REVIVE) had a mean MADRS total score at study entry of 29 points (ranging from 22 to 43 points), indicating moderate-to-severe depression. Although CG90 recommends pharmacological therapy in specific cases for the treatment of persistent subthreshold and mild depression, these fall outside the licensed indications for vortioxetine; this submission corresponds to CG90 guidance for moderate-to-severe depression only.

2.6 Issues relating to current clinical practice

2.6.1 Patient heterogeneity and treatment choice

MDD is a broad and heterogeneous disorder with a highly variable course, and an inconsistent response to treatment¹³. The diagnosis of MDD requires a distinct change in sadness or anhedonia plus at least four of the following symptoms: irritability, sleep, appetite, sexual desire, concentration, psychomotor retardation and suicidal thoughts⁴. Not all symptoms must be present to confirm a diagnosis of MDD, but rather diagnosis is made by a summation of symptom number and severity. Therefore, with such a wide variety of symptom combinations it is likely that many patients with an identical diagnosis of MDD could have an entirely different disease presentation⁴. Furthermore, evidence from the US suggests patients vary in their preferences for treatment, whether psychological, pharmacological or both^{85,86}. Faced with this heterogeneity, the clinician has to be able to

recognise all permutations of MDD symptomatology and make the appropriate treatment recommendation.

The currently available pharmacological treatments have different mechanisms of action and distinct side-effect liability^{87,88}. These differences are acknowledged by numerous guidelines^{10,61,89} that recommend taking into account the patients' individual needs and preferences, and matching them to the treatments' likely efficacy and side-effect profile. It has already been noted in section 2.1 that approximately one-third to one-half of patients treated for depression do not respond satisfactorily to initial antidepressant pharmacotherapy, which is usually an SSRI. Also, intolerable side-effects can lead to poor adherence or premature withdrawal. Clearly there is a need for treatments with distinct efficacy and especially side-effect profiles, in order to support best clinical practice in the patient who has failed initial therapy.

2.6.2 Inadequate outcomes from antidepressant therapy

2.6.2.1 Low rates of response and remission

Although antidepressant therapy is a long-established component of the management of MDD, inadequate response even to newer generations of antidepressants remains a concern. According to an EMA guideline on clinical investigation of medicines in depression, up to one third of patients experience a lack of efficacy with antidepressant treatment and up to 20% of patients are considered non-responders, even where compliance is good and treatment has been taken for an adequate period of time at the correct dosage⁶². In the STAR*D study¹¹, only one half of patients responded to initial SSRI treatment, while 16% experienced intolerable side-effects. In the same study, remission rates declined from 37% for initial treatment to 31%, 14% and 13% for patients receiving second and third and fourth treatment steps, respectively. Other studies, and other publications describing the STAR*D study, report rates of inadequate response of 50–60%, with more than two-thirds of patients failing to achieve remission¹²⁻¹⁴.

In more complicated cases, e.g. such as when a patient with an MDE fails to respond after an adequate trial of least two treatments from different classes at optimum dosage, or when a patient experiences frequent recurrences of depression, referral to specialist mental healthcare professionals may be indicated. Patients who are actively suicidal or whose depression has psychotic features will also need specialist referral and a few will need inpatient psychiatric admission¹⁰.

2.6.2.2 Antidepressant side-effects

Besides disappointing response and remission rates, intolerability to side-effects of antidepressant therapy is a further problem that may force patients to switch treatment¹⁵. It was noted in CG90 (full guidance)¹⁰ that the extent to which patients are able to tolerate an antidepressant is intertwined with adherence and therefore treatment outcomes. Studies show that as many as 50% of patients may discontinue antidepressant treatments within the first six months of therapy, citing adverse events as the main reason for discontinuation^{84,90}.

Summary tables comparing the side-effects of antidepressants are provided in The Psychotropic Drug Directory⁸⁷ (see Table A3) and the Maudsley Prescribing guideline⁸⁸ (see Table A4). The latter reflects the NICE guidance described in section 2.5.1 above in recommending switching to a different antidepressant if the initial antidepressant is poorly tolerated after titrating to therapeutic dosage. (N.B. The authors emphasise that scoring systems used in their tables are a rough guide only to side-effects.)

Table A3. Relative side-effects of antidepressants (after Psychotropic Drug Directory, Bazire⁸⁷)

Drug	Adult max dose mg/d	Elderly max dose mg/d	Relative side-effects (most will be dose-related)						
			Anti-cholinergic	Cardiac	Nausea ‡	Sedation	Overdose §	Pro-convulsant	Sexual dysfunction
Tricyclics									
Amitriptyline	200	75	●●●	●●●	●●	●●●	●●●	●●	●●
Clomipramine	250	75	●●●	●●	●●	●●	●	●●	●●●
Dosulepin (dothiepin)	150	75	●●	●●	○	●●●	●●●	●●	●●
Doxepin	300	<Ad	●	●●	●	●●	●●	●●	●●
Imipramine	300	50	●●	●●	●●	●	●●●	●●	●●
Lofepramine	210	<Ad	●●	●	●	●	○	○	●●
Nortipityline	150	50	●●	●	●●	●	●●	●	●●
Trimipramine	300	<Ad	●●●	●●	●	●●	●●	●	●●
SSRIs									
Citalopram	60	40	○	○	●●●	○	●	○	●●
Escitalopram	20	<20	○	○	●●	○	○	○	●●
Fluoxetine	(20)	(60)	○	○	●●	○	○	○	●●
Fluvoxamine	300	300	●	○	●●●	●	○	○	●
Paroxetine	50	40	○	○	●●	○	○	○	●●●
Sertraline	200	200	○	○	●●	○	○	○	●●
MAOIs									
Isocarboxazid	60	<Ad	●●	●●	●●	○	●●	○	●
Phenelzine	90	(90)	●	●	●●	●	●●●	○	●
Tranycypromine	CA30	(30)	●	●	●●	●	●●●	○	●
Others									
Agomelatine	50	50	○	○	○	○	○	○	○
Bupropion/amfebutamone (U)	-	-	●	○	●	○	●●	●●●	○
Duloxetine	120	Caution	○	○	●●	●	?	?	●●

Drug	Adult max dose mg/d	Elderly max dose mg/d	Relative side-effects (most will be dose-related)						
			Anti-cholinergic	Cardiac	Nausea ‡	Sedation	Overdose §	Pro-convulsant	Sexual dysfunction
Flupentixol	3	2	●●	○	○	●	●	?	●
Mianserin	90+	<Ad	●	○	○	●●●	○	○	●
Mirtazipine	45	45	○	○	○	●●	○	●●	●●
Moclobemide	600	600	●	○	●	○	○	?	●
Reboxetine	12	NR	●	●	●	○	○	○	○
Trazodone	600	+300	●	●	●●●	●●	●	○	●●
Tryptophan	6g	6g	○	○	●	●●	●	○	○
Venlafaxine	375	Same	○	●●	●●	●	●●	●	●●

Side-effects frequency (severity will be dose related)

- = Marked effect
 ●● = Moderate effect
 ● = Mild effect
 ○ = Little or minimal effect
 ? = No information or little reported
 U = Unlicensed in UK for depression

Other abbreviations

- Nausea ‡ = Typical serotonergic side-effect
 Adult max dose = Maximum adult oral antidepressant dose in the UK SmPC
 Elderly max dose = Maximum elderly oral antidepressant dose in the UK SmPC. Most state that half the adult dose may be sufficient
 Overdose § = Based on UK Fatal Toxicity Index (Henry et al, *BMJ* 1995;**310**:221-224). For review of epidemiology and relative toxicity of antidepressant drugs in overdose see Henry (*Drug Safety* 1997;**16**:374-90)

Table A4. Relative side-effects of antidepressants (after Maudsley Prescribing Guideline, Taylor⁸⁸)

Drug	Sedation	Hypotension	Anticholinergic effects
Selective serotonin reuptake inhibitors (SSRIs)			
Citalopram	+/-	-	-
Escitalopram	+/-	-	-
Fluoxetine	-	-	-
Fluvoxamine	+	-	-
Paroxetine	+	-	+
Sertraline	-	-	-
Tricyclics			
Amitriptyline	+++	+++	+++
Clomipramine	++	+++	++
Dosulepin	+++	+++	++
Doxepin	+++	++	+++
Imipramine	++	+++	+++
Lofepramine	+	+	++
Nortriptyline	+	++	+
Trimipramine	+++	+++	++
Monoamine oxidase inhibitors (MAOIs)			
Isocarboxazid	+	++	++
Phenelzine	+	+	+
Tranylcypromine	-	+	+
Reversible inhibitor of monoamine oxidase A (RIMA)			
Moclobemide	-	-	-
Other antidepressants			
Agomelatine	+	-	-
Duloxetine	+/-	-	-
Mianserin	++	-	-
Mirtazipine	+++	+/-	+
Reboxetine	+	-	+
Trazodone	+++	++	-
Venlafaxine	+/-	-	+/-
+++ high incidence/severity; ++ moderate; + low; - very low/none			

2.6.2.3 Treatment adherence

Treatment adherence is an important problem linked to lack of efficacy and tolerability. In a study of 5 primary care practices in England no more than 19% of patients took antidepressants in accordance with guidelines and only 41% reported continuing with treatment over six months of therapy¹⁶. In a US study⁹¹ of the effect of patient-physician communication about therapy duration and adverse effects on therapy discontinuation or medication switching within 3 months after start of SSRI therapy, it was found that patients

with 3 or more follow-up visits were more likely to continue using the initially prescribed antidepressant medication. These findings suggest that frequent patient-physician contact may increase the likelihood that patients will continue therapy.

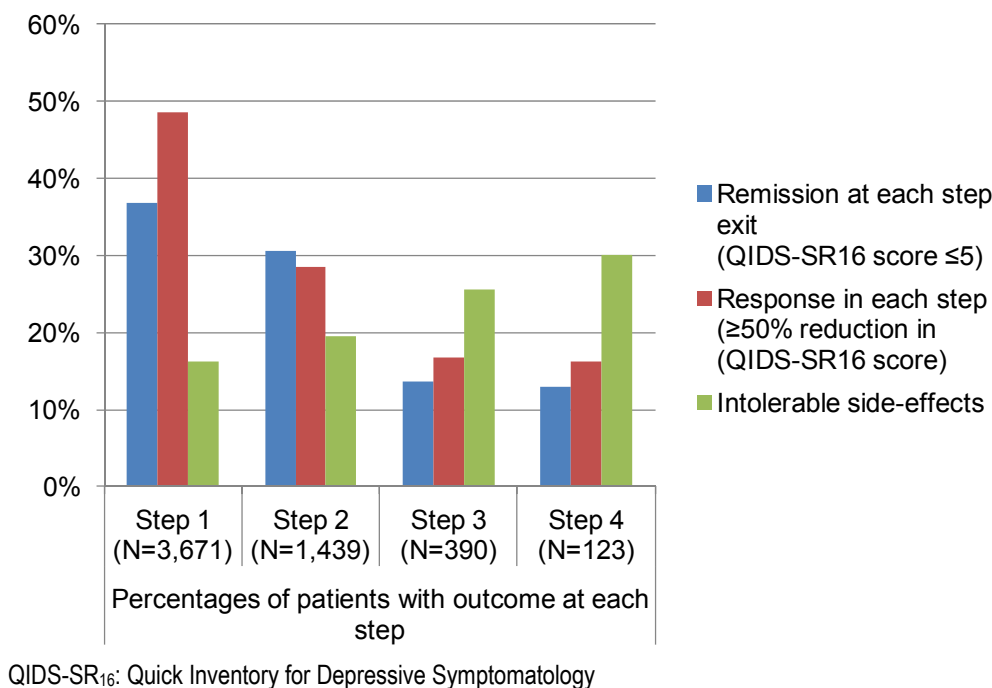
2.6.3 High rates of switching

As stated in section 2.5.2 above, vortioxetine will be positioned for use in a switch population. In view of the low rates of successful initial antidepressant treatment as described in the previous section, it is unsurprising that treatment switching is frequently required. Switching is normally prompted by one or more of three reasons described in the previous section:

- Inadequate response
- Tolerability concerns
- Resulting lack of adherence.

When there are concerns with initial treatment, they tend to appear early. Average times to switch of 1 to 3.5 months have been reported^{23,92-95}, with approximately 72% of switches occurring in the first 3 months⁹⁶. Switches due to problems with tolerability tend to occur earlier in treatment (2-4 weeks) with an individual antidepressant than switches due to a lack of efficacy (6-8 weeks)¹⁰. In a GPRD study, tricyclic antidepressant (TCA) users were found to have the highest switch rates (27%), followed by patients taking SNRIs (17%) and those on SSRIs having the lowest switch rates (15%)⁹⁶.

In the STAR*D study¹¹, remission rates diminished with successive switches: to 31%, 14% and 13% for the second, third and fourth treatment steps, respectively, as shown in Figure A9. Relapse rates were greater among patients who required more treatment steps to successfully treat their current episode, independent of whether the patient had achieved remission at the end of the acute study phase¹¹. In another study, an elevated risk of relapse or recurrence was observed in switch/augmentation patients compared with those on stable antidepressant therapy (OR=1.59, 95% CI=1.19-2.11, $P<0.01$), which was hypothesised by the authors to be related to a delayed, incomplete or never achieved optimal response⁹⁷.

Figure A9. Outcomes in outpatients with depression over successive steps of antidepressant treatment (after Rush 2006¹¹)

2.6.4 Choice of antidepressants when switching

As switching due to inadequate response or tolerability problems is frequently necessary, the availability of effective, well-tolerated options for subsequent lines of therapy is desirable. In particular, the question of in-class versus out-of-class switching is an important consideration. A meta-analysis of four trials that compared use of an alternative SSRI to a non-SSRI agent in patients switching from a SSRI found a modest advantage ($p=0.007$) for the latter, out-of-class strategy in achieving remission²⁵. The authors of a recent trial in patients who had failed to respond to two successive SSRIs concluded that the administration of antidepressants with different mechanisms of action is an effective switching strategy⁹⁸. Moreover, prescribers may find it intuitively attractive to have available an armamentarium of agents with different modes of action.

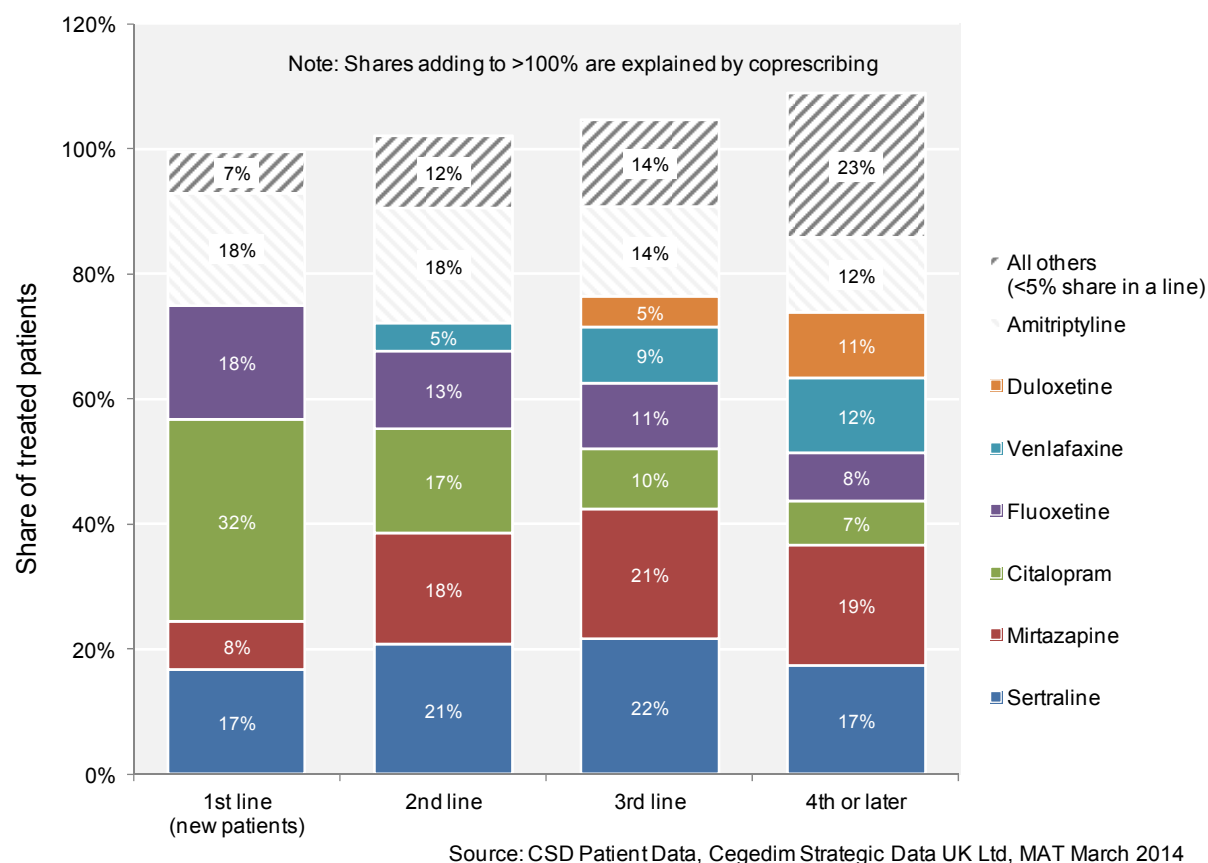
2.7 Main comparators and justification for their selection

The justification of the choice of relevant comparators was based on the recommendations of CG90, clinical opinion and prescribing data within the UK, subject to the availability of adequate clinical evidence in switch populations.

As previously noted, for initial switch therapy CG90 recommends considering a different SSRI or “a better tolerated newer-generation antidepressant”. The SNRIs (e.g. venlafaxine), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) should mainly be reserved for subsequent switches, as they “may be less well tolerated”. Based on these guidelines, the main comparators for vortioxetine as initial switch therapy are the SSRIs and better tolerated, newer-generation antidepressants. A strategy of augmentation of antidepressants is not considered a relevant comparison in this submission. CG90 states that augmentation tends to increase the side-effect and drug interaction burden, and that in primary care this strategy should only normally be started in consultation with a consultant psychiatrist.

To support the selection of the most relevant comparators in the first switch setting, longitudinal data supplied by Cegedim Strategic Data Ltd for the 12-month period April 2013–March 2014 were analysed to determine the market shares of patients prescribed an antidepressant by line of treatment, as shown in Figure A10⁹⁹. To identify the importance of individual antidepressants, all those with a share of 5% or greater at each line of treatment are shown individually; the remaining agents are grouped together as “all others”.

Figure A10. Pharmacological treatments prescribed for patients ever diagnosed with depression, by line of therapy⁹⁹.



Approximately 52% of patients prescribed second-line treatment were prescribed an SSRI, approximately 18% were prescribed mirtazapine and 18% were prescribed amitriptyline.

Expert opinion suggested that the rates of prescribing amitriptyline seemed implausibly high for the first- and second-line treatment of depression, but could be explained by the known use of amitriptyline to treat pain and sleep disturbance. The expert consensus was that the prescribing of amitriptyline for depression is restricted to psychiatrists in a secondary care setting, in view of this agent's unfavourable tolerability profile¹⁰ and its particular toxicity in overdose¹⁰⁰.

Examination of the CSD data by diagnosis revealed that while approximately 80% of prescriptions for SSRIs and mirtazapine were for patients whose diagnosis had ever included depression, this was true for only 48% of patients receiving amitriptyline.

Clinical expert opinion has indicated that amitriptyline is frequently used in patients with a diagnosis of other conditions including sleep disorders, neuropathic pain, chronic back pain and irritable bowel syndrome.

Therefore, it can be concluded that amitriptyline is seldom prescribed for its antidepressant properties alone, and the data presented above may substantially overestimate the use of amitriptyline for the primary treatment of depression. These statistics are consistent with the CG90 guideline for switching antidepressants, which proposes switching *“initially to a different SSRI or a better tolerated newer-generation antidepressant”* and *“subsequently an antidepressant of a different pharmacological class that may be less well tolerated, for example venlafaxine, a TCA or an MAOI”*.

With respect to the decision problem (as per positioning detailed in section 2.5.2 above), the second-line data best reflect the initial switch population in which use of vortioxetine is proposed. Taking the market data shown in Figure A10 (products with share of approximately 5% or over) together with the guidance in CG90 and the considerations described above, the most appropriate comparators are, in descending order of second-line (i.e. first switch) market share:

- Sertraline (SSRI)
- Mirtazapine (other)
- Citalopram (SSRI)
- Fluoxetine (SSRI)
- Venlafaxine (SNRI)

Within this submission, these five comparators to vortioxetine are considered the most relevant for patients with an MDE who experience an inadequate response to initial treatment with an SSRI or SNRI.

Lundbeck conducted systematic reviews (see sections 6.1 and 6.7) to identify data to allow direct or indirect comparisons between vortioxetine and all of these agents when used as second-line therapy. Studies were identified to support direct comparison with agomelatine and indirect comparison with sertraline, citalopram and venlafaxine XR. These comparators are highly relevant to the decision problem as discussed below:

- Citalopram and sertraline are the most commonly used antidepressants within the UK and, specifically, the most commonly used SSRIs 2nd line.
- Venlafaxine is the most commonly used SNRI in the UK and at 2nd line.
- Agomelatine: although not widely used within the UK it is recognised as an efficacious and well-tolerated antidepressant that has a mode of action distinct from the SSRIs and SNRIs⁸⁷. The most recent NICE surveillance review for CG90¹⁰¹ identified two meta-analyses^{31,102}, *“which indicate that agomelatine is at least as efficacious as escitalopram, fluoxetine, sertraline, venlafaxine and paroxetine in reducing depression scores for response and remission in patients with depression and severe depression”*.

No data were found to enable valid comparison with mirtazapine or fluoxetine in second-line use. As both are commonly used in the UK in this position, formal comparisons of each with vortioxetine would be desirable. Nevertheless, Lundbeck believes their absence would not be critical for the following reasons:

- Fluoxetine. Clinical opinion suggests that in switch patients this SSRI has a similar efficacy profile to other SSRIs but may well be less well tolerated (see NICE CG90 for guidance on use of fluoxetine). The cost of fluoxetine is slightly greater than citalopram (£1.09-£3.27 and £0.91-£1.10 for a 28-day course respectively) (MIMS app. Accessed: 25.11.2014). Therefore, it is expected that fluoxetine would be dominated by other SSRIs if all were included in an incremental cost-effectiveness analysis.
- Mirtazapine, although widely used second line, is not suitable for all such patients because of its distinct tolerability profile; it is one of the most sedative antidepressants apart from the TCAs⁸⁸ and is associated with weight gain. Clinical opinion suggests

that mirtazapine is usually chosen when its sedative effect is desirable, notably in patients suffering from insomnia but in whom daytime alertness is less important. Conversely, mirtazapine is not seen as a viable option for patients who depend on alertness, e.g. people in occupations requiring mental concentration or stamina, professional drivers and carers.

2.8 Issues concerning trials of antidepressants in MDD

2.8.1 High rates of trial failures

A well-known feature of trials of antidepressants in MDD is the difficulty in demonstrating efficacy of the active drug over placebo¹⁰³. Of the randomised, placebo-controlled studies conducted in support of an antidepressant claim, approximately 50% have failed⁵¹. Fava states “negative double-blind, placebo-controlled trials ... have become the rule more than the exception in psychiatric research¹⁰⁴. Particularly high placebo response rates are seen in trials of antidepressants, ranging from 29%-48% for pooled trials of various SSRIs in MDD¹⁰⁵, appear to contribute to the difficulty in demonstrating efficacy. Possible explanations for high placebo response are provided by expectancy theory and classical conditioning, as well as effects of therapeutic setting, measurement factors and natural history¹⁰⁶. Also, in this episodic disorder some sufferers improve spontaneously. Other factors may also be at play. Depression is a highly variable condition that may manifest as a wide range of psychological and somatic symptoms that differ between patients. Though trial designs may attempt to limit the variability of participants by defining eligibility criteria, such as severity, study populations tend to be heterogeneous in terms of individual symptoms. Assessments of outcome, whether patient-rated or clinician-rated, do not measure any underlying pathology or markers of disease but rely on scales to summarise subjective feelings over various domains of mood and activity.

The above issues contribute to a high failure rate of trials in MDD¹⁰⁴. To overcome these difficulties, clinical development programmes for regulatory approval of antidepressants tend to include a large number of trials, catering for the possibility that a proportion of trials may fail, or produce negative or difficult to interpret results. For instance, the NDA submission for fluoxetine, filed in the late 1980s, included 13 efficacy trials of which only 5 were positive¹⁰⁴.

2.8.2 The use of active references

To avoid difficulty in interpreting results from a trial of an experimental antidepressant, an active reference arm may be included. In a two-arm, placebo-controlled trial, lack of separation could indicate that (i) both placebo and treatment were effective or that (ii) neither was effective. But a three-arm efficacy trial that includes an active reference (AR) arm removes this ambiguity by testing the assay sensitivity of the trial. The AR should be a drug at a dosage that is known to be effective from prior placebo-controlled trials. Studies that include an AR as well as placebo and the intervention can help determine whether the trial was designed and implemented in such a way that differences between experimental intervention and placebo can be interpreted. If the AR failed to show separation from placebo, it could be concluded that the trial had failed, perhaps through some combination of flawed design or/and conduct. Only if the AR showed separation, but the experimental drug did not, could the experimental drug be concluded ineffective (i.e. a negative trial).

Known previous non-responders to the drug used as AR must be excluded from trials for ethical reasons^{107, 107-109}. Consequently, in trials with an AR the AR arm is likely to be enriched with previous responders. Such a bias in favour of the AR negates the potential to obtain valid comparative efficacy data between the study drug and the AR; only the comparison between the study drug and placebo can be assumed, other things being equal, to be unbiased.

2.9 Therapy to manage adverse reactions

Few specific recommendations are made in CG90¹⁰ for prescribing therapies to manage adverse reactions. CG90 states:

“If a person with depression develops side-effects early in antidepressant treatment, provide appropriate information and consider one of the following strategies:

monitor symptoms closely where side-effects are mild and acceptable to the person, or

stop the antidepressant, or change to a different antidepressant if the person prefers, or

in discussion with the person, consider short-term concomitant treatment with a benzodiazepine if anxiety, agitation and/or insomnia are problematic (except in people with chronic symptoms of anxiety); this should usually be for no longer than 2 weeks in order to prevent the development of dependence.”

Patient education delivered by a pharmacist or a nurse before initiating treatment with an antidepressant is an important part of medication management. This should include the monitoring of adverse reactions and the promotion of treatment adherence. Education enables patients to recognise adverse reactions as and when they occur and follow an agreed plan to deal with them. Lundbeck's understanding from discussion with clinical experts is that the usual approach when a patient finds side-effects intolerable is to switch the patient to a different medication, tailoring the choice by considering the nature of the side-effect and matching the patient's preferences to the side-effect profile of alternative drugs as recently proposed by Baghai¹¹⁰.

2.10 Resource implications for the NHS

The use of vortioxetine does not introduce any new particular resource implications for the NHS other than the funding of vortioxetine itself. It does not require additional infrastructure to be put in place and may be prescribed in the same manner as SSRIs and SNRIs within current general practice and specialist settings. The most recently introduced antidepressant, agomelatine, requires the monitoring of liver function; this condition does not apply to vortioxetine.

3 Equality

3.1 Identification of and response to equality issues

People with intellectual disability (ID) have high rates of all psychiatric disorders, with prevalence reaching approximately 40%¹¹¹. There is growing evidence for a general clustering of ID with other neuropsychiatric disorders^{112,113}. In a population-based study in Glasgow¹¹⁴, among people diagnosed with ID there was a point prevalence of a current episode of depression of 4.6% by clinical criteria (which included case reviews by nurses, GPs and psychiatrists), 3.8% according to Diagnostic Criteria-Learning Disabilities (DC-LD)¹¹⁵, 3.0% according to DCR-ICD10 criteria and 2.1% according to DSM-IV criteria⁵⁵. The authors stated that the point prevalence was higher than that reported for the UK general population¹¹⁶ when diagnosis by the first two, but not the last two, criteria is used for comparison.

DC-LD is a new classification system providing operationalised diagnostic criteria for psychiatric disorders, intended for use with adults with moderate to profound learning disabilities. It may also be used in conjunction with the ICD-10 and DSM-IV manuals when working with adults with mild learning disabilities. The differences in estimated prevalence according to the tools used for diagnosis suggest that depression may be more difficult to diagnose in patients with co-existing ID. The discrepancy may be a manifestation of the well-recognised phenomenon of diagnostic overshadowing in people with learning disabilities¹¹⁷.

As a recent report by the Royal College of Psychiatrists¹¹⁸ points out, “people with intellectual disability find it difficult to navigate through services and to negotiate the care they need. Therefore, it is essential that providers of services do not present barriers to their gaining access because of intellectual disability”. Therefore, Lundbeck concludes that although people with ID are more likely to suffer from depressive episodes, this particular at-risk section of the population may be at a disadvantage when it comes to receiving a specific diagnosis for depressive symptoms distinct from their other difficulties, and accessing the care they need.

Lundbeck has taken a neutral stance to equality issues in the analysis. No attempt has been made to allow for equality considerations issues analytically, for example by applying alternative utility weightings.

4 Innovation

4.1 Appraisal of level of innovation provided by vortioxetine

Conducting trials in depression proves challenging. An analysis of the Food and Drug Administration (FDA) database has shown that even for known effective and marketed antidepressants, up to 50% of trials had failed to show a statistically significant drug effect^{46,47}. The wide variation in patient response, the heterogeneity of symptoms, difficulties in objectively measuring disease severity and the high placebo effect are notable characteristics of MDD and its treatment that contribute to the high failure rate of trials¹¹⁹.

4.1.1 Commitment to invest

These challenges, amongst others, are faced across the board in mental health. As a consequence, much of the investment into mental health from the pharmaceutical industry has been diverted into other disease areas, particularly physical health where a return on investment is more certain given the regulatory requirements and current national and local cost-effectiveness criteria that are in place in many countries. This misallocation of resources has been echoed by the conclusions of a report assessing the rates of research investment by the pharmaceutical industry into mental health:

*"Despite high prevalence and unmet medical need, major pharmaceutical companies are de-emphasising or exiting psychiatry, thus removing significant capacity from efforts to discover new medicines,"*¹²⁰.

Despite these difficulties, Lundbeck is committed to its continued investment into the research and development of innovative medicines in mental health.

Lundbeck and clinical experts believe that vortioxetine could offer a significant and substantial impact on health related benefits for specific subgroups of patients as described within this section.

4.1.2 Addressing unmet needs

As discussed in section 2.1, a high proportion (30-50%) of patients fail to respond to initial antidepressant treatment^{11,62}. Despite the unmet need for more effective antidepressants, research within this difficult-to-treat patient population has been limited. Therefore, alongside the full regulatory trial package, Lundbeck undertook the REVIVE study trialling vortioxetine in patients who had not achieved an adequate efficacy response to a previous SSRI or SNRI, demonstrating significant and clinically meaningful superiority to the active comparator on the primary and the majority of the secondary endpoints. Direct (see section 6.5.2) and indirect (see section 6.7) evidence indicate that vortioxetine offers benefits over other antidepressants in terms of improved efficacy and tolerability in this clinically challenging patient group. It is thought that the benefits observed are attributable to the multimodal mechanism of action, which differs from all other antidepressants, making vortioxetine particularly suitable for patients who need a treatment different from SSRIs and SNRIs.

In addition to its benefits demonstrated in a switch population, there is substantial pre-clinical support for vortioxetine improving cognitive function⁵² and a growing clinical evidence base. Path analysis of Studies 202 (CONNECT) and 14122A (FOCUS) has shown that vortioxetine has an effect on cognitive functioning independent from its effect on MADRS within depressed patients. The cognitive enhancing effect of vortioxetine cannot be ascribed to its activity at any particular receptor, but is probably linked to its multimodal mechanism of

action^{52,121}. This multimodal activity indirectly leads to an increase in a number of different neurotransmitters associated with cognition, e.g. glutamate, acetylcholine, dopamine^{122,123}.

Cognitive dysfunction is increasingly recognised as an important component of morbidity in depression, and may manifest itself in several ways. Besides impairments in attention and memory, the ability to plan (executive function) and respond (psychomotor speed) may be adversely affected³⁹. Diminished ability to think, concentrate or take decisions is the second most-frequently occurring symptom cluster after depressed mood in patients encountering their first depressive episode¹²⁴.

Over recent years, the extent to which patients with MDD suffer from cognitive dysfunction has been researched. A 3-year study¹²⁵ assessing the presence of residual symptoms during and after depressive episodes found that three individual symptoms (cognitive problems, lack of energy and sleeping problems) dominated the course of depression and were present 85–94% of the time during depressive episodes and 39–44% of the time during remissions. In contrast, in market research 100% of respondents with MDD experienced depressed mood/diminished interest symptoms whereas only 21% still reported these symptoms after an episode¹²⁵. Patients also mentioned cognitive symptoms of depression as the most common cause of their impaired work productivity, with 46% of patients reporting 'lack of concentration' as affecting their productivity at work¹²⁶.

Given the evidence for its potential benefits with respect to cognitive dysfunction in MDD, Lundbeck and clinical experts believe that vortioxetine may represent an innovation in patients who are experiencing symptoms associated with cognitive dysfunction in MDD, such as lack of attention or concentration, memory and difficulties in making decisions.

Lundbeck is currently undertaking further clinical trials to investigate the effect of vortioxetine in patients with cognitive dysfunction accompanying MDD, including those who have failed to achieve an adequate response to first line (SSRI/SNRI) therapies (see section 1.6). Lundbeck has also applied for a licence variation, with the benefits of vortioxetine on cognitive dysfunction being added to section 5.1 of the SmPC. A decision from the EMA is expected in Q1 2015.

4.1.3 Health-related benefits excluded from QALY calculation.

At the current time the cognitive benefits of vortioxetine have not been included in the QALY calculation as data are lacking for vortioxetine and the relevant comparators in the specific population of interest (switch) in this submission.

A further element of benefit not included within the QALY calculation is the health impact that depression has on individuals other than the patient. It is not clear whether instruments such as EQ-5D that are designed primarily to assess the respondent's own HRQoL capture spillover effects on family members. During the development of the Depression and Family Functioning Scale (DFFS), it became apparent that depression affects family functioning through poorer communication, increased conflicts, decreased family interaction, and decreased intimacy¹²⁷. This instrument was administered in REVIVE to capture these wider effects and the potential benefits of the study treatments.

In the economic model presented in section 7, the assignment of utility values to the principal health states (depression, remission, no remission) driving the QALY calculation were derived from EQ-5D data gathered from participants in Study 14178A (REVIVE) experiencing these states. Although remission tended to be accompanied by improvements on the DFFS, utility values were based only on EQ-5D data, with no adjustments made for reported family functioning. As vortioxetine also demonstrated benefits over agomelatine on

the DFFS scale, the incremental QALY calculation may underestimate the true HRQoL benefits of vortioxetine.

An additional aspect of vortioxetine's profile that is not captured within the QALY calculation, is the lack of discontinuation symptoms associated with abrupt treatment cessation². Poor adherence to antidepressant medication is common and patients are often seen to miss consecutive doses of treatment for several days¹²⁸. Haddad and Anderson¹²⁹ note that such breaks in therapy can precipitate discontinuation symptoms. In their review of all antidepressants, they concluded that such symptoms are associated with 25 of the available antidepressants including those most widely used in the UK (citalopram, sertraline, fluoxetine, mirtazapine, venlafaxine), with common discontinuation symptoms including dizziness, headache, nausea and lethargy. Mostly these symptoms were short-lived and mild but in some cases they can be severe, lasting several weeks. As discontinuation symptoms are not included within the QALY calculation, the cost-effectiveness of vortioxetine may be underestimated versus treatments associated with such symptoms.

In addition to these points, a broader consideration is whether the preference-based measurement of HRQoL using the EQ-5D fully captures the impact of mental health conditions on quality of life. The preference-based measurement approach currently employed asks people to imagine having different health conditions and, based on this, rate such a health state. All preference-based methods suffer from a focusing illusion whereby people are likely to concentrate on the most salient aspects of the condition. In doing so, their perception may not reflect how they would experience the state in reality. As Fujiwara and Dolan⁴⁰ assert, *“Traditional valuation methods have understated the value of mental health (in relation to physical health) and, as a result, the value and social benefit of mental health interventions too”*.

4.1.4 Supporting data on innovation

The sources of evidence for the innovation of vortioxetine have been cited in the preceding sections.

5 Statement of the decision problem

Table A5. Comparison of scope for the STA with decision problem addressed by this submission

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with MDD	The decision problem addresses a subset of the population defined in the scope and the product licence: Adult patients with moderate-to-severe MDD who are experiencing an MDE, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to an alternative antidepressant.	SSRIs are recommended as initial antidepressant therapy, and all members of this class are now available as generics at low cost (less than £2 per month). Trials to assess the efficacy of vortioxetine in switch use (see section 6.1) show vortioxetine to be suitable for patients who have failed on an initial SSRI or SNRI. These factors suggest vortioxetine is likely to be more cost-effective in switch than in initial use. The efficacy and tolerability profile of vortioxetine qualifies it as a “newer generation, better-tolerated antidepressant” particularly suitable for switch use as per CG90.
Intervention	Vortioxetine	Vortioxetine	
Comparator(s)	SSRIs, TCAs and related agents, SNRIs, others	Agomelatine, citalopram, venlafaxine XL, sertraline, mirtazapine*, fluoxetine*.	Only comparators in frequent second-line use were considered relevant; antidepressants with a UK second-line market share >5% were identified (listed at left). See section 2.7 for full rationale. Of these antidepressants, switch clinical data were available to support direct or indirect comparisons of efficacy and tolerability with agomelatine, citalopram, venlafaxine XL, sertraline. * No suitable data were available for mirtazapine or fluoxetine. See section 6.7.4. for assessment of clinical evidence in switch.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Outcomes	Change from baseline severity of depression Remission of symptoms Anxiety Response to treatment (including response rate and time to response) Relapse (including relapse rate and time from remission to relapse) Hospitalisation Mortality Adverse effects of treatment (including adverse effects of treatment discontinuation) Health-related quality of life.	All of these except mortality. In addition, disability, family functioning, productivity (absenteeism and presenteeism).	Available clinical trial data are short-term (up to 1 year) and provide no direct evidence for longer-term course of MDD or differential mortality rates. Disability, family functioning, productivity are particularly relevant outcomes in MDD (see section 2.1)
Economic analysis	Reference case: ICER based on QALYs Appropriate time horizon Costs: NHS/PSS perspective	ICER based on QALYs 12-month time horizon	The economic analysis is consistent with the scope. Given the episodic nature of MDD, a 12-month time horizon is sufficient to capture the clinical endpoint (remission) and associated costs. Extrapolation beyond one year is not possible due to lack of evidence on relapse and recurrence rates.
Subgroups to be considered	If evidence allows, consider: Severity of depression (mild, moderate or severe) Clinical and cost effectiveness of vortioxetine in different positions in the treatment pathway.	Moderate-to-severe depression only. The CEA will consider only the population indicated in the decision problem, i.e. patients switching to switch antidepressant treatment	The population for the decision problem is already limited by severity (moderate-to-severe) and by positioning (after inadequate response to an initial antidepressant), and no further subgroups will be considered. The CG90 step-care principle does not advocate use of antidepressants in mild depression (except persistent sub-threshold depression). No data are available for vortioxetine in mild depression.
Special considerations, including issues related to equity or equality	None identified	See comments in section 3 on prevalence of depression among people with intellectual disability	Importance of ensuring access to care and diagnosis for people with intellectual disability

Section B – Clinical and cost effectiveness

6 Clinical evidence for vortioxetine

6.1 Identification of studies

A systematic literature review was conducted that aimed to retrieve all records relating to the clinical and safety aspects of the intervention of interest (vortioxetine; Brintellix®; Lu AA21004; 508233-74-7) including RCTs, non-RCTs, and safety studies, whether published, or unpublished, that were relevant to the decision problem.

Only studies in populations switching after initial treatment were considered appropriate sources of efficacy data, matching the proposed positioning of vortioxetine described in section 2.5.2. A similar constraint applies to efficacy data for comparators, the search for which is described later in section 6.7.1. The reason for restricting eligibility to such studies is that the relative efficacy of antidepressants cannot be assumed to be constant between initial and switch usage. In a meta-analysis²⁵ comparing within-class and across-class switches, patients randomised to switch to a non-SSRI antidepressant (bupropion, mirtazapine, venlafaxine) after initial SSRI therapy were more likely to experience remission than patients switched to a second SSRI (risk ratio 1.29, $p=0.007$). Pooled remission rates were 28% for non-SSRIs and 23.5% for SSRIs. These data suggest that differences in efficacy between non-SSRIs and SSRIs as initial treatment are not transferable to the switch setting. Such a finding is consistent with the clinical opinion supporting that it is rational to introduce a drug with an alternative pharmacological mode of action after the failure of an initial SSRI. The clinical evidence and opinion indicate that vortioxetine in particular is more suited to use in switching patients, in view of its multimodal activity distinct from all other antidepressants (as already described in section 1.2), and differences in clinical findings between the initial and switch settings, as reported later in this section.

This systematic literature review aimed to include studies relevant to searches required for the following sections:

- The search required for RCTs for the intervention of interest in Section 6.1
- The search required for non-RCTs for the intervention of interest in Section 6.8
- The search required for safety studies for the intervention of interest in Section 6.9.

As the same population, disease and intervention terms were required for all searches, one search was performed, but to identify trials of each study type, tailored inclusion/exclusion criteria were applied (see Table B1, Table B40 and Table B41).

6.1.1 Search strategy

One search strategy was constructed to be consistent with the decision problem investigating the effectiveness of vortioxetine for the treatment of adult patients with MDD or experiencing an episode (MDE) who have had an inadequate response to a previous antidepressant in terms of either efficacy or tolerability for their current episode and are thus eligible for a change in treatment (switch patients).

In order to ensure all switch patient studies were captured in the systematic review, a wide search was conducted with the population terms aiming to encompass all trials in adult MDD (switch and non-switch) patients featuring the intervention of interest. Following the identification of all studies and the first round of exclusions based on title and abstracts only, the list of records at the full-text review stage was then screened for studies which included the patient population fitting the switch definition as described above and in Table B1.

The search strategy combined vortioxetine and its alternative names with disease terms consistent with those used in the systematic review to inform the indirect treatment comparison (ITC) in Section 6.7. Search terms were not limited by outcome or study design, to ensure RCTs, non-RCTs and safety studies were all identified. The search strings are provided in Appendix 2.

The searches were limited to human studies and not restricted by language or geographical scope. No date limit was applied to the search. The following computerised bibliographic databases were searched as recommended by the Centre for Reviews and Dissemination¹³⁰:

- MEDLINE
- MEDLINE In-Process
- EMBASE
- PsycINFO
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Methodology Register
- NHS Economic Evaluation Database (NHS EED)
- Database of Abstracts of Reviews of Effects (DARE)
- Health Technology Assessment Database

In addition, the following registries were also searched in order to identify potentially relevant studies that are still in development or in current regulatory submission stages:

- US National Library of Medicine ClinicalTrials.gov
- WHO Clinical Trials
- Current Controlled Trials (www.Controlled-trials.com)

In addition to the above databases and registries, the following conferences were also searched for relevant literature:

- Annual Meeting of the American Psychiatric Association (APA) 166th – included in New research abstracts APA 2013
- Annual Meeting of the American Psychiatric Association (APA) 167th – included in New research abstracts APA 2014
- 29th World Congress of the Collegium Internationale Neuro- Psychopharmacologicum (CINP) – included in International Journal of Neuropsychopharmacology 2014
- 53rd Annual meeting of the American Society of Clinical Psychopharmacology (ASCP) New Clinical Drug Evaluation Unit (NCDEU) 2013
- 54th Annual meeting of the American Society of Clinical Psychopharmacology (ASCP) (NCDEU) 2014
- 21st European Congress of Psychiatry (EPA) - included in European Psychiatry 2013
- 22nd European Congress of Psychiatry (EPA) - included in European Psychiatry 2014
- 26th Congress of the European College of Neuropsychopharmacology (ECNP) – European Neuropsychopharmacology 2013
- 27th Congress of the European College of Neuropsychopharmacology (ECNP) – European Neuropsychopharmacology 2014

The initial search strategy was run on the 15 September 2014 and identified 297 records. To capture more recent records, an update of the initial search was undertaken on 28 November 2014 using the same methodology. This update identified an additional 43 hits, resulting in a total number of records of 340. Results of the updated systematic literature search are provided in the respective PRISMA study selection flow diagrams (Figure B1, Figure B15, Figure B17 and Figure B19).

6.2 Study selection

6.2.1 Eligibility criteria

The study selection process was conducted by two independent researchers who independently screened all records by title and abstract against the pre-determined eligibility criteria for selection of vortioxetine RCTs. If a unanimous decision on whether the study should be included or excluded from the search was not reached between the two researchers, a third independent researcher was consulted to reach a consensus. As noted in Section 6.1, the screening of records at the title/abstract stage were conducted for all adult patients with MDD before being specifically narrowed to the subset of switch patients at the full text review stage. Where the researchers were unable to exclude the article based on the title/abstract, the full publication was retrieved and evaluated against the eligibility criteria independently by two researchers. The eligibility criteria for Population, Intervention(s)/Comparator(s), Outcome(s) and Study design (PICOS) are displayed in Table B1.

Table B1. Eligibility criteria for selection of RCTs

	Inclusion criteria	Exclusion criteria
Population	As per decision problem: Adult patients with moderate-to-severe MDD who are experiencing an MDE, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to alternative antidepressant.	Patients without MDD. Patients not experiencing an MDE. Patients with MDD but not specifically switch populations. Paediatric patients.
Intervention	Must include a licensed vortioxetine regimen (5mg, 10mg, 15mg, 20mg tablets once daily).	Any study not containing vortioxetine as an intervention.
Comparator	SSRIs (e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline). TCAs (e.g. clomipramine, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, and amitriptyline). Tricyclic-related antidepressants (for example mianserin and trazodone). SNRIs (e.g. venlafaxine and duloxetine). Other antidepressants (for example mirtazapine, agomelatine, and reboxetine).	Non-antidepressants.
Outcomes	Change from baseline severity of depression. Remission of symptoms. Anxiety. Response to treatment (including response rate and time to response). Relapse (including relapse rate and time from remission to relapse). Hospitalisation. Mortality. Adverse effects of treatment (including adverse effects of treatment discontinuation). Health-related quality of life. Disability. Family functioning. Productivity (absenteeism/ presenteeism). Improvements in treatment related side-effects e.g. TESD. Improvement in cognitive functioning. Any other outcome.	No limitations.
Study design	RCTs of any duration, including cross-over RCTs if data were presented at cross-over.	Non-human. Articles reporting results of RCTs published elsewhere, e.g. reviews, meta-analyses/pooled analyses, editorials, notes, comments or letters. Non-RCTs.

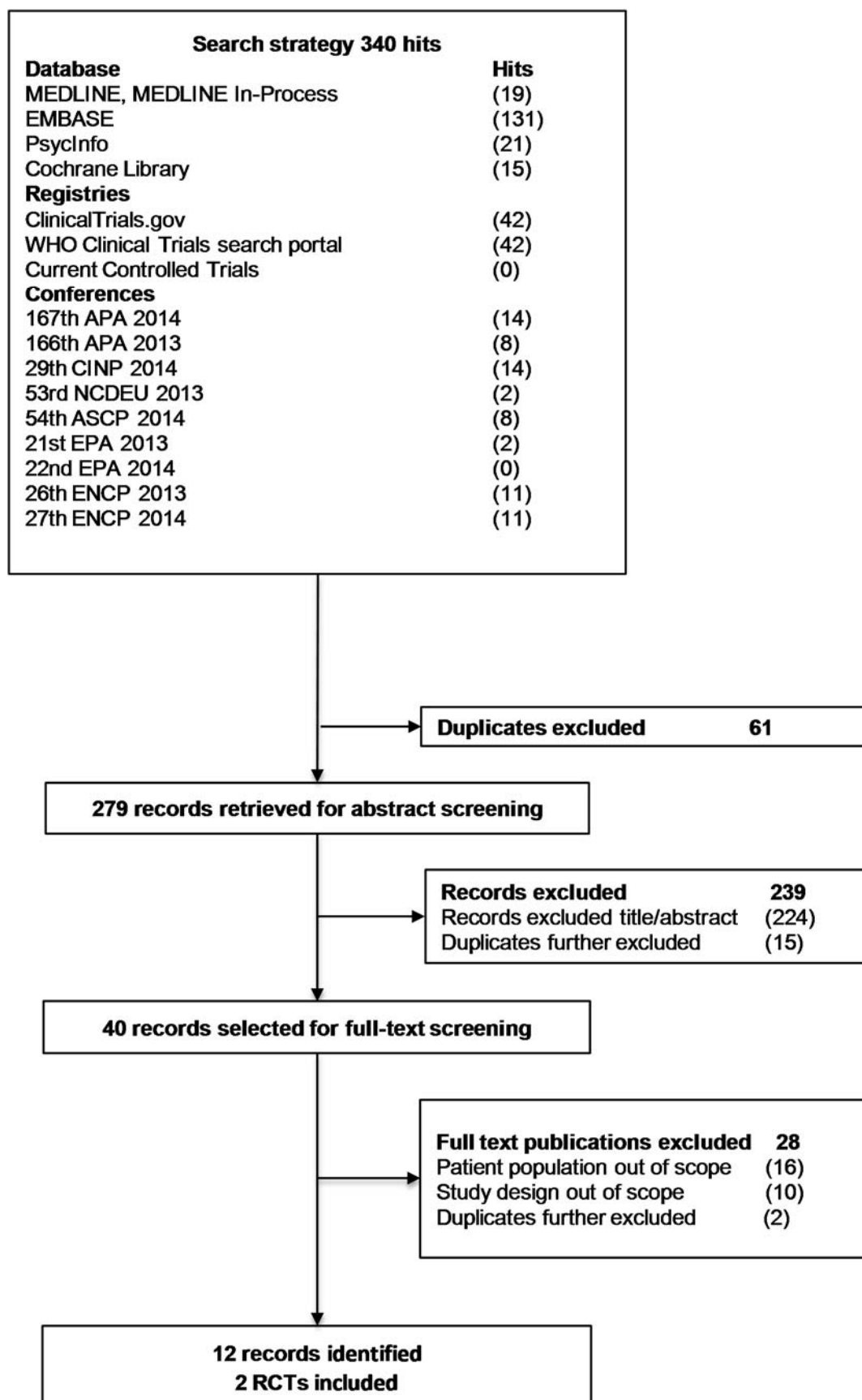
MDD: major depressive disorder; MDE: major depressive episode; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-noradrenaline reuptake inhibitor; TCA: tricyclic antidepressant; TESD: treatment-emergent sexual dysfunction; RCT: randomised controlled trial.

6.2.2 Flow diagram

The search identified 340 records from bibliographic databases (n=186), registries (n=84), conferences (n=70). Forty full texts were retrieved for the evaluation. Twelve records pertaining to two RCTs were identified for the switch population after full text screening.

A total of 24 studies were identified for vortioxetine in adult MDD patients, though 22 of these were excluded as these studies did not meet the inclusion criteria. Figure B1 presents the study selection process as a PRISMA flow diagram.

Figure B1. PRISMA flow diagram of the selection process for clinical studies of vortioxetine



Records of studies that were retained after full-text screening are first reported in this section by their ClinicalTrials.gov ID, as all such studies were recorded on this database. These IDs are cross-referenced to other bibliographic records.

6.2.3 Source references to RCTs

Table B2 **Error! Reference source not found.** and Table B3 present bibliographic details of the references to the two identified studies of vortioxetine in adult switch patients.

Table B2. Bibliographic details of studies in the switch population for NCT01488071 (REVIVE)

Clinical Trial Records - NCT01488071	
NCT01488071 (REVIVE) ¹³¹	A Study of Vortioxetine (Lu AA21004) in Comparison to Agomelatine in Adults Suffering From Major Depression With Inadequate Response to Previous Medication
Published articles	
Montgomery, 2014 ²⁶	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
Conference posters and abstracts	
Dragheim, 2013 ¹³²	A Randomized, Double-blind, Study of Vortioxetine versus Agomelatine in Adults with Major Depressive Disorder (MDD) Switched after Inadequate Response to SSRI or SNRI Treatment
Häggström, 2013 ¹³³	Randomized, Double-blind, Study of Vortioxetine versus Agomelatine in Adults with MDD After Inadequate Response to SSRI or SNRI Treatment
Häggström, 2013 ¹³⁴	A Randomised, Double-blind, Study of Vortioxetine Versus Agomelatine in Adults With Major Depressive Disorder (MDD) With Inadequate Response to SSRI/SNRI Treatment
Papakostas, 2014 ¹³⁵	Efficacy and Tolerability of Vortioxetine vs. Agomelatine is Independent of Previous Treatment in MDD Patients Switched After an Inadequate Response
Papakostas, 2014 ¹³⁶	In MDD Patients Switched After an Inadequate Response, the Efficacy and Tolerability of Vortioxetine versus Agomelatine is Independent of Previous Antidepressant Treatment
Papakostas, 2014 ¹³⁷	Efficacy and tolerability of vortioxetine is independent of previous treatment in MDD patients switched after an inadequate response

Table B3. Bibliographic details of studies in the switch population for NCT01364649

Clinical Trial Records - NCT01364649	
NCT01364649 ¹³⁸	Effect of Lu AA21004 Versus Escitalopram on Sexual Functioning in Adults With Well-Treated Major Depressive Disorder
Conference posters and abstracts	
Jacobsen, 2014 ²⁸	A Randomized, Double-blind, Head-to-head, Flexible-Dose Study of Vortioxetine vs Escitalopram in Sexual Functioning in Adults With Well Controlled Major Depressive Disorder Experiencing Treatment-Emergent Sexual Dysfunction
Jacobsen, 2014 ²⁹	A Head-to-head, Randomized, Comparison Study of Vortioxetine vs. Escitalopram in Patients Well Treated for MDD and Experiencing Treatment-emergent Sexual Dysfunction
Jacobsen, 2014 ¹³⁹	Vortioxetine Versus Escitalopram In Adults With Well-Treated Major Depressive Disorder Experiencing Treatment-Emergent Sexual Dysfunction

Table B4 shows the 22 studies of vortioxetine that were not conducted in the population of interest, i.e. a switch population.

Table B4. Clinical trials featuring the intervention of interest but excluded due to population

Adult MDD vortioxetine studies	
NCT00596817 ¹⁴⁰	Efficacy of Vortioxetine (Lu AA21004) in the Prevention of Relapse of Major Depressive Episodes
NCT00635219 ¹⁴¹	Randomised Placebo-controlled Duloxetine-referenced Efficacy and Safety Study of 2.5, 5 and 10mg of Vortioxetine (Lu AA21004) in Acute Treatment of Major Depressive Disorder
NCT00672620 ¹⁴²	Efficacy and Safety of Vortioxetine (Lu AA21004) in the Treatment of Patients With Major Depressive Disorder
NCT00672958 ¹⁴³	Efficacy and Safety of Vortioxetine (Lu AA21004) in Treating Adults With Major Depressive Disorder
NCT00694304 ¹⁴⁴	Open-label Safety Extension Study of 2.5, 5 and 10mg of Vortioxetine (Lu AA21004) in Long-term Treatment of Major Depressive Disorder in Adults
NCT00707980 ¹⁴⁵	Safety and Tolerability of Vortioxetine (Lu AA21004) in Adults With Major Depressive Disorder
NCT00735709 ¹⁴⁶	Efficacy Study of Vortioxetine (Lu AA21004) in Adults With Major Depressive Disorder
NCT00761306 ¹⁴⁷	Open-label Safety Extension Study of 5 and 10mg of Vortioxetine (Lu AA21004) in Long-term Treatment of Major Depressive Disorder in Adults
NCT00811252 ¹⁴⁸	Randomised Placebo-controlled Duloxetine-referenced Study of Efficacy and Safety of 5mg of Vortioxetine (Lu AA21004) in Acute Treatment of Major Depressive Disorder in Elderly Patients
NCT00839423 ¹⁴⁹	Randomised Placebo-controlled Venlafaxine-referenced Study of Efficacy and Safety of 5 and 10mg of Vortioxetine (Lu AA21004) in Acute Treatment of Major Depressive Disorder in Adults
NCT01140906 ¹⁵⁰	Randomised Placebo-controlled Duloxetine-referenced Study of Efficacy and Safety of 15 and 20mg of Vortioxetine (Lu AA21004) in Acute Treatment of Major Depressive Disorder in Adults
NCT01152996 ¹⁵¹	Safety and Tolerability of Vortioxetine (LuAA21004) - Open Label Extension Study
NCT01153009 ¹⁵²	Safety and Efficacy of Vortioxetine (Lu AA21004) in Adults With Major Depressive Disorder
NCT01163266 ¹⁵³	Efficacy and Safety Study of Vortioxetine (Lu AA21004) in Adults With Major Depressive Disorder
NCT01179516 ¹⁵⁴	Safety and Efficacy Study of Vortioxetine (Lu AA21004) in Adults With Major Depressive Disorder
NCT01255787 ¹⁵⁵	Efficacy and Safety Study of Vortioxetine (Lu AA21004) for Treatment of Major Depressive Disorder
NCT01323478 ¹⁵⁶	Open-label Safety Extension Study of 15 and 20mg of Vortioxetine (Lu AA21004) in Long-term Treatment of Major Depressive Disorder in Adults
NCT01355081 ¹⁵⁷	Efficacy Study of Lu AA21004 for Treatment of Major Depressive Disorder
NCT01395147 ¹⁵⁸	Long-Term Extension Study of Lu AA21004 in Participants With Major Depressive Disorder
NCT01422213 ¹⁵⁹	Efficacy Study of Vortioxetine on Cognitive Dysfunction in Adult Patients With Major Depressive Disorder (FOCUS)
NCT01564862 ¹⁶⁰	Efficacy of LuAA21004 on Cognitive Dysfunction in Major Depressive Disorder
NCT01571453 ¹⁶¹	Study of Vortioxetine (Lu AA21004) in Major Depressive Disorder in Asian Countries

6.2.4 List of relevant RCTs

The two identified studies conducted in a switch population are presented below in Table B5, together with references to internal clinical study reports and external publications. References are repeated only where the context requires through the remainder of this document.

Table B5. List of relevant RCTs for switch population

Manufacturer trial ID (acronym)	Intervention	Comparator	Population	Primary study references
14178A (REVIVE)	Vortioxetine 10mg-20mg flexible dosing	Agomelatine 25-50mg flexible dosing	Patients who have experienced an inadequate response to an SSRI or SNRI in their current MDE	Clinical Study Report ²⁷ ; NCT01488071 ¹³¹ ; Montgomery, 2014 ²⁶ ; Abstracts ^{132,133,135,162,163}
TAK318	Vortioxetine 10mg-20mg flexible dosing	Escitalopram 10-20mg flexible dosing	Patients who are well-controlled on an SSRI but experienced treatment emergent sexual dysfunction	Clinical Study Report ³⁰ ; NCT01364649 ¹³⁸ ; Abstracts ^{28,29}

REVIVE and TAK318 are currently the only trials that provide direct evidence for the efficacy of vortioxetine in patients who switch from an initial SSRI or SNRI within an MDE and therefore address the decision problem. These trials are described in detail in section 6.3 below. Synopses of trials in the full MDD population are provided in Appendix 14.

Study 14178A (REVIVE) was a 12-week, double-blind, parallel-group comparison of treatment with either vortioxetine or agomelatine in patients with moderate-to-severe MDD who had experienced inadequate response to monotherapy with an SSRI or SNRI. The relevance of this trial is that it investigates the outcomes of out-of-class switching following failure with an agent from one of two classes of antidepressant (SSRI or SNRI) commonly used as initial treatment.

Study TAK318 compared the effects of vortioxetine with an SSRI, escitalopram, on sexual functioning outcomes over 8 weeks of treatment of adult participants with well-treated MDD who were experiencing SSRI-induced sexual dysfunction. Treatment with antidepressants, including SSRIs, has been associated with sexual dysfunction, which can result in poor adherence to treatment. The relevance of Study TAK318 is that it investigates the outcomes of an out-of-class switch to vortioxetine with continuation of treatment with an SSRI, as a strategy to circumvent a specific troublesome side-effect.

6.2.5 Direct comparators

Studies 14178A (REVIVE, NCT01488071) and TAK318 (NCT01364649) each included an active comparator. Agomelatine, the comparator in REVIVE, is the most recently introduced antidepressant in the UK, but NICE has declined to recommend its use within the NHS for the treatment of MDEs as no evidence was submitted by the drug's manufacturer. Although agomelatine is seldom used within the NHS, a recent independent meta-analysis found it to be effective¹⁶⁴. Also, it is commonly prescribed in other European countries and fulfils the criteria for a "better tolerated, newer generation" antidepressant within the NICE treatment pathway, according to expert clinical advisors consulted by Lundbeck.

Escitalopram, the comparator in study TAK318, is an antidepressant within the SSRI class. Escitalopram is the pharmacologically active S-enantiomer of citalopram, which is a racemic mixture of R- and S-forms. Escitalopram is more effective than citalopram^{108,165,166}, though in the UK it has attained a market share of only approximately 1% of initially-switching patients, while citalopram is one of the market leading antidepressants (see Cegedim data in Figure A10). These differences in usage may be attributable to the absence until recently of

generic versions of escitalopram. Its positive clinical profile makes escitalopram an appropriate comparator to vortioxetine in Study TAK318.

No head-to-head studies were available in the switch population comparing vortioxetine to any other antidepressant drugs. See Section 6.7 for details of the indirect comparisons made in this submission using network meta-analysis.

6.2.6 Excluded studies

No completed studies of vortioxetine in switch populations with MDEs and hence of direct relevance to the decision problem have been excluded from further discussion. The only two studies investigating the use of vortioxetine in the switch population applicable to the decision problem were included for data extraction. Clinicaltrials.gov reported two additional trials in the switch population (NCT02272517¹⁶⁷ and NCT02279953¹⁶⁸) as not yet recruiting; this was excluded as no results are available.

The 22 non-switch studies that investigated vortioxetine in an adult MDD population, listed in Table B4, were excluded for the reasons stated in section 6.1.

6.2.7 Relevant non-RCTs

There were no non-RCT studies identified in the systematic literature review that investigated the use of vortioxetine as a switch therapy for adult patients with MDD. Further details on the study selection specific to non-RCTs can be found in Section 6.8.

6.3 Summary of methodology of relevant RCTs

6.3.1 (Instruction from NICE)

6.3.2 Methods

6.3.2.1 Study 14178A (REVIVE)

Study 14178A (REVIVE)^{26,27} was an interventional, prospective, multi-national, multi-site, randomised, double-blind, parallel-group, active-comparator (agomelatine), flexible-dose study.

A total of 500 patients (250 patients per treatment group) with MDD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria were planned for enrolment. Eligible patients had been treated with SSRI or SNRI monotherapy (SSRIs: citalopram, escitalopram, paroxetine, sertraline, and SNRIs: duloxetine, venlafaxine) and had experienced inadequate response to this treatment.

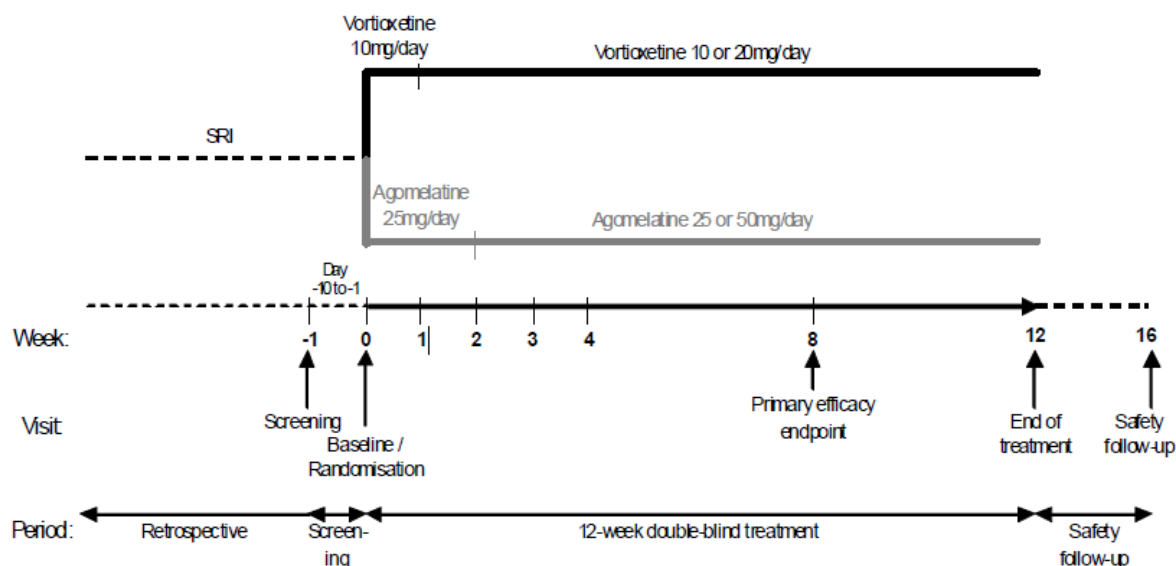
The trial scheme is shown in Figure B2. At the Baseline Visit, patients were switched from treatment with an SSRI or SNRI to treatment with vortioxetine or agomelatine. The study consisted of a Screening Period of 4 to 10 days before the Baseline Visit, followed by a 12-week double-blind treatment period with vortioxetine or agomelatine. The patients were randomised equally (1:1) to flexible doses of either vortioxetine (10 to 20mg/day) or agomelatine (25 to 50mg/day). The starting doses were vortioxetine 10mg/day or agomelatine 25mg/day²⁷.

The dose of vortioxetine was fixed at 10mg/day for the first week of treatment; at the end of Weeks 1, 2, 3, and 4, the dose could be increased to 20mg/day, but only on the basis of an unsatisfactory response on depressive symptoms, as judged by the investigator. For patients who did not tolerate the increased dose, the investigator could adjust the dose to

10mg/day at subsequent visits; the dose could not be increased above 20mg/day or decreased below 10mg/day; after Week 4, the dose had to remain fixed. The dose of agomelatine was fixed at 25mg/day for the first 2 weeks of treatment, as recommended in the SmPC for agomelatine; at the end of Weeks 2, 3, and 4, the dose could be increased to 50mg/day, but only on the basis of an unsatisfactory response on depressive symptoms, as judged by the investigator. For patients who did not tolerate the increased dose, the investigator could adjust the dose to 25mg/day at subsequent visits; the dose could not be increased above 50mg/day or decreased below 25mg/day; after Week 4, the dose had to remain fixed. As the allocated treatment was blinded, the investigator did not know whether the dose of vortioxetine or agomelatine was actually modified if the dose was adjusted at Week 1.

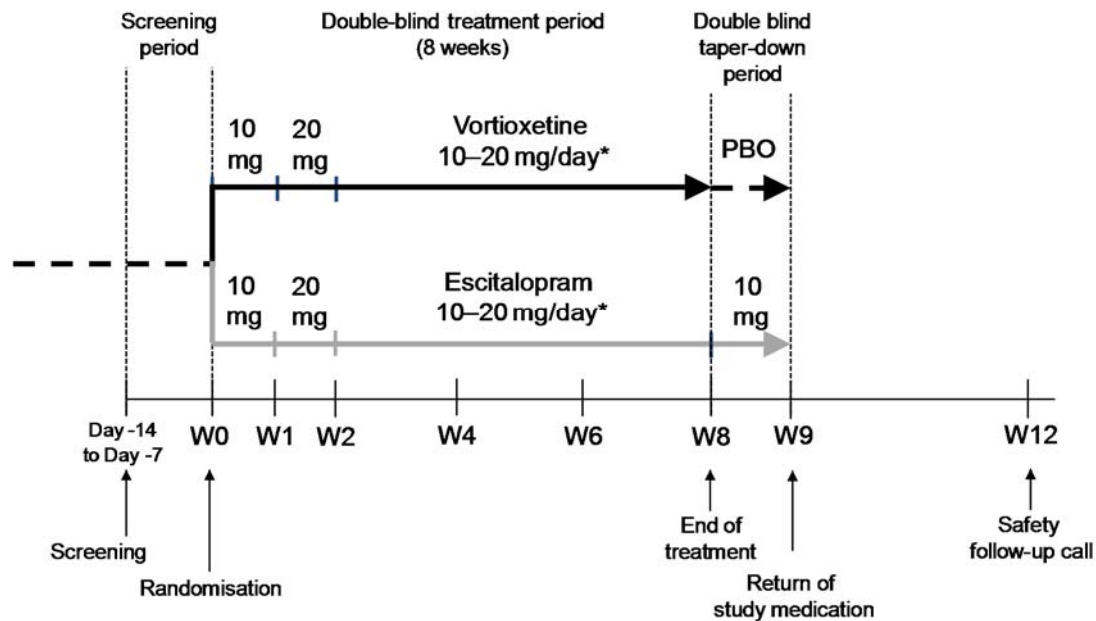
Patients were seen for efficacy and safety assessments weekly during the first 4 weeks of treatment and then every 4 weeks until the end of the 12-week treatment period. A safety follow-up contact was scheduled for 4 weeks after completion or withdrawal from the study.

Figure B2. Design of Study 14178A (REVIVE)²⁷



6.3.2.2 Study TAK318

Study TAK318²⁸⁻³⁰ was a phase IIIb, multicentre, randomised, double-blind, active-controlled (escitalopram), parallel-group, flexible-dose study comparing vortioxetine (10 and 20mg QD) with escitalopram (10 and 20mg QD) in subjects with well-treated MDD who were experiencing SSRI-induced sexual dysfunction.

Figure B3. Design of Study TAK318²⁸⁻³⁰

Subjects with a diagnosis of major depressive episode (MDE) according to the DSM-IV-TR for which they had been receiving SSRI monotherapy (only citalopram, paroxetine, or sertraline were allowed; escitalopram was not allowed) for at least 8 weeks prior to the Screening Visit, and who were experiencing sexual dysfunction were screened for eligibility. The MDE should have been well-treated, that is, currently stable (without clinically significant fluctuation in levels of depressive symptoms) as judged by the investigator, and with a Clinical Global Impression Scale-Severity of Illness Scale (CGI-S) total score ≤ 3 . Additionally, patients must have been experiencing SSRI-induced sexual dysfunction per investigator judgment and must have met the threshold criterion for sexual dysfunction as measured by the Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) total score (≤ 41 in women; ≤ 47 in men).

At Baseline, subjects who continued to fulfil all the inclusion criteria and none of the exclusion criteria were randomised equally (1:1) to 1 of 2 treatment arms for an 8 week, double-blind Treatment Period. Subjects were randomised to flexible doses of either vortioxetine 10/20mg QD or escitalopram 10/20mg QD. Subjects must have discontinued their current SSRI monotherapy treatment at Baseline. Randomised subjects received either vortioxetine 10mg or escitalopram 10mg for the first week. Subjects initiated the investigational drug the day after the Baseline Visit. At the Week 1 visit all subjects had their dose increased to 20mg/day of either vortioxetine or escitalopram. At the Week 2, 4, or 6 visits, investigators may have adjusted the dose based on subject response and tolerability as judged by the investigator. The dose was not to be increased above 20mg/day vortioxetine or escitalopram.

Subjects who completed the 8-week Treatment Period entered a 1-week, Double-Blind, Taper-Down Period. Subjects treated with vortioxetine (10/20mg QD) received placebo; and subjects treated with escitalopram (10/20mg QD) received 10mg QD escitalopram, during the Taper-Down Period. A Safety Follow-up phone call was made 4 weeks after completion of the 8-week Treatment Period.

Table B6. Comparative summary of methodology of the relevant RCTs

	Study 14178A (REVIVE) ²⁷	Study TAK318 ³⁰
Location	EU	USA and Canada
Design	DB, AC	DB, AC
Duration of study	12 weeks DB period	8 weeks DB period
Method of randomisation	At the Screening Visit, the patients were assigned a screening number. At the Baseline Visit, patients who fulfilled the selection criteria were assigned to treatment with either vortioxetine or agomelatine in a 1:1 ratio. Randomisation was executed using an IVRS/IWRS according to a randomisation list that was computer generated by H. Lundbeck A/S. Randomisation numbers were prepared for a total of 2000 patients, with 1000 numbers assigned to each of the two treatment groups. Block randomisation (in blocks of 4) ensured that equal numbers of patients entered each treatment group.	The block randomisation scheme and codes are reported in protocol appendix 16.1.7.
Method of blinding (care provider, patient and outcome assessor)	The study was double-blinded. Two sets of sealed envelopes containing IMP details for each patient in the double-blind period were prepared. One set was kept by each of the following: Global Pharmacovigilance (GPV), H. Lundbeck A/S, and the investigator or pharmacist. The randomisation code was only to be broken in an emergency situation in order to give the patient optimal treatment. If possible, the investigator was to consult the clinical research associate before code break. After code break, the clinical research associate was to be notified immediately, and the patient withdrawn from the study.	Per the protocol instructions, the study medication blind was not to be broken by the investigator unless information concerning the study medication was necessary for the medical treatment of the subject. If possible, the sponsor/designee was to be notified before the study medication blind was broken. If a medical emergency requiring unblinding occurred, the investigator (or designee) at the site was to contact the sponsor or designee to assess the necessity to break the study medication blind. For unblinding a subject, the study medication blind was to be obtained by accessing the IVRS. The sponsor/designee was to be notified immediately if the study medication blind was broken. The date, time, and reason the blind was broken would have been recorded in the source documents and the same information (except the time) recorded on the appropriate eCRF. If any site personnel were unblinded, study medication would have to be stopped immediately and the subject would have to be withdrawn from the study. The reason for withdrawal was to be recorded as "Protocol Deviation".
Numbers of subjects	All patients treated set (Full analysis set)	Full analysis set (per protocol set)
	Vortioxetine 253 (252) Agomelatine 242 (241)	Vortioxetine 217 (192) Escitalopram 207 (195)
Primary outcomes (including scoring methods and timings of assessments)	Change from Baseline in MADRS total score at week 8.	Change from Baseline in the CSFQ-14 total score after 8 weeks of treatment.

	Study 14178A (REVIVE) ²⁷	Study TAK318 ³⁰
Secondary outcomes (including scoring methods and timings of assessments)	Response (defined as a $\geq 50\%$ decrease from baseline in MADRS total score, or a CGI-I ≤ 2) Remission (defined as a MADRS total score ≤ 10 , or a CGI-S ≤ 2).	Change from Baseline in the CSFQ-14 total score at each visit assessed. Number of subjects with a shift in the CSFQ-14 from abnormal (defined as a CSFQ-14 total score ≤ 41 for women and ≤ 47 for men) at Baseline, to normal (defined as >41 for women and >47 for men) at each visit assessed.
Duration of follow-up	12 weeks + 4 weeks safety follow-up	8 weeks + 4 weeks safety follow-up

DB = Double-blind; AC = Active comparator; eCRF: electronic case record form; IVRS/IWRS: Interactive Voice/Web Response System; APTS = All patients treated set; FAS = Full analysis set; CSFQ-14: Changes in Sexual Functioning Questionnaire short-form; MADRS: Montgomery-Åsberg Depression Rating Scale; CGI-I: Clinical Global Impression - Improvement Scale; CGI-S: Clinical Global Impression - Severity Scale.

6.3.3 Participants

Table B7. Eligibility criteria for recruitment into the relevant RCTs

Inclusion criteria	Exclusion criteria
Study 14178A (REVIVE)²⁷	
1. The patient is able to read and understand the <i>Informed Consent Form</i>. 2. The patient has signed the <i>Informed Consent Form</i>. 3. The patient is willing and able to attend study appointments within the specified time windows. 4. The patient is being treated with antidepressant SRI monotherapy (SSRIs: citalopram, escitalopram, paroxetine, sertraline, and SNRIs: duloxetine, venlafaxine) that was prescribed to treat single episode of MDD (diagnostic code 296.2x) or recurrent MDD (diagnostic code 296.3x), according to DSM-IV-TRTM criteria, at the Screening and Baseline Visits. 5. The patient has depressive symptoms currently considered as non or partially responsive to no more than one adequate course (licensed doses for at least 6 weeks prior to the Screening Visit) of SRI monotherapy (SSRIs: citalopram, escitalopram, paroxetine, sertraline, and SNRIs: duloxetine, venlafaxine) and is candidate for a switch in the investigator's opinion. 6. The patient wants to stop taking his/her current SRI (SSRI/SNRI) treatment due to inadequate response and agrees to discontinue the current SRI (SSRI/SNRI) antidepressant at the Baseline Visit and for the study duration. 7. The patient has a MADRS total score ≥ 22 at the Screening and Baseline Visits. 8. The patient has a MADRS Item 1 (<i>apparent sadness</i>) score ≥ 3 at the Screening and Baseline Visits. 9. The patient has a reported duration of the current MDE of less than 1 year at the Screening Visit. 10. The patient is a man or woman, aged ≥ 18 and ≤ 75 years. 11. The patient is an inpatient in a psychiatric hospital or an outpatient at a psychiatric setting at the time of the study entry.	1. The patient has previously been enrolled in this study. 2. The patient is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel. 3. The patient is pregnant or breast-feeding. 4. The patient has a history of severe drug allergy or hypersensitivity, or known hypersensitivity to agomelatine or any of the excipients of the IMPs. 5. The patient has hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase insufficiency. 6. The patient has any current psychiatric disorder or Axis I disorder (DSM-IV-TRTM criteria), other than GAD and SAD, as assessed using the Mini International Neuropsychiatric Interview (MINI). Non excluded Axis I disorder, must demonstrate MDD as the primary diagnosis. 7. The patient has a current diagnosis of MDD with post-partum onset or MDD with a seasonal pattern (DSM-IV-TRTM criteria). 8. The patient has a current or has had a diagnosis of dysthymic disorder within 3 months preceding the onset of current episode (DSM-IV-TRTM criteria). 9. The patient has borderline, schizotypal, schizoid, paranoid, histrionic, antisocial personality disorders (Axis II) as comorbid or primary diagnosis (DSM-IV-TRTM criteria). 10. The patient has history of previous major depressive episodes considered as treatment resistant, defined as inadequate response (incomplete or no therapeutic response) to two prior courses of at least 6 weeks of conventional antidepressant drugs in adequate dosages or, the patient has treatment-resistant depression in the investigator's judgement.

Inclusion criteria	Exclusion criteria
12. The patient, if a woman, must: – agree not to try to become pregnant during the study, AND – use adequate, highly effective contraception (defined as those that result in a low failure rate [that is, <1% per year] when used consistently and correctly, for example, implants, injectables, combined oral contraceptives in combination with a double barrier method, some intrauterine devices, sexual abstinence, vasectomised partner), OR – For United Kingdom only (SCA01): during the study and 30 days after the last dose of IMP use adequate, highly effective contraception (defined as those that result in a low failure rate [that is, <1% per year] when used consistently and correctly, for example, implants, injectables, combined oral contraceptives in combination with a double barrier method, some intrauterine devices, sexual abstinence [if in line with the subject's normal lifestyle], vasectomised partner), OR – have had her last natural menstruation ≥ 24 months prior to the Screening Visit, OR – have been surgically sterilised prior to the Screening Visit, OR – have had a hysterectomy prior to the Screening Visit.	11. The patient has a history of lack of response to previous adequate treatment with agomelatine. 12. The patient has a current diagnosis or history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, including major depression with psychotic features (DSM-IV-TR™ criteria). 13. The patient suffers from mental retardation, organic mental disorders, or mental disorders due to a general medical condition (DSM-IV-TR™ criteria). 14. The patient has a diagnosis of alcohol or other substance abuse or dependence (excluding nicotine or caffeine) (DSM-IV-TR™ criteria) that has not been in sustained full remission for at least 2 years prior to the Screening Visit. 15. The patient has a history of moderate or severe head trauma (for example, loss of consciousness for more than 1 hour) or other neurological disorders or systemic medical diseases that are, in the opinion of the investigator, likely to affect central nervous system functioning. 16. The patient is at significant risk of suicide or has a MADRS Item 10 (<i>suicidal thoughts</i>) score ≥ 5, or has attempted suicide <6 months prior to the Screening Visit. 17. The patient is currently receiving formal cognitive or behavioural therapy or systematic psychotherapy, or plans to start such therapy during the study. 18. The patient has received electroconvulsive therapy for the current episode or <6 months prior to the Screening Visit. 19. The patient has a history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin, that has not been in remission for >5 years prior to the first dose of IMP. 20. The patient has or has had one or more of the following conditions that is/are considered clinically relevant in the context of the study: – neurodegenerative disorder or neurodegenerative features (such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease) – cardiovascular disease – seizure disorder or encephalopathy – congestive heart failure – cardiac hypertrophy – arrhythmia – bradycardia (pulse <50 beats per minute [bpm]) – respiratory disease – hepatic impairment (for example, cirrhosis or active liver disease) or renal insufficiency – metabolic disorder – endocrinological disorder – gastrointestinal disorder – haematological disorder – infectious disorder – any clinically significant immunological condition – dermatological disorder – venereal disease. 21. The patient takes or has taken disallowed recent or concomitant medication or it is anticipated that the patient

Inclusion criteria	Exclusion criteria
	will require treatment with at least one of the disallowed concomitant medications during the study. 22. The patient has clinically significant abnormal vital signs at the Screening Visit. 23. The patient has a value of thyroid stimulating hormone (TSH) outside the normal range at the Screening Visit. Patients with thyroid disease may be enrolled in the study provided they are stable and euthyroid. 24. The patient has one or more clinical laboratory test values outside the reference range, based on the blood and urine samples taken at the Screening Visit, that are of potential risk to the patient's safety, or the patient has, at the Screening Visit: – a serum creatinine value >1.5 times the upper limit of the reference range (ULN) – a serum total bilirubin value >1.5 times ULN – a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 times ULN 25. The patient has, at the Screening Visit, any of the following: – an abnormal ECG that is, in the investigator's opinion, clinically significant – a PR interval >250 ms – a QRS interval >130 ms – a QTcF interval >450 ms (for men) or >470 ms (for women) (based on the Fridericia correction where QTcF = QT/RR^{0.33}). 26. The patient has a disease or takes medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with the conduct or interpretation of the study. 27. The patient is, in the investigator's opinion, unlikely to comply with the protocol) or is unsuitable for any reason. 28. The patient has previously been exposed to vortioxetine.
Study TAK318³⁰	
Subject was a man or a woman aged between 18 and 55 years, inclusive, who was currently being treated with SSRI monotherapy (only citalopram, paroxetine, or sertraline allowed) for at least 8 weeks, which was prescribed to treat an MDE, according to the DSM-IV-TR criteria. The depression was currently well treated and stable; and the subject had a CGI-S score of ≤3. The subject was currently experiencing treatment-emergent sexual dysfunction (TESD) (defined as a CSFQ-14 total score ≤41 for women and ≤47 for men), considered to be attributable to the current SSRI monotherapy and was suitable for a switch.	The subject had received any investigational compound <30 days before Screening or 5 half-lives prior to Screening. 2. The subject had previously participated in this study. 3. The subject had participated in a previous clinical study with Lu AA21004 compound. 4. The subject was an immediate family member, study site employee, or was in a dependent relationship with a study site employee who was involved in the conduct of this study (e.g., spouse, parent, child, sibling) or may have consented under duress. 5. Subjects who had sexual dysfunction associated with an aetiology other than SSRI treatment or current MDE (e.g., due to a medical condition, such as diabetes or hypertension, a medication, a genital anatomical deformity, or alcohol abuse). 6. Nonsexually active subject or subject who anticipated decreasing frequency of sexual activity (i.e., sexual activity anticipated to lead to orgasm or that would normally lead to orgasm, which could have included sexual intercourse, oral sex, masturbation, sexual fantasies, and/or thinking of sexual activity) during the course of the study below the

Inclusion criteria	Exclusion criteria
	level at study initiation. 7. Male subjects with a history of premature ejaculation in the past year. 8. The subject had major relationship changes during the preceding SSRI treatment period or planned to have major relationship changes during the course of the study. 9. The subject or subject's sexual partner(s) planned to initiate treatment for sexual dysfunction during the study. 10. The subject had 1 or more of the following: a) Any current psychiatric disorder other than MDD as defined in the DSM-IV-TR (as assessed by the MINI Version 6.0.0). b) Current or history of manic or hypomanic episode, schizophrenia, or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in the DSM-IV-TR. c) Current diagnosis of alcohol or other substance abuse or dependence (excluding nicotine or caffeine) as defined in the DSM-IV-TR that had not been in sustained full remission for at least 2 years prior to Screening. (Subject must also have had negative urine drug screen prior to Baseline). d) Presence or history of a clinically significant neurological disorder (including epilepsy). e) Neurodegenerative disorder (Alzheimer disease, Parkinson disease, multiple sclerosis, Huntington disease, etc). f) Any Axis II disorder that might have compromised the study. 11. The subject had known sensitivity to escitalopram. 12. Subjects received mood stabilizers (including anticonvulsants), antipsychotics, or antidepressant medications (except citalopram, paroxetine, or sertraline monotherapy) within 8 weeks prior to screening. 13. The subject was required to take excluded medications or it was anticipated that the subject would require treatment with at least 1 of the disallowed concomitant medications during the study evaluation period as specified in the Excluded Medications Section of the protocol. 14. The subject had received electroconvulsive therapy, vagal nerve stimulation, or repetitive transcranial magnetic stimulation within 6 months prior to Screening. 15. The subject had initiated formal cognitive or behavioral therapy, systemic psychotherapy within less than 6 months of study Screening, or had plans to initiate such therapy during the study. 16. The subject had a significant risk of suicide according to the investigator's clinical judgment or had a score ≥ 5 on item 10 (suicidal thoughts) of the MADRS or had made a suicide attempt in the previous 6 months. 17. If female, the subject was pregnant or lactating or intending to become pregnant before, during, or within 30 days after participating in this study; or intended to donate ova during such time period. 18. The subject had a clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or

Inclusion criteria	Exclusion criteria
	cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatologic, immunologic, infectious, skin and subcutaneous tissue disorders, or metabolic disturbance. Note: For the purposes of this protocol diabetes and obstructive sleep apnoea were considered unstable due to the potential impact on sexual functioning and may have impacted assessment of the primary endpoint. 19. The subject had a previous history of cancer that had been in remission for less than 5 years prior to the first dose of investigational drug. This criterion did not include those subjects with basal cell or stage I squamous cell carcinoma of the skin. 20. The subject had 1 or more laboratory value outside the normal range, based on the blood or urine samples taken at the Screening Visit, that were considered by the investigator to be clinically significant; or the subject had any of the following values at the Screening Visit: a) A serum creatinine value >1.5 times the upper limits of normal ($\times$ULN). b) A total serum total bilirubin value >1.5$\times$ULN. c) A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2$\times$ULN. d) Haemoglobin A1C value greater than 7.0%. 21. The subject had a body mass index (BMI) >35. 22. The subject had clinically significant abnormal vital signs as determined by the investigator. 23. The subject had an abnormal ECG as determined by the central reader and confirmed as clinically significant by the investigator. 24. The subject had a disease or had taken medication that, in the opinion of the investigator, could have interfered with the assessments of safety, tolerability, or efficacy. 25. The subject, in the opinion of the investigator, was unlikely to comply with the clinical study protocol or is unsuitable for any reason.

DSM-IV-TR™: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ;IMP: investigational medicinal product; MDD: major depressive disorder; MDE: major depressive episode; MADRS: Montgomery-Åsberg Depression Rating Scale; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-noradrenaline reuptake inhibitor.

6.3.4 Patient characteristics at baseline

6.3.4.1 Study 14178A (REVIVE)

Table B8 provides baseline patient demographic and clinical characteristics for Study 14178A (REVIVE).

Table B8. Study 14178A (REVIVE). Baseline characteristics of participants²⁷

Baseline characteristic	Vortioxetine	Agomelatine	Total
Number of patients: APTS ¹ , (FAS ²)	253 (252)	242 (241)	495 (493)
Mean (median) age (years) ¹	47.0 (48.0)	45.6 (46.0)	46.3 (47.0)
Sex (% female) ¹	77.1%	72.3%	74.7%
Race (% white) ¹	99.6%	100.0%	99.8%
Mean $\pm$ sd (median) duration of current episode (weeks) ¹	18.6 $\pm$ 10.4 (16.0)	19.2 $\pm$ 10.9 (16.0)	18.9 $\pm$ 10.6 (16.0)
Mean $\pm$ sd (median) number of previous episodes ¹	2.6 $\pm$ 2.1 (2.0)	2.4 $\pm$ 1.8 (2.0)	2.5 $\pm$ 2.0 (2.0)
Mean $\pm$ sd (median) MADRS total baseline score ²	29.1 $\pm$ 4.4 (29.0)	28.7 $\pm$ 4.0 (28.0)	28.9 $\pm$ 4.2 (28.0)
Mean CGI-S $\pm$ sd (median) total baseline score ²	4.4 $\pm$ 0.6 (4.0)	4.4 $\pm$ 0.6 (4.0)	4.4 $\pm$ 0.6 (4.0)
Mean $\pm$ sd (median) HAM-A total baseline score ²	21.6 $\pm$ 6.3 (21.0)	21.4 $\pm$ 6.2 (21.0)	21.5 $\pm$ 6.2 (21.0)

¹ denotes analyses based on APTS (all patients treated set). ² denotes analyses based on FAS (full analysis set). SD: standard deviation. See section 6.3.6.1.1 for definitions of analysis sets. CGI-S: Clinical Global Impression - Severity Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale.

The baseline MADRS total score of 29 for both groups (ranging from 22 to 43 points) was consistent with patients experiencing moderate to severe MDD. The use of antidepressants taken immediately before switching to either vortioxetine or agomelatine was comparable between groups. Overall, 24.5% of the patients in the vortioxetine group and 21.9% of patients in the agomelatine group had received previous treatment with SNRIs (duloxetine or venlafaxine), while the remaining patients had received previous SSRI treatment (sertraline, escitalopram, citalopram or paroxetine).

6.3.4.2 Study TAK318

Table B9 provides baseline patient demographic and clinical characteristics for Study TAK318.

Table B9. Study TAK318. Baseline characteristics of participants³⁰

Participant characteristic	Vortioxetine (n=255)	Escitalopram (n=222)
Age, years Mean $\pm$ sd (range)	39.3 $\pm$ 10.0 (19–55)	40.2 $\pm$ 10.0 (19–55)
Sex		
Male	97 (43.1%)	87 (39.2%)
Female	128 (56.9%)	135 (60.8%)
Race		
Caucasian	178 (79.1%)	181 (81.5%)
Black	41 (18.2%)	35 (15.8%)
Asian	4 (1.8%)	3 (1.4%)
Other	2 (0.9%)	3 (1.4%)
BMI, kg/m ² , mean $\pm$ sd	27.5 $\pm$ 4.4	27.9 $\pm$ 4.4
CSFQ-14 total score Mean $\pm$ se (range)	36.1 $\pm$ 0.39 (21–47)	36.0 $\pm$ 0.40 (21–47)
MADRS total score* Mean $\pm$ sd (range)	7.9 $\pm$ 6.3 (0–34)	8.3 $\pm$ 6.5 (0–34)
CGI-S Mean $\pm$ sd (range)	2.0 $\pm$ 0.8 (1–3)	2.0 $\pm$ 0.8 (1–3)

sd: standard deviation; se: standard error; BMI: body mass index; CGI-S: Clinical Global Impression - Severity Scale; CSFQ-14: Changes in Sexual Functioning Questionnaire Short-Form; MADRS: Montgomery-Åsberg Depression Rating Scale.

6.3.5 Outcomes

Table B10. Primary and secondary outcomes of the RCTs

	Study 14178A (REVIVE) ²⁷	Study TAK318 ³⁰
Outcome measures	Efficacy: Montgomery and Åsberg Depression Rating Scale (MADRS) ¹⁶⁹ . See description below. Hamilton Anxiety Rating Scale (HAM-A) ^{170,171} . Clinical Global Impression – Severity of Illness (CGI-S) ¹⁷² . Clinical Global Impression – Global Improvement (CGI-I) ¹⁷² . Sheehan Disability Scale (SDS) ¹⁷³ . HRQoL and global functioning EuroQoL 5 Dimensions (EQ-5D) ¹⁷⁴ . Work Limitations Questionnaire (WLQ) ¹⁷⁵ . Depression and Family Functioning Scale (DFFS) ¹²⁷ . Healthcare resource utilisation	Efficacy: Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) ¹⁷⁶ . Montgomery and Åsberg Depression Rating Scale (MADRS) ¹⁶⁹ . Clinical Global Impression – Severity of Illness (CGI-S) ¹⁷² . Clinical Global Impression – Global Improvement (CGI-I) ¹⁷² . Profile of Mood States (POMS) ¹⁷⁷ Safety: Columbia-Suicide Severity Rating Scale (C-SSRS) ^{178,179} .
Primary endpoint(s)	Change from Baseline in MADRS total score at Week 8	Change from Baseline in the CSFQ-14 total score after 8 weeks of treatment
Secondary and additional endpoint(s)	Response (defined as a $\geq 50\%$ decrease from baseline in MADRS total score, or a CGI-I ≤ 2). Remission (defined as a MADRS total score ≤ 10 , or a CGI-S ≤ 2). Change from Baseline in the MADRS total score at each visit assessed. Change from Baseline in CGI-S at each visit assessed. Mean score in the CGI-I at each visit assessed. CGI-S remission rates at Week 8, with remission	Change from Baseline in the CSFQ-14 total score at each visit assessed. Number of subjects with a shift in the CSFQ-14 from abnormal (defined as a CSFQ-14 total score ≤ 41 for women and ≤ 47 for men) at Baseline, to normal (defined as >41 for women and >47 for men) at each visit assessed. Change from Baseline in CSFQ-14 subscales 5 dimensions (pleasure, desire/frequency, desire/interest, arousal/erection, and

	Study 14178A (REVIVE) ²⁷	Study TAK318 ³⁰
	defined as a CGI-S score ≤ 2. Change from Baseline in the SDS at Weeks 4, 8 and 12. EQ-5D profile at Baseline, Weeks 4, 8 and 12. EQ-5D utility score at Baseline, Weeks 4, 8 and 12 (derived from profile responses). DFFS and WLQ at Baseline, Weeks 4, 8 and 12. Healthcare resource utilisation at Baseline, Weeks 8 and 12. Change from Baseline in the MADRS total score at each visit assessed. Change from Baseline in CGI-S at each visit assessed. Mean score in the CGI-I at each visit assessed. CGI-S remission rates at Week 8, with remission defined as a CGI-S score ≤ 2. Change from Baseline in the SDS at Weeks 4, 8 and 12. EQ-5D profile at Baseline, Weeks 4, 8 and 12. EQ-5D utility score at Baseline, Weeks 4, 8 and 12 (derived from profile responses). DFFS and WLQ at Baseline, Weeks 4, 8 and 12. Healthcare resource utilisation at Baseline, Weeks 8 and 12.	orgasm/ejaculation) and 3 phases of sexual functioning (desire, arousal, and orgasm/completion) at each visit assessed. Percentage of responders according to the CSFQ-14 (defined as CSFQ-14 total score increase from Baseline ≥ 3) at each visit assessed. Change from Baseline in CSFQ-14 total score in CGI-S remitters (as defined as a CGI-S score ≤ 2) and in CGI-S nonremitters at each visit assessed. Change from Baseline in the MADRS total score at each visit assessed. Change from Baseline in CGI-S at each visit assessed. Mean score in the CGI-I at each visit assessed. CGI-S remission rates at Week 8, with remission defined as a CGI-S score ≤ 2. Change from Baseline in POMS—brief form total score at each visit assessed.
Safety assessments	AEs, vital signs, ECGs, laboratory values, weight and physical examination findings. Pregnancy.	AEs, vital signs, ECGs, laboratory values, weight and physical examination findings. Pregnancy. C-SSRS at each visit assessed.
Reliability, validity and current status	The reliability and validity of all the above instruments has been demonstrated and, apart from the recently-developed DFFS, their use in clinical and economic studies is well established. See references in main text.	The reliability and validity of all the above instruments has been demonstrated. See references.

AE: adverse event; ECG: electrocardiogram; FAS: Full analysis set.

6.3.6 Statistical analysis and definition of study groups

6.3.6.1 Study 14178A (REVIVE)^{27,180}

6.3.6.1.1 Analysis sets

The following analysis sets were defined:

- All Patients Randomised Set (APRS): all randomised patients;
- All Patients Treated Set (APTS): all patients in the APRS who took at least one dose of double-blind study drug;
- Full Analysis Set (FAS): all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the primary efficacy variable (MADRS);
- Per Protocol Set (PPS): all patients in the FAS who:
 - ◊ did not have any major protocol violation;
 - ◊ did not disrupt treatment for >6 consecutive days;
 - ◊ did not have >2 days between SRI and first dose of study drug;
 - ◊ had received study drug until at least the Week 4 visit;

- ◇ did not take disallowed concomitant medication judged to interfere with the treatment response during the treatment period
- ◇ had a compliance rate of $\geq 70\%$ until completion or withdrawal.

Based on the definitions above, the patients and data were classified into analysis sets at a Classification Meeting held after all the data had been entered into the study database and verified, and before the randomisation code was broken.

6.3.6.1.2 Hypotheses

For the primary outcome (change from baseline in MADRS total score at week 8), a primary efficacy hypothesis of non-inferiority of vortioxetine to agomelatine was tested using estimates from a mixed model for repeated measurements (MMRM), including treatment, week, and site group as fixed factors and the baseline score as a covariate. The model also included interaction between week and baseline score, as well as interaction between week and treatment. An unstructured covariance structure was used to model the within-patient variance and the estimation method was a restricted maximum likelihood (REML)-based approach. The analysis was based on the missing-at-random (MAR) assumption and performed using all available observed cases (OC) data. The treatment differences expressed as a comparison of adjusted mean changes were presented together with p-values and 95% confidence intervals.

Non-inferiority was considered established if the upper bound of the two-sided 95% confidence interval of the difference between treatment groups in MADRS total score at Week 8 did not exceed 2 MADRS units vs. agomelatine. The prespecified margin of 2 MADRS units was specified according to the recommendation that the non-inferiority margin should be between one-third and one-half of the advantage of the active comparator over placebo and correspond with the minimum difference that would be considered clinically important¹⁸¹.

6.3.6.1.3 Power and sample size calculations

A minimum of 500 patients (250 patients per treatment group) were planned for randomisation. The sample size calculation was based on a non-inferiority comparison of the treatment groups in the change from baseline to Week 8 in MADRS total score using a two-sided 95% confidence interval against a margin of 2 points. Assuming a standard deviation of 9.5 points and a true advantage of 0.7 points for vortioxetine, a total of 400 patients (200 per treatment group) were needed to provide a power of $\geq 80\%$ for correctly concluding non-inferiority. To account for an expected withdrawal rate of 20%, a total of 500 patients (250 per treatment group) were planned for randomisation. The calculation was based on a standard formula for a two-group t-test for equal means.

6.3.6.1.4 Handling of missing data and withdrawals

For analyses based on last observation carried forward (LOCF) per visit, missing values for efficacy assessments were imputed using the last observed value immediately prior to the missing value. Data from the Withdrawal Visit were assigned to a nominal visit using visit windows. If two competing assessments had the same nominal visit, then the originally observed visit was kept for by-visit analyses, whereas the Withdrawal Visit, which by definition is always the later of the two, was used for the LOCF analyses. Efficacy and other safety data from visits >7 days after the last dose of IMP were listed but excluded from summaries and analyses.

6.3.6.2 Study TAK318^{30,182}

6.3.6.2.1 Analysis sets

The following analysis sets were defined:

Full analysis set (FAS): included all subjects who were randomised, received at least one dose of study drug, and had at least one valid post-baseline value for assessment of primary efficacy. In FAS efficacy summaries, subjects were analysed by the treatment to which they were randomised.

Per Protocol Set (PPS): included all FAS subjects who had no major protocol violations. If more than 5% of the total subjects in the FAS have major protocol violations, analyses based on the PPS was performed for the primary efficacy variable only.

Safety Set: included all subjects who were randomised and received at least 1 dose of double-blind study medication. In safety summaries, subjects were analysed according to the treatment they received. In the event that a subject receives more than 1 treatment, the actual treatment was defined as the one that is used most frequently. If the 2 most common treatments were used with equal frequency, then the randomised treatment was used as the actual treatment.

6.3.6.2.2 Hypotheses

There were no formal statements of statistical hypotheses in the statistical analysis plan¹⁸². The hypotheses were implicitly defined through the description of the comparisons to be made. The analysis of primary variable was specified in the statistical analysis plan as below:

“Change from Baseline in CSFQ-14 total score after 8 weeks of treatment will be the primary endpoint. Primary analysis will be based on a mixed model for repeated measurements (MMRM) analysis of covariance with treatment, centre, week, treatment-by-week interaction as fixed effects, Baseline CSFQ-14 total score-by-week as covariate, and a completely unstructured covariance matrix. Comparisons between Lu AA21004 and Escitalopram will be performed on Week 8 and all other assessment points. The primary analysis will be performed using observed case data only. The statistical tests will be 2-sided comparing Lu AA21004 to Escitalopram. Ninety-five percent confidence intervals (CIs) will be presented together with the estimated p-values.”

6.3.6.2.3 Power and sample size calculations

A minimum of 500 patients (250 patients per treatment group) were planned for randomisation. The sample size calculation was based on a non-inferiority comparison of the treatment groups in the change from baseline to Week 8 in MADRS total score using a two-sided 95% confidence interval against a margin of 2 points. Assuming a standard deviation of 9.5 points and a true advantage of 0.7 points for vortioxetine, a total of 400 patients (200 per treatment group) were needed to provide a power of $\geq 80\%$ for correctly concluding non-inferiority. To account for an expected withdrawal rate of 20%, a total of 500 patients (250 per treatment group) were planned for randomisation. The calculation was based on a standard formula for a two-group t-test for equal means.

6.3.6.2.4 Handling of missing data and withdrawals

For analyses based on last observation carried forward (LOCF) per visit, missing values for efficacy assessments were imputed using the last observed value immediately prior to the missing value. Data from the Withdrawal Visit were assigned to a nominal visit using visit windows. If two competing assessments had the same nominal visit, then the originally observed visit was kept for by-visit analyses, whereas the Withdrawal Visit, which by definition is always the later of the two, was used for the LOCF analyses. Efficacy and other safety data from visits >7 days after the last dose of IMP were listed but excluded from summaries and analyses.

6.3.7 Subgroup analyses

6.3.7.1 Study 14178A (REVIVE)²⁷

The analysis of the primary efficacy endpoint based on the FAS was repeated based on the PPS, as a pre-planned analysis. The sensitivity analysis of the primary endpoint included an ANCOVA based on the FAS using the last observation carried forward (LOCF), including site group, treatment, and baseline MADRS total score as fixed effects. The treatment differences expressed as a comparison of adjusted means were calculated together with *p*-values and 95% confidence intervals.

The analyses were repeated in subgroups, as follows:

- Sex
- Age (≤ 50 vs. > 50 years, < 65 vs. ≥ 65 years)
- Baseline severity (MADRS score < 30 vs. ≥ 30)
- Baseline anxiety (HAM-A score < 20 vs. ≥ 20)
- Class of previous antidepressant (SSRI or SNRI)

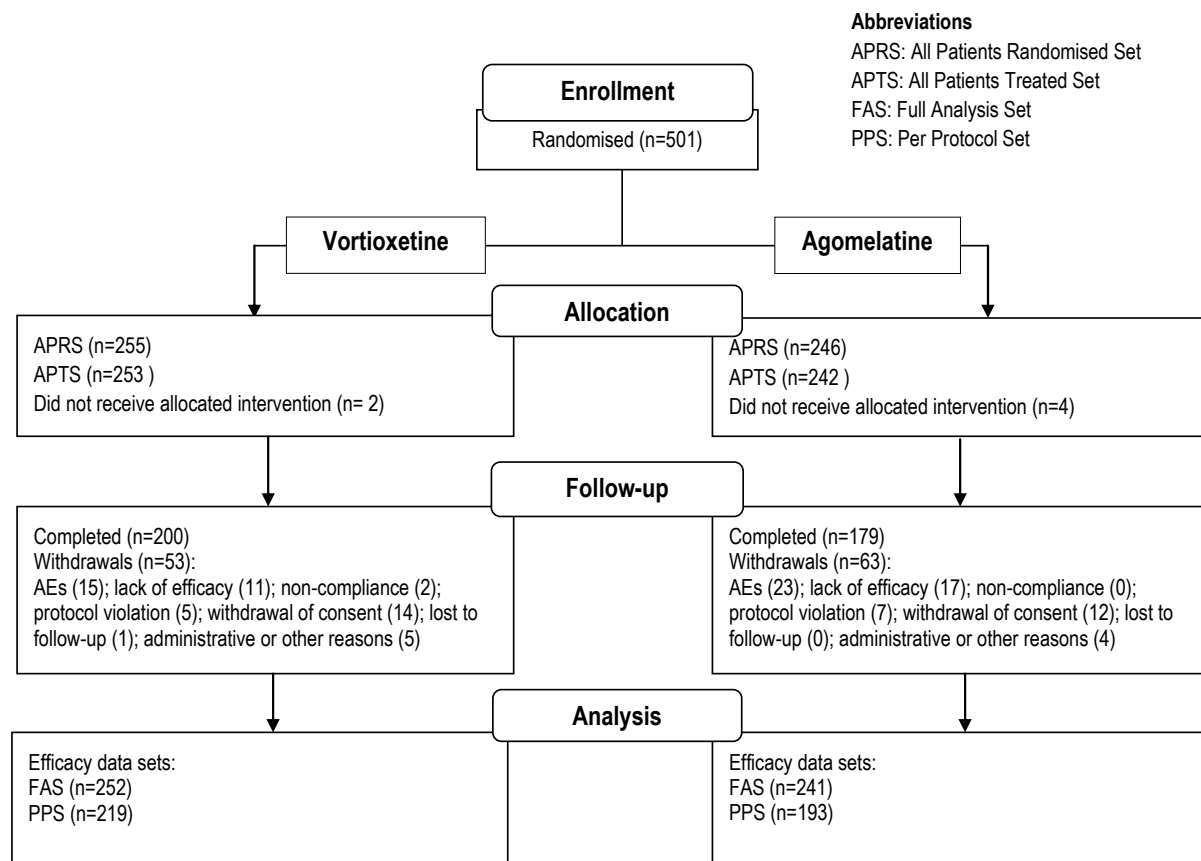
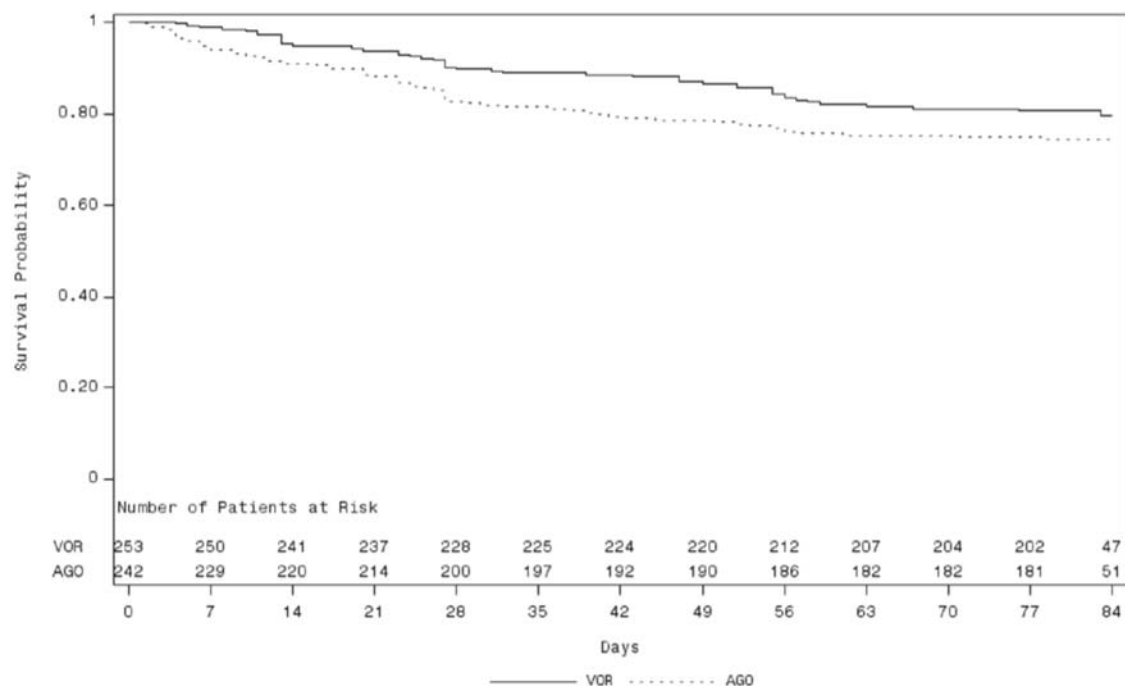
6.3.7.2 Study TAK318³⁰

Subgroup analyses were performed when each of the subgroups contained at least 20% of the total subjects in the study. For the primary efficacy variable, subgroup analyses by age, sex, Baseline CSFQ-14, and CGI-S remitter were performed. Treatment groups were compared within each subgroup.

6.3.8 Participant flow

6.3.8.1 Study 14178A (REVIVE)²⁷

A modified CONSORT flow diagram of the disposition of patients in Study 14178A (REVIVE) is provided in Figure B4. The number of patients screened for potential participation was not available. In the vortioxetine group, 21% of the patients withdrew from the study compared to 26% in the agomelatine group. Fewer patients in the vortioxetine group (5.9%) than in the agomelatine group (9.5%) had AEs contributing to withdrawal. Also, lack of efficacy was reported by fewer patients in the vortioxetine group (4.3%) compared to the agomelatine group (7.0%). To understand the pattern of withdrawals better, a Kaplan-Meier analysis of time to withdrawal was performed (see Figure B5), which indicated that patients on agomelatine tended to withdraw earlier than those on vortioxetine.

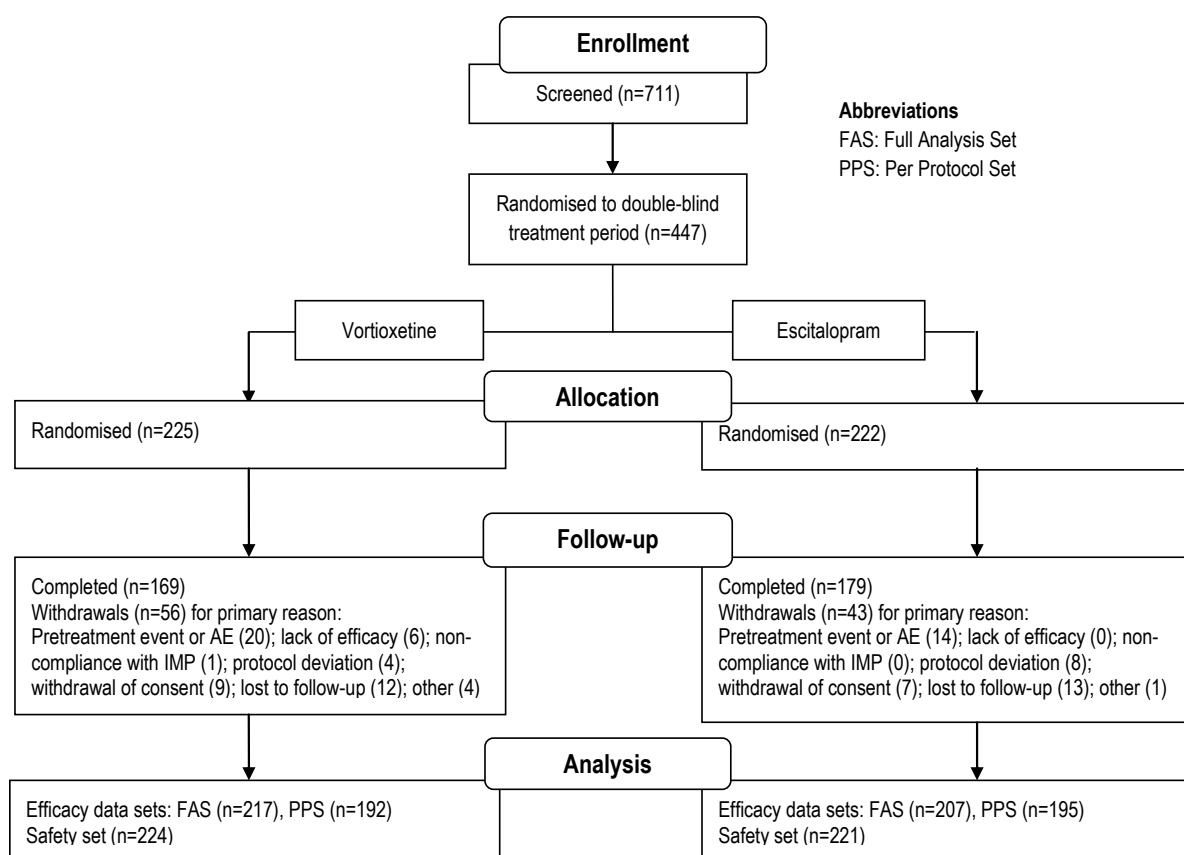
Figure B4. Study 14178A (REVIVE)²⁷. Modified CONSORT flow diagram of patient disposition**Figure B5. Study 14178A (REVIVE). Kaplan-Meier analysis of time to withdrawal (APTS)²⁷**Source: CSR²⁷ Figure 1.

6.3.8.2 Study TAK318³⁰

A modified CONSORT flow diagram of the disposition of patients in Study TAK318 is provided in Figure B6. In total, 711 patients were screened for entry into this study (Figure 10). Of these, 447 patients (62.9%) were randomised (1:1) at 66 sites in the US and Canada (225 patients in the vortioxetine group and 222 patients in the escitalopram group).

A total of 348 patients (77.9%) completed the study, and 99 patients (22.1%) prematurely discontinued the study: 56 patients (24.9%) in the vortioxetine group and 43 patients (19.4%) in the escitalopram group. The most common reasons for study discontinuation included: AEs (7.6%); lost to follow-up (5.6%) and withdrawal of consent (3.6%). All of the patients who discontinued the study due to lack of efficacy were in the vortioxetine group (2.7%), possibly as a result of the change in treatment from an SSRI to vortioxetine in this group.

Figure B6. Study TAK318³⁰. Modified CONSORT flow diagram of patient disposition



6.4 Critical appraisal of relevant RCTs

6.4.1.1 Study 14178A (REVIVE)

A critical appraisal of Study 14178A (REVIVE) is made in Table B11.

Table B11. Critical appraisal of Study 14178A (REVIVE)

Criteria	Methodology used ²⁷	Appraisal	Adequacy (Yes/No)
Was the method used to generate random allocations adequate?	At the Screening Visit, the patients were assigned a screening number. At the Baseline Visit, patients who fulfilled the selection criteria were assigned to treatment with either vortioxetine or agomelatine in a 1:1 ratio. Randomisation was executed using an IV/WRS according to a randomisation list that was computer generated by H. Lundbeck A/S. Randomisation numbers were prepared for a total of 2000 patients, with 1000 numbers assigned to each of the two treatment groups. Block randomisation (in blocks of 4) ensured that equal numbers of patients entered each treatment group.		Yes
Was the allocation adequately concealed?	The study was double-blinded. Two sets of sealed envelopes containing IMP details for each patient in the double-blind period were prepared. One set was kept by each of the following: Global Pharmacovigilance (GPV), H. Lundbeck A/S, and the investigator or pharmacist. The randomisation code was only to be broken in an emergency situation in order to give the patient optimal treatment. If possible, the investigator was to consult the clinical research associate before code break. After code break, the clinical research associate was to be notified immediately, and the patient withdrawn from the study.	During the study, the randomisation code was broken for one patient as the patient had a SAE <i>oedema peripheral</i> considered <i>probable related</i> to study treatment. At the time of the event, the patient received vortioxetine 20mg/day and had been treated for a total of 14 days. A potentially unintended unblinding was discovered for a patient who withdrew and returned the unused study drug. One capsule in the returned wallet card had been damaged so the capsule content was visible. The patient was excluded from the PPS.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Block randomisation (see above).	As Table B8 shows, the randomisation procedure served to ensure the patients were well-matched in prognostic factors.	Yes
Were the care providers, participants and assessors blind to treatment allocation? If not, what might be the likely impact on the risk of bias?	Blinding: Two sets of sealed envelopes containing IMP details for each patient in the double-blind period were prepared. One set was kept by each of the following: Global Pharmacovigilance, H. Lundbeck A/S, and the investigator or pharmacist. The randomisation code was only to be broken in an emergency situation in order to give the patient optimal treatment. If possible, the investigator was to consult the CRA before code break. After code break, the CRA was to be notified immediately, and the patient withdrawn from the study.	See allocation question. No substantive bias is likely to have occurred as a result of the removal of a single patient.	Yes

Criteria	Methodology used ²⁷	Appraisal	Adequacy (Yes/No)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No.	No.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no such evidence. This submission was prepared by an independent contractor who had access to the integrated Clinical Study Report.	No.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. The efficacy analyses were conducted on the FAS and the primary analysis was repeated on the PPS. The primary analyses employed an MMRM model, in which missing data are not explicitly imputed but use all available data to estimate unobserved data points. Kaplan-Meier curves of time to withdrawal were generated to gain better understanding of the pattern of missingness, and suggested time to dropout was partly explained by treatment assignment.	The use of MMRM in preference to LOCF is standard practice to minimise bias from missing observations. However, MMRM assumes that data are Missing At Random, which is not known. Therefore, it may not fully compensate for informative but unobserved missingness ¹⁸³ .	Yes

IVRS/WRS: Interactive Voice/Web Response System; IMP: Investigational medicinal product; CRA: Clinical Research Associate; PPS: Per protocol set; FAS: Full analysis set; MMRM: Mixed model for repeated measures; LOCF: Last observation carried forward.

6.4.1.2 Study TAK318

A critical appraisal of Study TAK318 is made in Table B12.

Table B12. Critical appraisal of Study TAK318

Criteria	Methodology used ³⁰	Appraisal	Adequacy (Yes/No/NA)
Was the method used to generate random allocations adequate?	The investigator or the investigator's designee contacted the IVRS at Screening to obtain the subject study number. At Baseline the investigator or his/her designee again contacted IVRS to randomize the subject. Subjects were assigned in a 1:1 ratio to the treatments of vortioxetine and escitalopram. Subject randomization across treatments was balanced at the site level. During the baseline visit contact, the investigator or designee provided the necessary subject identifying information, including the subject number (assigned at Screening). The medication numbers of the study medication to be dispensed were then provided by the IVRS. At subsequent drug-dispensing visits, the investigator or designee again contacted the IVRS to request additional study medication for a subject. The medication number of the study medication to be dispensed was provided by the IVRS. The assigned medication number was recorded in the subject's eCRF. Subjects who completed the 8-week Treatment Period entered a 1-week Double-Blind Taper-Down Period. The investigator or the investigator's designee again contacted the IVRS at Visit 7 to request additional study medication for a subject for the discontinuation period. During the discontinuation period, subjects received double-blind taper-down study medication: subjects treated with vortioxetine received placebo and subjects on escitalopram received 10mg QD of escitalopram. Subjects who withdraw early were offered taper-down study medication.		Yes
Was the allocation adequately concealed?	Per the protocol instructions, the study medication blind was not to be broken by the investigator unless information concerning the study medication was necessary for the medical treatment of the subject. If possible, the sponsor/designee was to be notified before the study medication blind was broken. If a medical emergency requiring unblinding occurred, the investigator (or designee) at the site was to contact the sponsor or designee to assess the necessity to break the study medication blind. For unblinding a subject, the study medication blind was to be obtained by accessing the IVRS. The sponsor/designee was to be notified immediately if the study medication blind was broken. The date, time, and reason the blind was broken would have been recorded in the source documents and the same information (except the time) recorded on the appropriate eCRF. If any site personnel were unblinded, study medication would have to be stopped immediately and the subject would have to be withdrawn from the study. The reason for withdrawal was to be recorded as "Protocol Deviation".	The study medication blind was not broken for any subject in this study.	Yes

Criteria	Methodology used ³⁰	Appraisal	Adequacy (Yes/No/NA)
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Ethnicity was different between the 2 groups, with 16.2% of subjects reporting to be Hispanic or Latino in the escitalopram group compared with 6.2% in the vortioxetine group	Imbalances were either too small or involved too few subjects to affect the primary endpoint	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The investigator and all site personnel were blinded. The protocol specified (abridged here) that the study medication blind shall not be broken by the investigator unless information concerning the study medication is necessary for the medical treatment of the subject. If any site personnel is unblinded, study medication must be stopped immediately and the subject must be withdrawn from the study. The reason for withdrawal should be recorded as "Protocol Deviation".		Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		Withdrawals were not strongly skewed to one group or the other, so are unlikely to have statistically affected the study outcomes.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?		No	Yes

Criteria	Methodology used ³⁰	Appraisal	Adequacy (Yes/No/NA)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. All analyses were conducted on the FAS. The SAP specified that if >5% of subjects had protocol violations, analysis would be repeated on the PPS. The primary endpoint was analysed using an MMRM model, using observed case data only. Sensitivity analyses were carried out using an ANCOVA model on observed case only data and imputation by LOCF.		Yes

IVRS: Interactive Voice Response System; eCRF: Electronic case record form; QD: once daily; FAS: full analysis set; PPS: Per protocol set; SAP: Statistical analysis plan; MMRM: Mixed model for repeated measures; ANCOVA: analysis of covariance; LOCF: Last observation carried forward.

6.5 Results

6.5.1 Presentation of data

Studies 14178A (REVIVE)²⁷ and 318³⁰ address different questions and utilise different outcome measures, so do not lend themselves to summary reporting together in a single table. Consequently, results are reported for each study in turn: Study 14178A in section 6.5.2 and Study TAK318 in section 6.5.3.

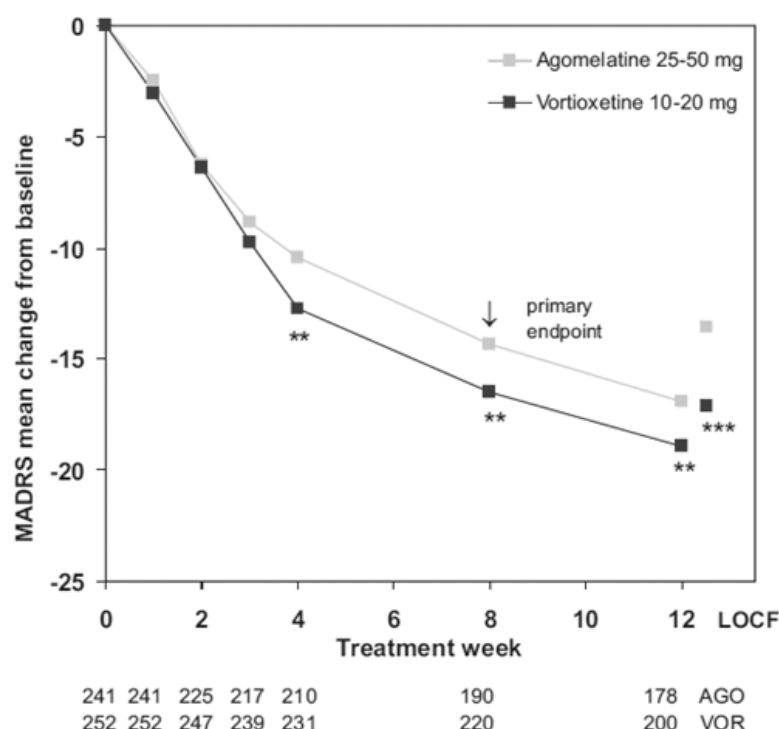
6.5.2 Study 14178A (REVIVE): results²⁷

6.5.2.1 Dosage

The majority of subjects received the 50mg dose of agomelatine (71.7%) and 20mg dose of vortioxetine (64.7%) from Weeks 4-12.

6.5.2.2 Efficacy

The MMRM estimates for the mean change from baseline in MADRS total score at Week 8 were -16.5 and -14.4 points in the vortioxetine group and the agomelatine group, respectively, giving a mean difference of -2.16 points in favour of vortioxetine (95% CI: -3.51 to -0.81; $p = 0.002$). Non-inferiority was established, as the upper bound of the 95% CI for the vortioxetine and agomelatine comparison was -0.81 MADRS points, below the non-inferiority margin of +2 MADRS points versus agomelatine. As the two-sided 95% CI for the difference between the means excluded zero and was in favour of vortioxetine, vortioxetine was superior to agomelatine. The results were confirmed by both sensitivity analyses (MMRM analysis of PPS; ANCOVA based on the FAS using LOCF). Data for all assessment points to Week 12 are shown in Figure B7.

Figure B7. Study 14178A (REVIVE). Estimated change from baseline in MADRS total scores from baseline to Week 12 (FAS, MMRM) and LOCF (FAS, ANCOVA) at Week 12²⁷.

Vortioxetine was consistently statistically significantly better than agomelatine based on analyses of the secondary efficacy endpoints (MADRS total score, HAM-A total score, CGI-S score, CGI-I score) and HRQoL and overall functioning scores [SDS total score, EQ-5D Summary Index, WLQ Global Productivity Index, and DFFS total score] at Weeks 8 and 12 (FAS, MMRM), except for WLQ at Week 12. The results of the secondary efficacy analyses are summarised in Table B13.

Table B13. Study 14178A (REVIVE). Primary and secondary efficacy outcomes: scale score differences²⁷

Efficacy variables	Vortioxetine: difference to agomelatine			
	Week 8		Week 12	
	MMRM	LOCF, ANCOVA	MMRM	LOCF, ANCOVA
Δ MADRS total score	-2.2**†	-3.1***	-2.0**	-3.5***
Δ HAM-A total score	-1.9***	-2.4***	-1.9***	-2.8***
Δ CGI-S score	-0.3**	-0.4***	-0.3**	-0.4***
Δ CGI-I score	-0.25**	-0.4***	-0.25**	-0.5***

Source: CSR²⁷ Panel 25. Δ = change from baseline. Mean values are presented. *p<0.05; **p<0.01; ***p<0.001 versus agomelatine. † Primary efficacy analysis. Vortioxetine: Baseline N=252, Week 8 N=220, Week 12 N=200. Agomelatine: Baseline N=241, Week 8 N=190, Week 12 N=178. MADRS: Montgomery-Åsberg Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; CGI-S: Clinical Global Impression - Severity Scale; CGI-I: Clinical Global Impression - Improvement Scale; MMRM: Mixed model for repeated measures; LOCF: Last observation carried forward; ANCOVA: analysis of covariance.

The proportion of MADRS and CGI-I responders was statistically significantly higher in the vortioxetine group than in the agomelatine group at Weeks 8 and 12. At Week 12, nearly three-quarters of the patients in the vortioxetine group were responders (FAS, LOCF, logistic

regression). As Table B14 shows, the proportion of MADRS and CGI-S remitters was statistically significantly higher in the vortioxetine group than in the agomelatine group at Weeks 8 and 12. At Week 12, more than half of the patients in the vortioxetine group were remitters (FAS, LOCF, logistic regression).

Table B14. Study 14178A (REVIVE). Proportion of responders and remitters (FAS, LOCF, LREG)²⁷

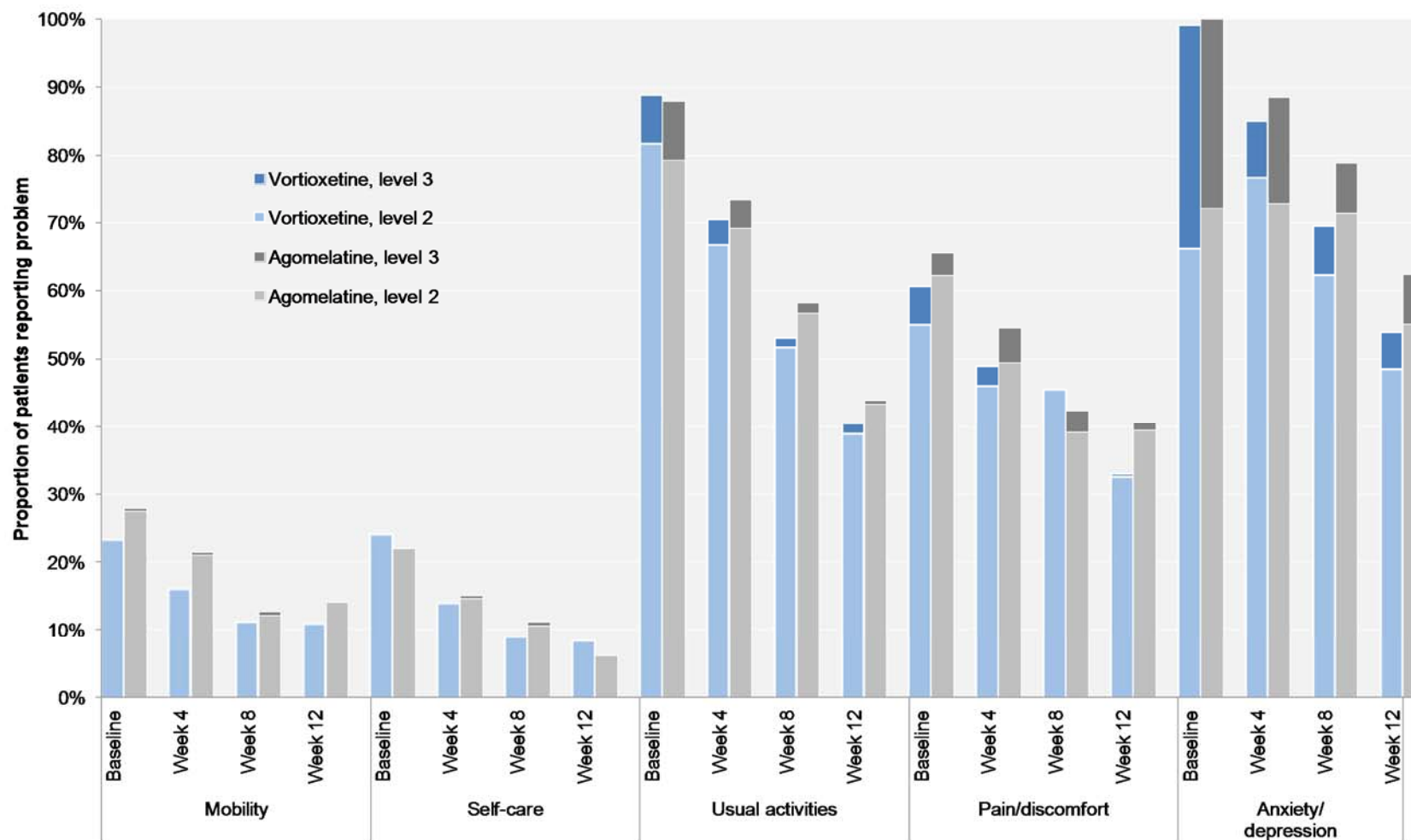
Endpoint	Week 8				Week 12			
	Vortioxetine		Agomelatine		Vortioxetine		Agomelatine	
	n	%	n	%	n	%	n	%
Response								
MADRS	155	62%**	114	47%	176	70%**	135	56%
CGI-I	186	74%***	140	58%	187	74%*	154	64%
Remission								
MADRS	102	41%**	71	30%	139	55%***	95	39%
CGI-I	104	41%*	78	32%	140	56%**	106	44%

Source: CSR²⁷ Panel 30. *p <0.05; **p <0.01; ***p <0.001 versus agomelatine. FAS: full analysis set; LOCF: Last observation carried forward; LREG: logistic regression; MADRS: Montgomery-Åsberg Depression Rating Scale; CGI-I: Clinical Global Impression - Improvement Scale.

6.5.2.3 EQ-5D and other PROs

The EQ-5D was administered at the baseline and Week 4, 8 and 12 assessments²⁷. In the original 3-level version of EQ-5D used in REVIVE, statements describing health in each domain at level 1 correspond to no problems on a domain, at level 2 to an intermediate degree of problems and at level 3 to a severe degree of problems¹⁷⁴. Figure B8 illustrates the comparative extent of problems (i.e. level 2 and 3 responses) reported by patients on each domain and the trends over the period of assessment, for each treatment group¹⁸⁴. As expected, the anxiety/depression domain gave rise to the greatest frequency of problems, with approximately 70% of patients reporting “I am moderately anxious or depressed” (level 2) and almost all of the remainder reporting “I am extremely anxious or depressed” (level 3) at baseline. However, almost 90% of patients reported problems with usual activities and over 60% with pain/discomfort at baseline, illustrating the burden of MDEs is not only psychological in nature. A minority of patients (less than 30%) reported problems with mobility or self-care. The graph illustrates that the level of problem reporting numerically declined smoothly over the course of 12 weeks of treatment on each domain (N.B. no statistical testing for differences was performed on these profile data). For anxiety/depression, 54% and 62% of patients in the vortioxetine and agomelatine groups, respectively, reported any problem at week 12. Across the five domains, the reduction in problem reporting for vortioxetine relative to agomelatine suggests the hypothesis that vortioxetine may be associated with greater gains in health utility.

Figure B8. Study 14178A (REVIVE). EQ-5D profile: proportions of patients reporting problems, by treatment and assessment point (FAS, OC)



Source: Derived from TLGs of supplementary analysis¹⁸⁴. EQ-5D: EuroQoL Questionnaire 5-Dimension.

The EQ-5D profile data were scored on a summary index, using the UK tariff (Dolan 1997)¹⁸⁵; summary statistics of index scores at each assessment point are shown in Table B15. The mean EQ-5D summary index increased in both treatment groups over the 12-week treatment period from 0.53 (vortioxetine) and 0.55 (agomelatine) at baseline to 0.81 (vortioxetine) and 0.78 (agomelatine) at Week 12 (FAS, OC).

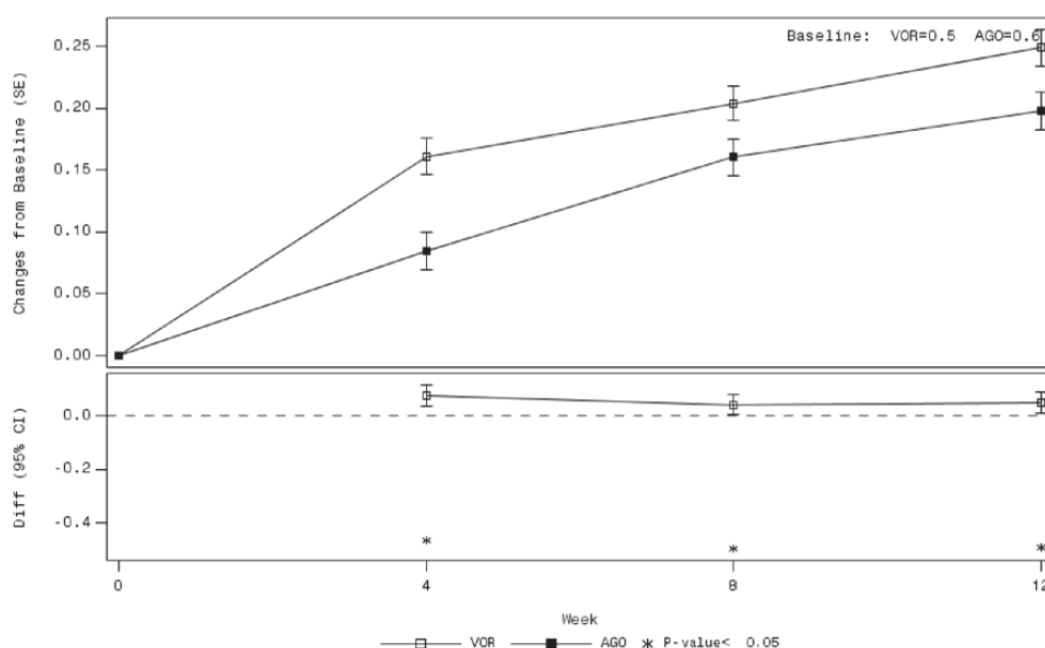
Table B15. Study 14178A (REVIVE). EQ-5D summary index scores (FAS, OC)²⁷

Assessment	Vortioxetine			Agomelatine		
	N	Mean	sd	N	Mean	sd
Baseline	252	0.53	0.28	241	0.55	0.27
Week 4	241	0.70	0.22	233	0.64	0.27
Week 8	220	0.76	0.19	189	0.73	0.23
Week 12	200	0.81	0.21	178	0.78	0.22

Source: CSR²⁷ Table 195. Sd: standard deviation; FAS: full analysis set. OC: observed cases. sd: standard deviation

When comparing changes in utility score from baseline between the two groups, greater improvements were seen in the vortioxetine group than in the agomelatine group from week 4 onwards, as shown in Figure B9. At week 4, the changes from baseline scores were 0.16 and 0.08 for the two groups, respectively, ($p < 0.001$); at week 8, 0.20 and 0.16 ($p = 0.03$) and at week 12, 0.25 and 0.20 ($p = 0.01$) (FAS, MMRM). Slightly greater differences were seen in the sensitivity analysis using ANCOVA (FAS, LOCF): see Table B16.

Figure B9. Study 14178A (REVIVE). Mean changes from baseline in EQ-5D summary index and mean treatment differences to agomelatine (FAS, MMRM)²⁷



Source: CSR²⁷, Panel 33. FAS: full analysis set; MMRM: mixed model for repeated measures.

Quality-adjusted survival over 12 weeks was calculated for each study group using the areas under the utility curves from each assessment point (see Figure B9). The area between these curves thus represents the mean quality-adjusted survival difference between the two treatments over 12 weeks of treatment.

Table B16 summarises differences between vortioxetine and agomelatine on all socioeconomic PRO instruments administered in REVIVE. Differences in favour of vortioxetine were seen for all outcomes at week 8 and all except the SDS family life domain and WLQ global score at week 12 using MMRM analysis.

Table B16. Study 14178A (REVIVE). Secondary efficacy outcomes: socioeconomic PROs (FAS)²⁷

Efficacy variables	Vortioxetine: change from baseline			
	Week 8		Week 12	
	MMRM	LOCF, ANCOVA	MMRM	LOCF, ANCOVA
Δ SDS total score	-2.22**	-2.71***	-1.75*	-2.75***
Δ SDS work	-0.70**	-0.88***	-0.55*	-0.86**
Δ SDS social life	-0.66**	-0.77***	-0.55*	-0.76**
Δ SDS family life	-0.58**	-0.76***	-0.43	-0.70**
Δ EQ-5D summary	0.04*	0.05**	0.05*	0.07**
Δ WLQ global	-0.01*	-0.01*	-0.01	-0.01
Δ DFFS total score	-2.92**	-2.91**	-2.54*	-3.04**

Source: CSR²⁷ Panel 31. Δ = change from baseline. Mean values are presented. *p<0.05; **p<0.01; ***p<0.001 versus agomelatine. MMRM: Mixed model for repeated measures; LOCF: Last observation carried forward; ANCOVA: analysis of covariance; SDS: Sheehan Disability Scale; EQ-5D: EuroQoL Questionnaire 5-Dimension; WLQ: Work Limitations Questionnaire; DFFS: Depression and Family Functioning Scale..

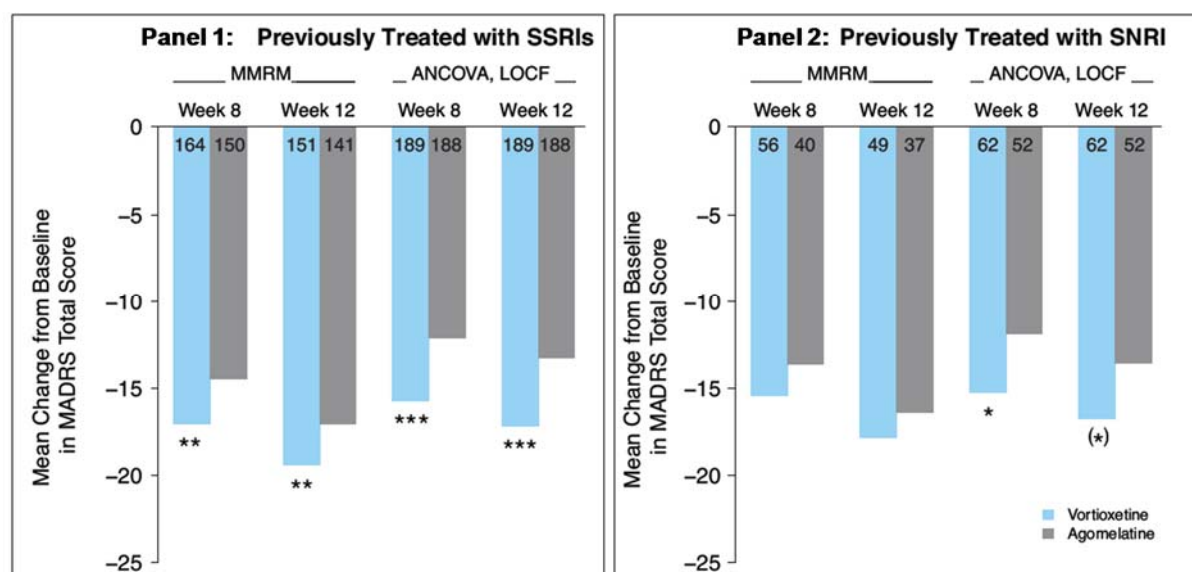
6.5.2.4 Subgroup analyses

In the subgroup analyses, there was a trend towards improvement for vortioxetine vs. agomelatine across all subgroups and many reached statistical significance despite the study being powered for equivalence on the primary endpoint.

One of the subgroup analyses was by previous class of treatment (SSRI or SNRI). For both vortioxetine and agomelatine, the mean MADRS total score decreased (improved) throughout the 12-week treatment period both for patients previously treated with either class of antidepressant¹³⁶.

For patients previously treated with an SSRI, the differences between vortioxetine (n=164) and agomelatine (n=150) at Week 8 on MADRS total score (FAS, MMRM) was -2.6 (95% CI: -4.1 to -1.0; p=0.0013). The robustness of the results was shown by sensitivity analyses using ANCOVA (FAS, LOCF), where the mean difference to agomelatine at Week 8 on MADRS total score was -3.6 (95% CI: -5.4 to -1.9; p<0.0001). Similar results were seen at Week 12 (Figure B10, Panel 1). For patients previously treated with an SNRI, the differences between vortioxetine (n=56) and agomelatine (n=40) at Week 8 on MADRS total score (FAS, MMRM) was -1.8 (95% CI: -4.8 to 1.2; p=0.2254) (Figure 2). For the sensitivity analyses using ANCOVA (FAS, LOCF) the mean difference to agomelatine at Week 8 on MADRS total score was -3.4 (95% CI: -6.6 to -0.1; p=0.0420). Similar results were seen at Week 12 (Figure B10, Panel 2).

It can be concluded that the efficacy advantage of vortioxetine over agomelatine is independent of previous treatments class (SSRI or SNRI).

Figure B10. Study 14178A (REVIVE). Subgroup analysis of primary efficacy endpoint by previous class of treatment^{135,137}

Source: Poster (Papakostas 2014)^{135,137}. Derived from subgroup analysis reported in CSR²⁷, various tables. FAS: full-analysis set, LOCF: last observation carried forward, MMRM: mixed model, repeated measures. Patient numbers at each visit are shown below the x-axis for each treatment group. (*) p=0.06; *p<0.05; **p<0.01; ***p<0.001 versus agomelatine.

6.5.2.5 Safety and tolerability²⁷

As shown in Table B17, fewer patients withdrew due to AEs in the vortioxetine group (5.9%) than in the agomelatine group (9.5%) over the 12-week treatment period. Approximately half of the patients in each treatment group had one or more treatment-emergent adverse events (TEAEs) during this period. The only TEAEs leading to withdrawal of 2 or more patients in either treatment group were vomiting (1.2%) and nausea (0.8%) in the vortioxetine group and dizziness (2.1%), anxiety (0.8%) and headache (0.8%) in the agomelatine group.

TEAEs occurring with an incidence of $\geq 5\%$ during the 12-week treatment period for vortioxetine and agomelatine, respectively, were nausea (16.2% and 9.1%), headache (10.3% and 13.2%), dizziness (7.1% and 11.6%) and somnolence (4.0% and 7.9%). Most of these values were comparable to those in the overall clinical data package – both in the total population and in the subgroup that had received prior pharmacotherapy. Fewer patients in the vortioxetine group compared to the agomelatine group experienced SAEs (1.2% vs. 1.7%, respectively) over the 12-week treatment period. No clinically relevant changes over time or differences between treatment groups were seen in clinical laboratory test results, vital signs, weight, or ECG parameters.

Table B17. Study 14178A (REVIVE): summary of adverse events reported over 12-week treatment period²⁷

Event	Vortioxetine (10mg-20mg)	Agomelatine (25mg-50mg)
	n=253	n=242
Patient-years of exposure	50	45
Adverse event		
Patients with TEAEs, n (%)	137 (54.2%)	127 (52.5%)
Patients with SAEs, n (%)	3 (1.2%)	4 (1.7%)
Patients with AEs leading to withdrawal, n (%)	14 (5.5%)	20 (8.3%)
Patients with TEAEs with an incidence of ≥5% in any treatment group (APTS):		
Nausea (%)	41 (16.2%)	22 (9.1%)
Headache, n (%)	26 (10.3%)	32 (13.2%)
Dizziness, n (%)	18 (7.1%)	28 (11.6%)
Somnolence, n (%)	10 (4.0%)	19 (7.9%)

TEAE: Treatment-emergent adverse event; SAE: serious adverse event; AE: adverse event.

TEAEs of special interest include nausea, sexual dysfunction and sleep disturbances, as these are all commonly observed following antidepressant treatment. In addition, the TEAEs with an onset during Weeks 1 and 2 are described.

The tolerability profile of vortioxetine seen in REVIVE reflected that seen in the short-term adverse events pool of 12 studies from the regulatory package (see Appendix 15).

Nausea

The overall incidence of nausea was higher in the vortioxetine group compared to the agomelatine group (16.2% and 9.1%, respectively). However, all events were either mild or moderate for both groups. The majority of events had an onset within the first week of treatment, and most of the events were transient. Furthermore, the incidence of nausea in this study, at 16% in the vortioxetine arm, was lower compared to the incidence in the MDD population in the overall clinical package (above 20% on 5mg and 10mg, and around 30% on doses above 10mg).

Sexual dysfunction

The incidence of TEAEs related to sexual dysfunction was low. One patient (0.4%) in the vortioxetine group reported anorgasmia and decreased libido, and no patients in the agomelatine group reported problems. The events were considered mild in intensity and did not lead to withdrawal.

Sleep-related TEAEs

The overall incidence of sleep-related TEAEs was similar in the vortioxetine group compared to the agomelatine group (11.1% and 10.7%, respectively). In total, fewer patients in the vortioxetine group than in the agomelatine group experienced somnolence (10 patients (4.0%) vs. 19 patients (7.9%), respectively). Four patients in the vortioxetine group and one patient in the agomelatine group experienced severe insomnia. TEAEs related to sleep disturbance are summarised in Table B18.

Table B18. Study 14178A (REVIVE): sleep-related adverse events²⁷

Event	Vortioxetine (10mg-20mg)	Agomelatine (25mg-50mg)
	n=253	n=242
Patient-years of exposure	50	45
Patients with sleep-related TEAEs	28 (11.1%)	26 (10.7%)
Insomnia	12 (4.7%)	3 (1.2%)
Somnolence	10 (4.0%)	19 (7.9%)
Initial Insomnia	3 (1.2%)	1 (0.4%)
Middle Insomnia	2 (0.8%)	1 (0.4%)
Sleep Disorder	1 (0.4%)	1 (0.4%)
Terminal Insomnia	0 (0.0%)	1 (0.4%)

TEAE: Treatment-emergent adverse event.

In conclusion, in Study 14178A (REVIVE) vortioxetine was reported to be as least as well tolerated as agomelatine, an antidepressant that is known to be well tolerated. Fewer patients withdrew due to AEs and there was a lower incidence of serious adverse events (SAEs) in the vortioxetine group than in the agomelatine group. Furthermore, fewer patients in the vortioxetine group experienced somnolence compared to the agomelatine group.

6.5.2.6 Conclusions

In MDD patients with an inadequate response to SSRI/SNRI treatment, switching to vortioxetine resulted in a significant and clinically relevant improvement versus agomelatine on the primary endpoint at Week 8 (significance from Week 4). In this challenging patient group, vortioxetine showed a significant benefit versus agomelatine on the primary and the majority of secondary efficacy endpoints²⁷. The remission rate after 8 and 12 weeks was significantly higher for patients receiving vortioxetine than for those receiving agomelatine.

Vortioxetine shows consistent benefits in reduction of total MADRS score over agomelatine regardless of previous treatment. The significant advantage of vortioxetine compared to agomelatine seen in the overall functioning and HRQoL assessments confirms the clinical relevance of the findings. The differences in EQ-5D index values in favour of vortioxetine from week 4 through to the end of the study were underpinned by the reporting of problems on EQ-5D domains, with improvements mainly in anxiety/depression but also pain/discomfort and usual activities (Figure B8). Differences seen in scores on the Sheehan Disability Scale, the Depression Family Functioning scale represent important extrapersonal outcomes favouring vortioxetine that may not be captured by the EQ-5D. Vortioxetine and agomelatine were well tolerated with few treatment discontinuations.

6.5.3 Study TAK318³⁰

6.5.3.1 Dosage

This was a flexible-dose study in which the dose of vortioxetine or escitalopram after the first two weeks of the study was based on investigator judgement. The majority of subjects received the 20mg dose of escitalopram (71.9%) or vortioxetine (65.6%) from Weeks 2-8.

6.5.3.2 Study TAK318: primary endpoint

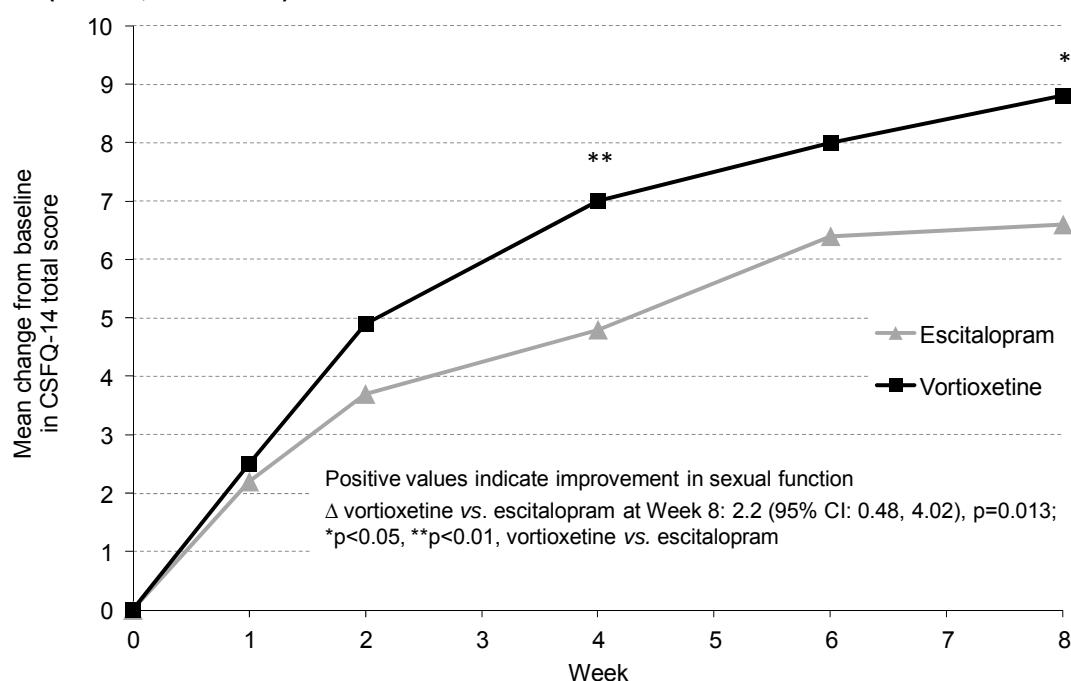
The primary endpoint was change from Baseline in the CSFQ-14 total score after 8 weeks of treatment (FAS, MMRM). Sexual functioning improved from Baseline in both groups, but to a greater extent in the vortioxetine group, with a mean difference at 8 weeks of 2.2 points between groups ($p=0.013$) (see Table B19 and Figure B11). Similar results were obtained across different analyses (MMRM, LOCF, OC, PMM) and using the Per Protocol Set.

Table B19. Study TAK318³⁰. Analysis of primary endpoint: change from Baseline in the CSFQ-14 total score after 8 weeks of treatment (FAS, MMRM)

	Vortioxetine 10-20mg	Escitalopram (10-20mg)
Baseline		
N	217	207
LS mean $\pm$ se [†]	36.1 $\pm$ 0.39	36.0 $\pm$ 0.40
P value, vortioxetine vs. escitalopram [†]	0.820	
Change from Baseline at Week 8		
N	165	173
Change from Baseline LS mean $\pm$ se	8.8 $\pm$ 0.64	6.6 $\pm$ 0.64
P value, vortioxetine vs. escitalopram [†]	0.013	
LS mean differences $\pm$ se from escitalopram [†]	2.2 $\pm$ 0.90	
95% CI for differences	0.48-4.02	

CI: confidence interval; LS: least squares; se: standard error.

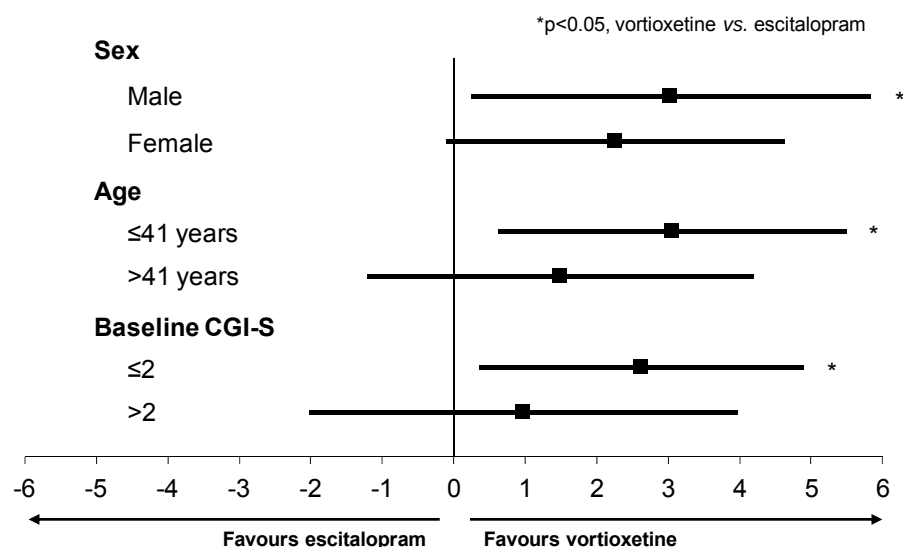
Figure B11. Study TAK318³⁰. Change from baseline in CSFQ-14 total score by visit (MMRM, LS means)



In the analysis of change from Baseline in CSFQ-14 at Week 8 by dichotomous subgroups defined by age, sex and baseline CGI-S score (see Figure B12), vortioxetine was superior to escitalopram in subjects who were aged ≤ 41 years ($p=0.014$), male ($p=0.034$) or a CGI-S

remitter at Baseline ($p=0.024$). In the counterpart subgroups, vortioxetine was numerically but not statistically superior to escitalopram.

Figure B12. Study TAK318³⁰. Comparative effect of vortioxetine and escitalopram treatment in patient subgroups on CSFQ-14 total score at Week 8 (MMRM, FAS, LS means)

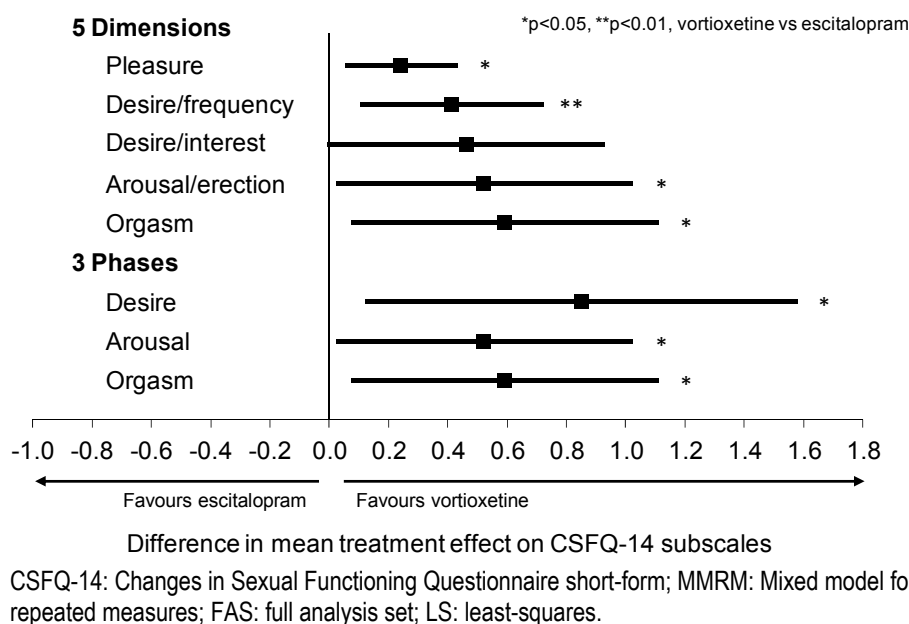


6.5.3.3 Study TAK318: secondary endpoints³⁰

The mean change from Baseline in the CSFQ-14 total score by visit was superior in the vortioxetine group vs the escitalopram group at Week 4 ($p=0.004$) and Week 8 ($p=0.013$) and close to the threshold for significance at Week 6 ($p=0.057$) (Figure B11).

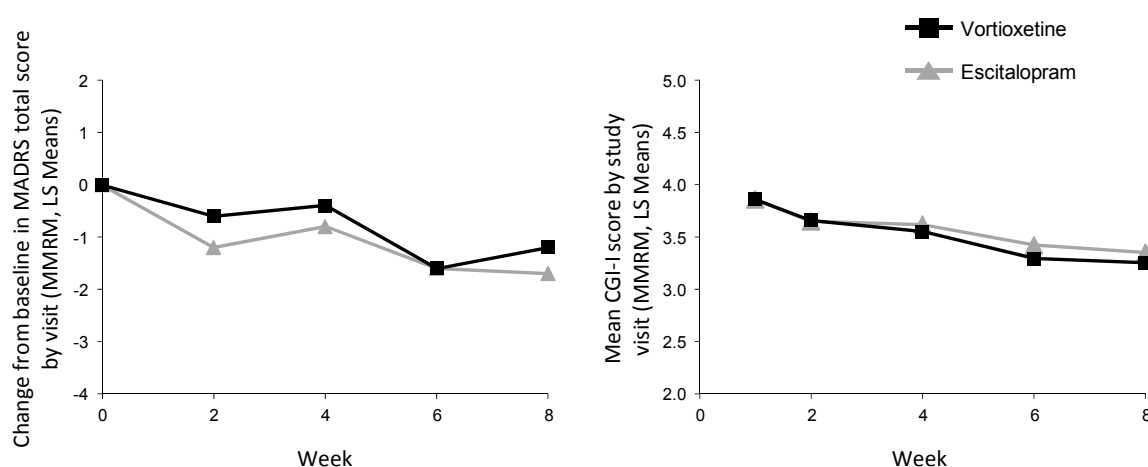
Another secondary endpoint was the number (percentage) of subjects with a shift in the CSFQ-14 total score from abnormal at Baseline to normal by visit. While the percentage of subjects who shifted from abnormal at Baseline to normal was numerically greater in the vortioxetine group at every visit, the difference between the treatment groups did not reach the threshold for statistical significance. When the analysis was conducted using observed cases, the percentage of patients who shifted from abnormal at baseline to normal was significantly greater in the vortioxetine group at week 6 ($p=0.013$) and week 8 ($p=0.018$) vs escitalopram.

The change from Baseline in CSFQ-14 subscales: 5-dimensions (pleasure, desire/frequency, desire/interest, arousal/erection, and orgasm/ejaculation) and 3-phases of sexual functioning (desire, arousal, and orgasm/completion) was assessed. The LS mean differences at Week 8 demonstrated statistically significant improvement for the vortioxetine group over the escitalopram group for the 5-dimension subscale measures of pleasure ($p=0.015$), desire/frequency ($p=0.010$), arousal/erection ($p=0.042$), and orgasm ($p=0.026$) (see Figure B13). The LS mean difference at Week 8 for desire/interest was close to the threshold for statistical significance ($p=0.058$). For the 3 phases of sexual functioning, the LS mean differences at Week 8 demonstrated statistically significant improvements for the vortioxetine group over the escitalopram group for desire ($p=0.022$), arousal ($p=0.042$), and orgasm ($p=0.026$).

Figure B13. Study TAK318³⁰. Difference between vortioxetine and escitalopram on CSFQ-14 subscales at Week 8 (MMRM, FAS, LS Means)

The percentage of responders was assessed according to the CSFQ-14 (defined as CSFQ-14 total score increase from Baseline ≥ 3) at each visit. The percentage of responders increased at each study visit in the vortioxetine group, but was not significantly different from escitalopram at any of the visits.

With respect to effectiveness of treatment on depression symptoms over the randomised phase, the MADRS total score, CGI-S, CGI-I, and POMS total score were maintained or improved slightly over the course of treatment, with similar responses observed between the escitalopram and vortioxetine treatment groups at Week 8 (see Figure B14).

Figure B14. Study TAK318. Changes in clinical measures of depressive symptoms over 8 weeks of treatment with vortioxetine and escitalopram (FAS, MMRM)³⁰

CSFQ-14: Changes in Sexual Functioning Questionnaire short-form; MMRM: Mixed model for repeated measures; FAS: full analysis set; LS: least-squares; MADRS: Montgomery-Åsberg Depression Rating Scale; CGI-I: Clinical Global Impression - Improvement Scale.

6.5.3.4 Study TAK318: adverse events³⁰

An overview of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) is presented in Table B20, based on the Safety Set. Consistent with the primary endpoint of this study, TEAEs of sexual dysfunction were spontaneously reported by 9 subjects (4.1%), all in the escitalopram group.

Table B20. Study TAK318. Treatment-emergent adverse events (Safety Set)³⁰

	Vortioxetine (N=224)		Escitalopram (N=221)		Total (N=445)	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Any TEAEs	378	146 (65.2%)	325	137 (62.0%)	703	283 (63.6%)
Related	257	120 (53.6%)	209	104 (47.1%)	466	224 (50.3%)
Not related	121	26 (11.6%)	116	33 (14.9%)	237	59 (13.3%)
Mild	212	52 (24.1%)	184	64 (29.0%)	396	118 (26.5%)
Moderate	157	86 (38.4%)	133	66 (29.9%)	290	152 (34.2%)
Severe	9	6 (2.7%)	8	7 (3.2%)	17	13 (2.9%)
Leading to discontinuation	24	21 (9.4%)	14	14 (6.3%)	38	35 (7.9%)
SAEs	5	3 (1.3%)	1	1 (0.5%)	6	4 (0.9)
Related	1	1 (0.4%)	1	1 (0.5%)	2	2 (0.4%)
Not related	4	2 (0.9%)	0	0	4	2 (0.4%)
Leading to discontinuation	1	1 (0.4%)	0	0	1	1 (0.2%)
Deaths	0	0	0	0	0	0

TEAE: Treatment-emergent adverse event; SAE: serious adverse event.

6.5.3.5 Conclusions³⁰

For the primary endpoint of change from Baseline in CSFQ-14 total scores at Week 8, vortioxetine was statistically superior to escitalopram. With respect to secondary endpoints, change from Baseline in CFSQ-14 total score by visit, vortioxetine was superior to escitalopram at Weeks 4 and 8 and close to the threshold for significance at Week 6. The percentage of subjects with a shift in the CSFQ-14 from abnormal at Baseline, to normal, was numerically greater in the vortioxetine group at every visit. Vortioxetine was superior to escitalopram for 4 of the 5 dimensions of the CSFQ-14 and for all 3 phases of sexual functioning. TEAEs of sexual dysfunction were only reported by subjects in the escitalopram group, consistent with the results on the CSFQ-14. Taken together, the CFSQ-14 results show that vortioxetine is superior to escitalopram in improving sexual functioning in subjects with SSRI-induced sexual dysfunction.

Both vortioxetine and escitalopram maintained and slightly improved the depressive symptoms seen with the prior SSRI treatment as assessed by MADRS, CGI-S, and CGI-I scores. Vortioxetine was generally well-tolerated in this study.

6.6 Meta-analysis

There were two trials of vortioxetine in switch populations, and these studies were dissimilar in design and methodology. Study 14178A (REVIVE) was an efficacy study in patients switching due to lack of efficacy, while Study 318 was a tolerability study in patients who were well-treated but experiencing TESD. Study 14178A (REVIVE) compared vortioxetine

with agomelatine and Study 318 compared vortioxetine with escitalopram. Hence, no meta-analysis of these studies was possible.

6.7 Indirect and mixed treatment comparisons

6.7.1 Strategies to retrieve relevant clinical data on comparators

As shown in section 6.1, a head-to-head study, REVIVE^{26,27}, has been undertaken comparing vortioxetine to agomelatine in a switch population. As further antidepressant comparators are also relevant to the decision problem, a systematic review was undertaken to assess the feasibility of conducting indirect/mixed treatment comparisons in the switch population.

The US Agency for Healthcare Research and Quality (AHRQ) had previously commissioned a systematic review which was undertaken by McMaster University to evaluate treatment strategies in patients who failed to respond to SSRIs as initial treatment.¹⁸⁶ The aim of the Lundbeck review was to evaluate different treatment strategies in patients who had experienced an inadequate response to either an initial SSRI or an SNRI, in line with the population included within REVIVE. As the AHRQ search was considered to be of high quality and well reported, the AHRQ search strategy was adapted for the Lundbeck review to include SNRIs as a previous treatment option and to restrict the switch therapy to monotherapies. The systematic review was conducted and reported in-line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

6.7.2 Study identification, selection and methodology

6.7.2.1 Databases and registries searched

The following key biomedical electronic literature databases were searched from the year 1980 to 27 March 2014 (Table B21). The search strategies used for retrieving data from the published literature are provided in Section 10.4, Appendix 4.

Table B21. Databases examined for the literature search

Data source	Platform
Embase®	Embase.com; http://www.embase.com/
MEDLINE®	
MEDLINE® In-process	PubMed; http://www.ncbi.nlm.nih.gov/sites/entrez
MEDLINE®	
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane library; http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html
Cochrane Database of Systematic Reviews (CDSR)	
PsycINFO®	http://www.apa.org/pubs/databases/psycinfo/index.aspx

*PsycINFO® was searched on 29 July 2014; EMBASE: *Excerpta Medica* Database; MEDLINE: Medical Literature Analysis and Retrieval System Online

The key biomedical literature databases (MEDLINE® and Embase®) plus databases focusing on randomised studies (CENTRAL and CDSR) were searched for the review. MEDLINE® In-Process was also searched to ensure that non-indexed citations were retrieved. Studies listed in MEDLINE were searched via two platforms (embase.com and PubMed) and duplicate studies were removed prior to screening. Searches were also undertaken in the PsycINFO® database.

In addition to the electronic literature databases, the following clinical trial registries were searched:

- ClinicalTrials.gov
- Current Controlled Clinical Trials
- World Health Organisation (WHO) Clinical Trials

Finally, bibliographic screening of relevant systematic reviews and meta-analyses was conducted to identify any other relevant studies and validate the retrieved evidence.

6.7.2.2 Study identification

To be included in this review, trials had to meet the following pre-defined eligibility criteria. The rationale for these inclusion criteria is provided in Table B22. The current review aimed to provide a comprehensive overview of studies assessing different antidepressants as monotherapies (consistent with the treatments relevant to the decision problem). Given the small number of studies in switch populations found in previous reviews, it was not expected that a large literature would be found in this search. Therefore, the initial search included non-RCTs to supplement the limited evidence expected from RCTs, and it applied no restriction on the definition of 'inadequate response'.

Table B22. Eligibility criteria for studies to be included in the systematic review

Criteria	Inclusion criteria	Rationale
Study designs	Randomised controlled trials (RCTs). Non-randomised controlled trials.	RCTs are the gold standard of clinical evidence, minimising the risk of confounding factors and allowing the comparison of the relative efficacy of the interventions Non-RCTs will supplement evidence provided by RCTs.
Patient population	Sex: Male or female. Age: ≥ 18 years. Race: Any. Disease: MDD, dysthymia, or subsyndromal depression. Line of therapy: Patients who have demonstrated inadequate response to an adequate duration of treatment of the current MDE with a single prior: SSRI (fluoxetine, citalopram, fluvoxamine, sertraline, escitalopram, and paroxetine) or SNRIs (duloxetine, venlafaxine, desvenlafaxine) 80% or more of patients had to have received an SSRI or SNRI as their previous treatment.	The average age of the onset of major depression is between 20 years and 40 years. MDD can occur both in males and females Clinical trials and other studies usually enrol participants of all races. Focusing the inclusion on a particular race(s) would pose problems in conducting reviews and would limit the findings of the review to a particular race only. Moreover, the objective of the review does not restrict it to any particular race.
Interventions	Fluoxetine Citalopram Fluvoxamine Sertraline Paroxetine Escitalopram Duloxetine Hydrochloride Venlafaxine Desvenlafaxine Milnacipran Phenelzine Tranylcypromine Emsam Moclobemide Doxepin Clomipramine Amitriptyline Desipramine Trimipramine Imipramine Protriptyline Maprotiline Agomelatine Mianserin Reboxetine Trazodone Mirtazapine Nefazodone Bupropion Vortioxetine Vilazodone Cognitive behavioural therapy Interpersonal therapy, and other psychotherapies Light therapy Exercise Complementary and alternative medicine therapies including: Whole system medicines Mind body medicine (manipulative and body based practices), e.g. energy medicine biologically based practices	Interventions used in clinical practice amongst patients with inadequate response to prior SSRI/SNRI therapy The review included intervention to comprehensively cover evidence pertaining monotherapy option including: (i) optimisation strategy (increasing the dose or extending the duration of the SSRI), (ii) switching to another SSRI, (iii) switching to another class of antidepressants, or (iv) switching to a non-pharmacological intervention.
Comparators	Placebo. Any of the included interventions administered as monotherapy. Any non-pharmacological therapy Changing the dose or duration of the same SSRI/SNRI.	Selected to enable both direct and indirect comparisons between the interventions of interest.
Language	English.	The restriction would not limit results as substantial data are available in English.
Publication timeframe	1980 to present.	The search was limited to publications from 1980 onwards, as SSRIs/SNRIs were not in use before this year.

MDD: major depressive disorder; RCT: Randomised Controlled Trials; SSRI: Selective-Serotonin Reuptake Inhibitors; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors; The key differences in the current review and the AHRQ review were: (i) The current review focused on evidence comparing monotherapies while the AHRQ review included studies evaluating both monotherapies and combined therapies; (ii) The current review included patients with inadequate response to prior SSRI or SNRI therapy while the AHRQ review included patients not responding to prior SSRI therapy only.

For the purposes of screening studies for potential inclusion into an evidence network and ITC, a set of further eligibility criteria was applied to the results of the search, limiting the studies to randomised, blinded, comparative trials that would be sufficiently comparable to REVIVE. These additional criteria and the rationale for them are shown in Table B23.

Table B23. Study design criteria for eligibility into the network for the indirect treatment comparison

	Criteria	Rationale
Inclusion	Compares switch vs. switch regimens of at least 2 different antidepressant monotherapies Adequate randomisation and blinding required; but subgroup analyses may be permitted if there is no evidence of systematic bias Reporting of outcomes at clinically relevant time points (between 6-14 weeks).	The purpose of the SLR is to allow a comparison of vortioxetine to other antidepressant monotherapies, in line with the decision problem. Due to the high placebo-response rates in antidepressant trials ¹⁰³ , it is important that randomisation is undertaken and allocation of treatment is concealed as a patient's perception of the efficacy of the treatment can influence their response ¹⁰⁶ . Reporting of outcomes outside of the relevant time-window may lead to inaccurate estimations of relative treatment effects.
Exclusion	Compares treatment regimens other than switch vs. switch of at least 2 different antidepressant monotherapies (e.g. dose escalation or adjunct therapy) Inadequately blinded study/open-label.	Dose escalation and titration (within licence) of antidepressants is normal clinical practice. To compare 2 doses of one antidepressant is therefore uninformative in determining the comparative efficacy of vortioxetine as would be seen in real-world patients. Adjunct therapy and combination therapy was excluded as they are reserved for difficult-to-treat patients referred for specialist care. Inadequate blinding and allocation concealment can increase the risk of reporting bias which is of particular relevance in MDD.

MDD: major depressive disorder; SLR: systematic literature review..

6.7.2.3 Data extraction

Bibliographic details and abstracts of all citations detected through a literature search were downloaded into a proprietary structured query language (SQL) internet database designed for systematic reviews.

First-pass of citations

Citations were first screened based on the abstract supplied with each citation. Each citation was screened by two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer. Citations that did not match the eligibility criteria were excluded at this 'first-pass'; however, where the criteria were unclear, citations were included. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded at the first-pass stage. Full-text copies of all references that could potentially meet the eligibility criteria were obtained.

Second-pass of citations

The eligibility criteria were applied to the full-text citations. Each full-text was screened by two independent reviewers, and any discrepancies between reviewers were reconciled by a third, independent reviewer. Data presented in the studies included after this stage were extracted into data extraction grids.

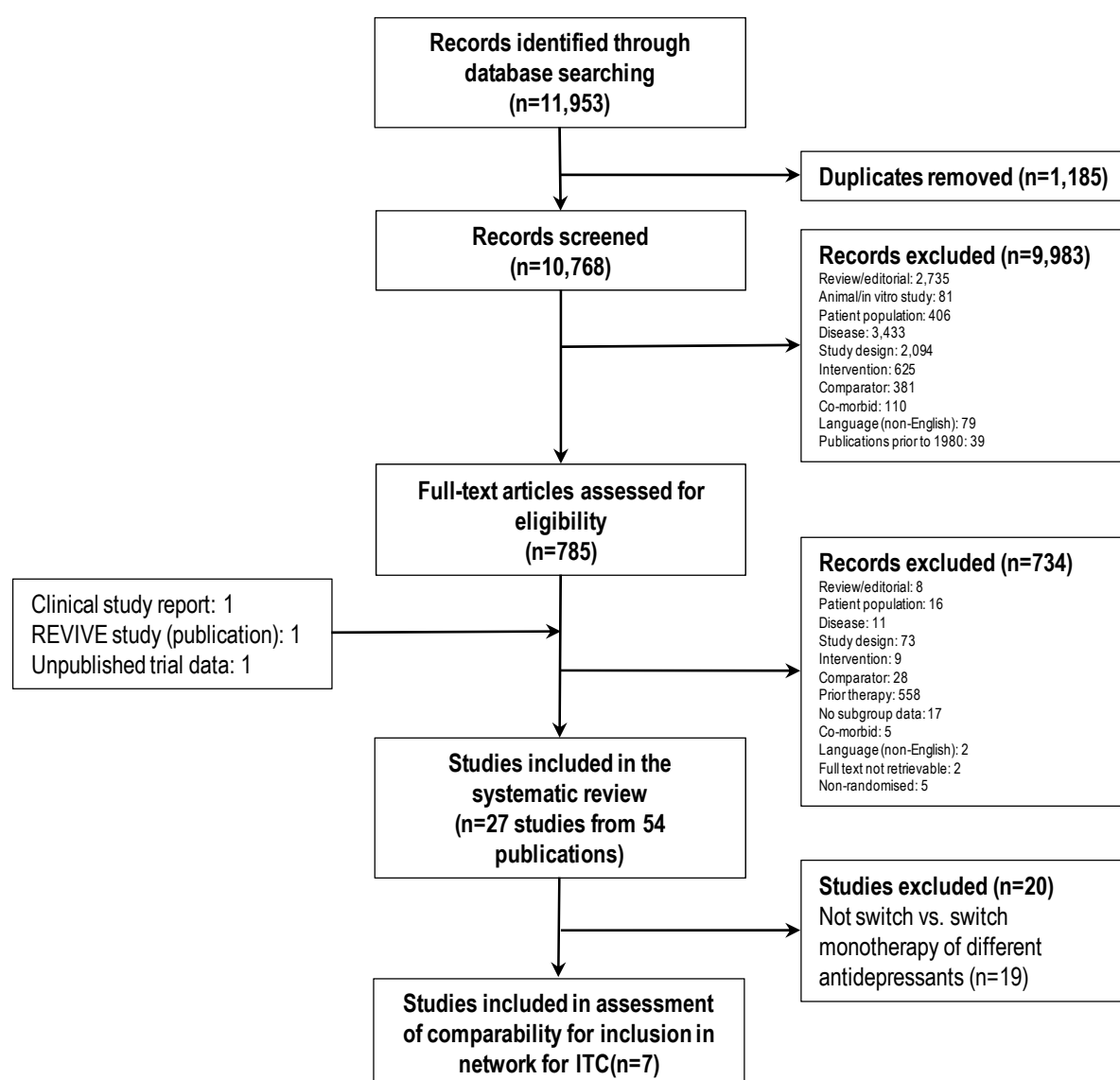
Extraction of relevant data

The final extraction grid is provided in the systematic review report. Data extraction was undertaken by a single reviewer with a quality check undertaken by an independent reviewer. Where more than one publication was identified as describing a single trial, the

data were compiled into a single entry in the data extraction table to avoid double counting of patients and studies. Each publication was referenced in the table to recognise that more than one publication may have contributed to the entry. Where more than one publication per study was available, the primary publication was used to inform the study description as far as possible, before additional data were extracted from secondary publications.

6.7.2.4 Flow diagram

Figure B15 shows the flow of studies through the systematic review process. The search of literature databases yielded 11,953 separate references. Due to the overlap of coverage between the databases, 1,185 abstracts were found to be duplicates. Following the first-stage screening of these citations, 785 potentially relevant references were identified. Full-text reports of these citations were obtained for more detailed evaluation. In addition to the references retrieved from electronic literature databases, one study of bupropion was identified by hand-searching of trial registry data. For the REVIVE study, in addition to the references retrieved by the searches conducted for vortioxetine (see section 6.1-6.5 and Table B2), the clinical study report²⁷ was obtained from Lundbeck. Following detailed examination of the 788 references, 734 references were excluded. Multiple publications for a single study were linked together. Following linking of references, 27 studies from 54 publications met the inclusion criteria and were included for data extraction.

Figure B15. Flow diagram of the search for eligible studies for the indirect treatment comparison

6.7.2.5 Study selection

A total of 27 RCTs were identified as meeting the inclusion criteria for the overall systematic review and were retained for data extraction¹⁸⁷. These studies were further assessed for their potential to be included in an ITC between vortioxetine and other potential switch monotherapies, based on the eligibility criteria in Table B23. Across the 27 studies, different approaches to treat patients with inadequate response to prior therapy were evaluated, not all of which addressed the ITC study question. Some studies evaluated switch therapies, dose up-titrations or reassessment of initial therapy for different antidepressant monotherapies. Studies that did not compare switch vs. switch regimens of at least two different antidepressant monotherapies did not address the specific study question and were excluded (excluding switch vs. dose escalation etc). Table D17 in Appendix section 10.4.8 details the 27 studies along with the rationale for exclusion where appropriate. Nineteen studies were eliminated on this basis. A further trial, Birkenhager 2004¹⁸⁸, could not be linked into a potential evidence network and was excluded from further consideration, leaving 7 studies for potential inclusion in an ITC.

Table B24 lists primary published literature references to each of these 7 studies. References are cited alongside the respective study ID (first author, publication year); elsewhere in this section studies are referred to by study ID only. Six of the 7 remaining studies were published as journal articles. Data for study AK1102365 were obtained from an unpublished report identified through trial registry searching¹⁸⁹. This study is referred to hereafter as GSK 2009. For Study 14178A (REVIVE) a clinical study report (CSR)²⁷ was available as well the primary publication (Montgomery 2014²⁶). In this section, REVIVE is referred to by its primary literature reference, Montgomery 2014, but other publications and the CSR were used for the purposes of data extraction. The review also identified post-hoc analyses (Kasper 2013)³² of two RCTs (Olié and Kasper 2007¹⁹⁰ and Kasper 2010¹⁹¹). The post-hoc analyses reported on subgroups of previously-treated patients.

Table B24. List of studies retained from the systematic review for potential inclusion in the indirect treatment comparison

Study ID	N	Intervention	Comparator	Linked publications
GSK 2009 (AK1102365) ^{189,192}	325	Bupropion SR 200-300mg	Placebo	-
Olié and Kasper 2007 ¹⁹⁰	94 [^]	Agomelatine 25-50mg	Placebo	Kasper 2013 ³²
Kasper 2010 ¹⁹¹	177 [^]	Agomelatine 25-50mg	Sertraline 50-100mg	Kasper 2013 ³²
Lenox-Smith 2008 ¹⁹³	406	Venlafaxine ER 75-300mg	Citalopram 20-60mg	-
Montgomery 2014 ²⁶ : Study 14178A (REVIVE) ²⁷	501	Vortioxetine 10-20mg	Agomelatine 25-50mg	Häggström 2013 ^{133,134}
Rosso 2012 ⁹⁸	49	Bupropion 150-300mg	Duloxetine 60-120mg	-
Rush 2006a ¹¹ (STAR*D)	789	Bupropion 150-400mg	Sertraline 50-200mg Venlafaxine 37.5-375mg Cognitive therapy	Rush 2006b ¹⁹⁴ , Trivedi 2006 ¹⁹⁵ , Warden 2009 ¹⁹⁶

ER: Extended Release; QD: Per day; *Patients were prior treated with duloxetine 120mg QD;

**Patients were prior treated with duloxetine 60mg QD Duloxetine 120mg QD; [^]Data extracted from post-hoc publication (Kasper 2013) for subgroup of prior treated population

Kasper 2010 and Olié and Kasper 2007 were two trials studying agomelatine in the full MDD population, the first versus sertraline and the latter versus placebo. In 2013, a post-hoc analysis of each of these two trials was published (Kasper 2013) reporting data for pre-treated subgroups of patients. Data from these two trials have been extracted separately with data entries reported here made under the respective primary publication. Kasper 2013 is attached as a secondary link to both these studies. It was used to extract information pertaining to patient populations such as disease severity, prior therapy (as this is the population of interest to the review) and the efficacy and tolerability data. Olié and Kasper 2007 and Kasper 2010 were used to extract information pertaining to study characteristics such as method of randomisation, blinding and inclusion/exclusion criteria. Also, these references were used to undertake the critical appraisal of studies as the NICE quality checklists mainly cover the methodological aspects of the studies and in this context, all relevant data for doing this assessment were taken into account.

6.7.2.6 Quality assessment of retained studies

An overview of the quality assessment of the retained studies is provided in Table B25.

Table B25. Overview of quality of retained studies (NICE checklist)

Study ID	Question						
	1	2	3	4	5	6	7
AK1102365							
Olié and Kasper 2007							
Kasper 2010							
Lenox-Smith 2008							
Montgomery 2014							
Rosso 2012							
Rush 2006							

Legend: Adequate Unclear Not adequate

NICE checklist questions:

1. Was randomisation carried out appropriately?
2. Was the concealment of treatment allocation appropriate?
3. Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded what might be the likely impact on the risk of bias (for each outcome)?
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?
7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

All but two of the studies were blinded trials (whether double- or single-blind). However, the method of blinding of patients and assessors were reported for only two studies (Kasper 2010; Montgomery 2014). The validity of Rosso 2012 was judged to be high risk as it was an open-label study.

Of the seven included studies, four reported an adequate method of generating random sequence numbers (Olié and Kasper 2007; Kasper 2010; Montgomery 2014; Rush 2006a). As described, data for the Kasper studies were obtained from the post-hoc publication Kasper 2013 as only this reference evaluates the patient population of interest to this review. However, for the critical appraisal, quality assessment for methodological parameters is based on the primary publications i.e. Olié and Kasper 2007 and Kasper 2010. An interactive voice response system was used to generate random sequence numbers among all four of these studies. For one study (Rosso 2012) the method of randomisation was inadequate, being based on the order of enrolment using an allocation schedule generated prior to the study or depending on the day of inclusion as even or odd. The concealment of allocation was deemed to be low risk in four of the seven studies (Olié and Kasper 2007; Kasper 2010; Montgomery 2014; Rush 2006a). All studies reported comparable baseline demographics between the treatment groups being studied.

Withdrawals were adequately reported in six of the seven included studies. In Rush 2006a the total number of withdrawals and reasons for withdrawals were not adequately reported. This study reported discontinuation due to intolerance, wherein pooled data of all patients who discontinued the study before week 4 regardless of the reason and all who did so at or after week 4 if they cited intolerable side-effects as the reason were reported.

Statistical analyses were adequately reported for all studies.

6.7.2.7 Study characteristics

Table B26 details the design characteristics of the studies described in this section that were considered for inclusion in the ITC; Table B27 provides details of the primary and secondary outcomes in each study.

Study phase

One study was a phase IV trial (Rush 2006a), three were Phase III trials (GSK 2009; Kasper 2010; Montgomery 2014), while the study phase was unclear in the remaining three studies (Olié and Kasper 2007; Rosso 2012; Lenox-Smith 2008).

Sample size and study duration

The studies varied in terms of sample size. Two studies (Montgomery 2014 and Rush 2006a) were large in sample size recruiting more than 500 patients. Fewer than 100 patients were recruited in two studies, including the post-hoc analysis by Kasper evaluating agomelatine against placebo (Rosso 2012; Kasper 2013).

The duration of studies ranged from 6 to 14 weeks. Three (Montgomery 2014, GSK 2009 and Lenox-Smith 2008) were 12-week studies. Patients in Rush 2006a were followed for 14 weeks and patients in the remaining studies for 6 weeks.

Primary efficacy measure

The primary efficacy measure was HAM-D score in six studies and MADRS in one (Montgomery 2014). The difference in scales was not expected to effect the comparability of results as HAM-D and MADRS total scores are highly correlated and composite endpoints based on both scales have been generally accepted¹⁹⁷.

Outcome of interest: remission

All studies included an evaluation of remission. The definition of remission was reported either using the HAM-D or the MADRS scale. Four studies reported remission using HAM-D scale (Rush 2006a; Rosso 2012; GSK 2009; Lenox-Smith 2008). Across these studies, patients achieving a HAM-D ≤ 7 were defined as remitters in Rush 2006a, GSK 2009, Rosso 2012 study, and Lenox-Smith 2008. Lenox-Smith reported a HAM-D remission rate only for a subgroup of patients who were severely depressed at baseline (defined as HAM-D >31). For the post-hoc analyses of Olié and Kasper 2007 and Kasper 2010 in Kasper 2013, remission rates could be derived from the reported HAM-D scores, as detailed in Appendix Section 10.16.1^{198,199}. In Montgomery 2014, remission was defined as patients achieving a MADRS ≤ 10 .

Time points for assessments

The studies varied in terms of time points for assessments. Remission was assessed at 14 weeks in Rush 2006a, whereas these assessments were done at 6 weeks in the post-hoc analysis by Kasper, at 8 and 12 weeks in Montgomery 2014 (primary endpoint: 8 weeks; the full study duration: 12 weeks), and at 12 weeks in GSK 2009 and Lenox-Smith 2008. Rosso (2012) assessed remission at 6 weeks.

Participant characteristics

Table B28 details the participant characteristics of the studies considered for inclusion in the ITC.

Age and sex

The mean age of the recruited patient population was comparable (42-47 years) in 5 of the 7 studies. However, GSK 2009 recruited relatively younger patients (mean age: 36 years).

The studies also varied in terms of the percentage of the male population. The percentages of female patients were lower in Rush 2006a study and GSK 2009 (45.3% to 58.7%) than the other studies. Clinical opinion suggested that sex has little, if any impact on the effect of an antidepressant and the trial populations were considered representative of the general population of patients with MDEs.

For one of the studies the baseline demographic characteristics of the patient population were not available (Lenox-Smith 2008). This was because remission data was reported only for severely depressed patients (HAM-D score >31); however, the baseline clinical characteristics for this sub-group were not reported.

Disease severity

Six studies reported baseline severity using the HAM-D scale. Of these studies, Rush 2006a and AK1102365 recruited patients with moderate depression and a mean baseline score of 17 to 24. The remaining studies included severely depressed patients with a mean baseline score of >24 (Rosso 2012; Kasper 2013; Lenox-Smith 2008). Montgomery 2014 reported baseline severity using the MADRS scale; the mean MADRS total score was 28.9 (range: 22 to 43) indicating that the patients had moderate- to-severe MDD.

Treatment duration

Duration of treatment was reported by only two studies, Montgomery 2014 and Rush 2006a, in which mean treatment duration was comparable at 8-10 weeks.

Previous treatment and definitions

All except two studies included only patients who had received prior treatment with SSRI or SNRIs (Table B29).

In Olié and Kasper 2007, the percentage of previously treated patients was <90% (SSRI: 69% and SNRI: 12.8%), while in Kasper 2010 the corresponding proportions were 67% and 20.4%. The percentages for prior SSRI and SNRI treated patients are not mutually exclusive and the possibility of overlap in these values cannot be ruled out. Further, in the post-hoc analysis of these two trials (Kasper 2013), the patient population was defined as pre-treated patients in the preceding year before inclusion, which does not strictly meet the criterion for switch within an MDE as the previous treatment may refer to a previous depression episode. Therefore the population in Kasper 2013 may be slightly wider than the target population in the other assessed studies.

The studies varied in terms of the definition of inadequate responders. Given this variability, it was considered that the review should not be restricted by the definitions used. In one study, GSK 2009, inadequate response was defined as less than 50% reduction in the baseline values using HAM-D or MADRS scales. In Rush 2006a, patients with lack of remission defined as a score on QIDS-C-16>5 after citalopram therapy were eligible for next step treatment.

Table B26. Summary of trials assessed for inclusion in the mixed treatment comparison: methodological characteristics

Study ID	Source data	Interventions	Type of treatment	Phase	Sample size	Diagnostic criteria	Blinding status	Study duration (assessment points)	Primary outcome (remission definition)	Secondary outcomes
Montgomery 2014 (REVIVE)	Clinical study report	Vortioxetine	Switch therapy	III	501	DSM-IV	Double-blind	12 weeks (2, 4, 8 and 12)	MADRS score (≤ 10)	MADRS response, MADRS remission, HAM-A, CGI-I response, CGI-I score, CGI-S score, CGI-S remission, SDS, HRQoL, EuroQoL, WLQ, DFFS, health economic assessments, safety, withdrawals
		Agomelatine	Switch therapy							
Kasper 2010	Journal article	Agomelatine	Switch therapy	III	177*	DSM-IV	Double-blind	6 weeks (6)	HAM-D ₁₇ score (≤ 7)	CGI-Response, HAM-D ₁₇ response, withdrawals due to AEs
		Sertraline	Switch therapy							
Olié and Kasper 2007	Journal article	Agomelatine	Switch therapy	Unclear	94*	DSM-IV	Double-blind	6 weeks (6)	HAM-D ₁₇ score (≤ 7)	CGI-Response, HAM-D ₁₇ response, withdrawals due to AEs
		Placebo	Switch therapy							
Rush 2006a (STAR*D)*	Journal article	Bupropion	Switch therapy	IV	727	DSM-IV	Assessor blind	14 weeks (14)	HAM-D ₁₇ score (≤ 7)	QIDS-SR ₁₆ , FIBSER, withdrawals, safety, remission, response
		Sertraline, venlafaxine	Switch therapy							
Rosso 2012	Journal article	Bupropion	Switch therapy	Unclear	49	DSM-IV	Assessor blind	6 weeks (6)	HAM-D ₁₇ score (≤ 7)	CGI-S score, response, remission, GAF score, withdrawals
		Duloxetine	Switch therapy							
GSK 2009 (AK1102365)	Unpublished data	Bupropion	Switch therapy	III	325	Unclear	Double-blind	12 weeks (8 and 12)	HAM-D ₁₇ score (≤ 7)	HAM-D ₁₇ remission, HAM-D ₁₇ response, CGI-S score, CGI-I response, withdrawals, safety
		Placebo	Switch therapy							
Lenox-Smith 2008†	Journal article	Venlafaxine	Switch therapy	Unclear	112	DSM-IV	Double-blind	12 weeks (12)	HAM-D ₂₁ score (≤ 7)	Remission, MADRS score, CGI-S score, CGI-I score, safety, withdrawals
		Citalopram	Switch therapy							

*Baseline patient data corresponds to number of patients treated with pharmacological interventions. †Represents baseline data for subgroup of patients who were severely depressed at baseline (defined as HAM-D > 31). CGI-I: Clinical Global Impression – Improvement; CGI-S: Clinical Global Impression – Severity; AE: adverse event; HAM-D: Hamilton Depression Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale, QIDS-SR₁₆: Quick Inventory for Depressive Symptomatology; FIBSER: Frequency, Intensity, and Burden of Side Effects Ratings.

Table B27. Summary of trials assessed for inclusion in the indirect treatment comparison: primary and secondary outcomes

Study ID	HAM-D Response	HAM-D Remission	HAM-D score	MADRS Response	MADRS Remission	MADRS score	CGI – I Response	CGI – I score	CGI – S Response	CGI – S Remission	CGI – S score	IDS score	QIDS SR-16 response	QIDS SR-16 remission	QIDS SR-16 score	Time to response	Time to remission	Withdrawals
GSK 2009 (AK1102365)	✓	✓	✓†	-	-	-	✓	-	-	-	✓*	-	-	-	-	✓	-	✓
Kasper 2007	✓	-	✓	-	-	-	✓	-	-	-		-	-	-	-	-	-	✓
Kasper 2010	✓	-	✓	-	-	-	✓	-	-	-		-	-	-	-	-	-	✓
Lenox-Smith 2008#	-	-	✓*‡	-	-	-	-	-	-	-		-	-	-	-	-	-	✓
Montgomery 2014 (REVIVE)	-	-	-	✓	✓	✓†	✓	✓	-	✓	✓†	-	-	-	-	-	-	✓
Rosso 2012	✓	✓	✓	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	✓
Rush 2006a (STAR*D)	-	✓	-	-	-	-	-	-	-	-		-	✓	✓	✓	✓	✓	✓
Cut-off used for defining response/remission across studies	≥50% RFB§	≤7 or ≤8	-	≥50% RFB§	≤8, ≤10 or ≤12	-	≤2	-	≤2	≤2	-	-	≥50% RFB§	≤5	-	-	-	-

* Change from baseline reported. † Both score and change from baseline were reported. ‡ HAM-D₂₁ score (all others HAM-D₁₇). HAM-D: Hamilton Depression Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; CGI-I: Clinical Global Impression – Improvement; CGI-S: Clinical Global Impression – Severity; QIDS-SR₁₆: Quick Inventory for Depressive Symptomatology; § RFB: reduction from baseline.

Table B28. Summary of trials included in the mixed treatment comparison: participant characteristics

Study	Age (years), mean $\pm$ sd	Sex: % female	Median duration of current episode (months)	Baseline severity	Treatment duration (weeks), mean $\pm$ sd
Montgomery 2014 (REVIVE)	46 $\pm$ 12	74.7%	3.7	CGI-S: 4.4 $\pm$ 0.6; MADRS: 28.9 $\pm$ 4.2 HAM-D ₁₇ : 23.3 $\pm$ 2.) §	Vortioxetine: 10.4 $\pm$ 3.0; Agomelatine: 9.7 $\pm$ 3.9
Kasper 2010**	44 $\pm$ 10	73.5%	3.1	CGI-I: 4.7 $\pm$ 0.7; HAM-D ₁₇ : 26.5 $\pm$ 3.0	Not reported
Olié and Kasper 2007**	44.9 $\pm$ 10	73.0%	2.0	CGI-I: 5.0 $\pm$ 0.7; HAM-D ₁₇ : 27.8 $\pm$ 2.8	Not reported
Rush 2006 (STAR*D) †	42 $\pm$ 13	58.7%	Not reported	HAM-D ₁₇ : 18.9 $\pm$ 7.3; QIDS SR-16: 13.2 $\pm$ 7.3	Bupropion: 8.3 $\pm$ 5.0; Sertraline: 9.1 $\pm$ 5.0; Venlafaxine: 9.3 $\pm$ 5.1
Rosso 2012	47 $\pm$ 13	67.7%	Not reported	CGI-S: 5.0 $\pm$ 0.9; HAM-D ₁₇ : 28.1 $\pm$ 4.7	Not reported
GSK 2009 (AK1102365)	36	45.3%	Not reported	HAM-D ₁₇ : 19 $\pm$ 4	Not reported
Lenox-Smith 2008 ‡	Not reported	Not reported	Not reported	HAM-D ₂₁ : >31	12 weeks, followed by 1- week taper period

*Data extracted from post-hoc publication (Kasper 2013) for subgroup of prior-treated patients.

† Baseline patient data corresponds to number of patients treated with pharmacological interventions.

‡ Represents baseline data for subgroup of patients who were severely depressed at baseline (defined as HAM-D >31).

§ HAM-D scores were calculated using transformation equation by Heo 2007.

CGI-I: Clinical Global Impression – Improvement; CGI-S: Clinical Global Impression – Severity; HAM-D: Hamilton Depression Rating Scale;

MADRS: Montgomery-Åsberg Depression Rating Scale; sd: standard deviation.

Table B29. Summary of trials assessed for inclusion in the indirect treatment comparison: prior therapy status

Study	Proportion of patients with prior SSRI/SNRI treatment	Prior antidepressants used (percentages of patients)	Prior information collected	Duration of previous treatment in weeks mean (sd)	Definition of inadequate response for current episode
Montgomery 2014 (REVIVE)	100%	Sertraline (24%), escitalopram (19%), citalopram (19%), paroxetine (15%), venlafaxine (17%), duloxetine (6%)	Retrospectively (self-reported as patients who wanted to switch treatment and were, in the investigator's clinical opinion, candidates for a treatment switch from their current treatment)	23.78 (41.06)	Incomplete or no therapeutic response to two prior courses of at least 6 weeks of conventional antidepressant drugs in adequate dosages
Kasper 2010*	87.1% [SSRI: 66.7% and SNRI: 20.4%, not mutually exclusive]	Fluoxetine 16.4%, citalopram 25.4%, paroxetine 20.9%, sertraline 10.2%; others 37.9%, of which: venlafaxine 20.4%, tianeptine 4.5%, mianserin 5.7%, mirtazapine 6.8%; NSMRIs 20.3%: amitriptyline 8.5%	Retrospectively (Not reported)	Not reported	Previously treated patients (who have been treated with antidepressants at least once during the year before inclusion)
Olié and Kasper 2007*	81.9% [SSRI: 69.1% and SNRI: 12.8%, not mutually exclusive]	Fluoxetine 23.4%, citalopram 20.2%, paroxetine 14.9%, sertraline 18.1%; others 35.1%, of which: venlafaxine 12.8%, tianeptine 8.5%, mianserin 7.5%, mirtazapine 6.4%; NSMRIs 10.6%: amitriptyline 3.2%	Retrospectively (Not reported)	Not reported	Previously treated patients (who have been treated with antidepressants at least once during the year before inclusion)
Rush 2006 (STAR*D)	100%	Citalopram	Prospectively	10.0 (4.2)	Patients who had no remission of symptoms or could not tolerate the SSRI citalopram, QIDS-SR ₁₆ score ≥ 5 at last visit of study phase
Rosso 2012	100%	Fluoxetine (trial 1: 3.7%, trial 2: 11.1%) fluvoxamine (trial 1: 7.4%, trial 2: 0%), citalopram (trial 1: 29.6%, trial 2: 29.6%), sertraline (trial 1: 14.8%, trial 2: 18.5%), escitalopram (trial 1: 11.1%, trial 2: 14.8%), paroxetine (trial 1: 33.3%, trial 2: 25.9%)	Retrospectively (medical history from tertiary referral centre)	4 weeks	Patients had to be resistant to two adequate SSRI treatments

Study	Proportion of patients with prior SSRI/SNRI treatment	Prior antidepressants used (percentages of patients)	Prior information collected	Duration of previous treatment in weeks mean (sd)	Definition of inadequate response for current episode
GSK 2009 (AK1102365)	100%	Paroxetine	Prospectively	4 weeks	HAM-D ₁₇ ≥ 14 and % decrease of HAM-D ₁₇ was $\leq 50\%$
Lenox-Smith 2008	100%	SSRI monotherapy other than citalopram	Retrospectively (medical records)	8 weeks	Patients with HAM-D ₂₁ $\geq 20\%$

*Data extracted from post-hoc publication (Kasper 2013) for subgroup of prior-treated patients.

SNRI: Serotonin norepinephrine reuptake inhibitors; SSRI: Selective serotonin reuptake inhibitors; CGI-I: Clinical Global Impression – Improvement; CGI-S: Clinical Global Impression – Severity; HAM-D: Hamilton Depression Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: Major Depressive Disorder; QIDS-SR₁₆: Quick Inventory for Depressive Symptomatology

6.7.3 Trials included in indirect comparison

Based on a final assessment of the seven retained studies against the criteria described in the previous section, it was concluded that all except Rosso 2012⁹⁸ were sufficiently comparable and robust in quality to allow their inclusion into an indirect treatment comparison. The basis for the inclusion and exclusion decisions is detailed in Table B30. Rosso 2012 was excluded because the method of randomisation, based on day of enrolment to the study, was deemed inadequate.

Table B30. Indirect treatment comparison: summary basis of study inclusion/exclusion decisions

Study ID	Decision	Rationale if excluded
Montgomery 2014 (REVIVE)	Include	n/a
Kasper 2010	Include (sensitivity analysis)	Clinical expert opinion indicated that patients who entered into a placebo-controlled study may be inherently different to those included in an active-controlled study. Advice was taken to include this placebo-controlled trial only in a sensitivity analyses of the ITC.
Olié and Kasper 2007	Include	n/a
GSK 2009 (AK110236)	Include (sensitivity analysis)	Rationale as for Kasper 2010.
Rush 2006a (STAR*D)	Include	n/a
Lenox-Smith 2008	Include	n/a
Rosso 2012	Exclude	Inadequate randomisation (by day of the week) and blinding (single-blind) threaten the validity of this trial.

n/a: not applicable

6.7.3.1 Limitations of potential evidence network in light of relevant comparators

In section 2.7, sertraline, fluoxetine, mirtazapine, venlafaxine and citalopram were highlighted as being relevant comparators in the initial switch treatment setting, based on the recommendations of CG90, UK prescribing data and expert clinical opinion.

As the systematic review as detailed above provided data for only 3 of the 5 of these relevant comparators, external expert advice was sought on a resolution to this problem. It was decided to repeat the review of the studies of mirtazapine and fluoxetine that had been excluded at full-text review in order to assess the possibility of loosening the eligibility criteria, such that these comparators could be included in the planned ITC without unduly compromising its validity. Following in-depth reviews with expert clinicians and health economists, it was concluded that no studies of mirtazapine and fluoxetine could justifiably be included. Details of the supplementary search for these studies can be found in Appendix Section 10.4.9. Finally, the English language criterion was removed from the search, but none of the additional studies identified were considered eligible against the remaining criteria.

6.7.4 Study selection for the indirect treatment comparison

6.7.4.1 Study selection

The literature review and detailed assessment of individual studies described in the previous section led to the trials and indicated antidepressants shown in Table B31 being included in

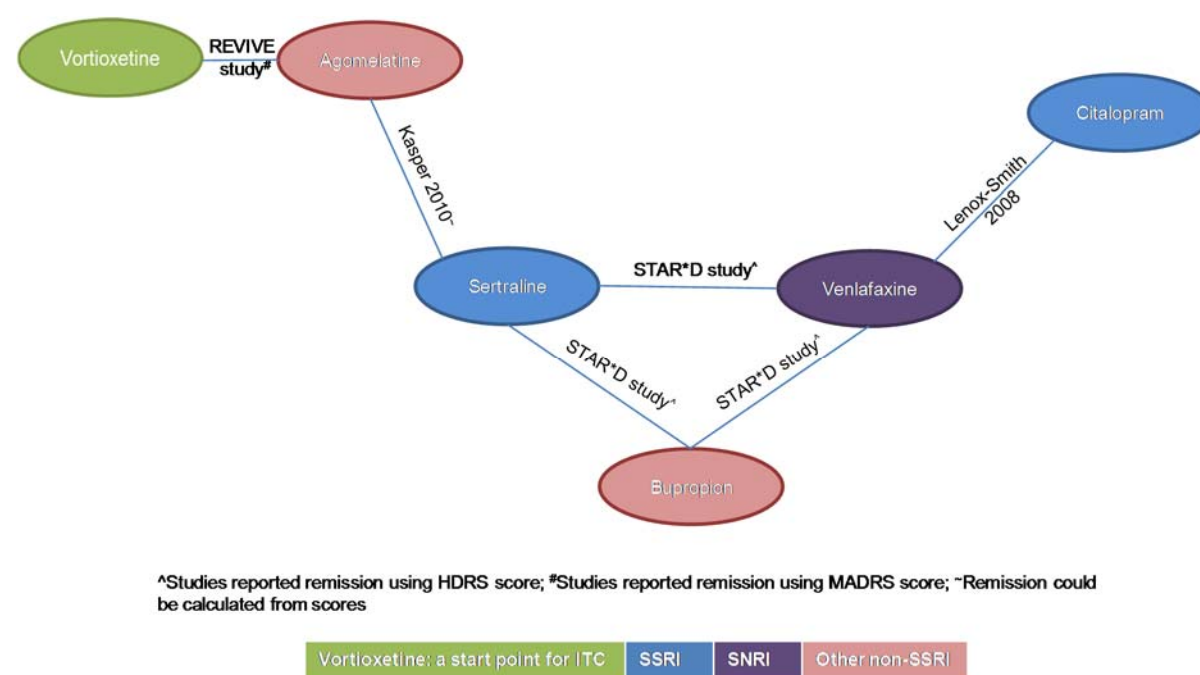
the network supporting the indirect comparison. The objective of this ITC was to provide comparative evidence for populating the cost-effectiveness model.

Table B31. Trials included in the indirect treatment comparison

Study	Vortioxetine	Agomelatine	Venlafaxine	Sertraline	Bupropion	Citalopram
Montgomery 2014 (REVIVE) ²⁶	X	X				
Kasper 2010 ¹⁹¹		X		X		
Rush 2006 (STAR*D) ¹¹			X	X	X	
Lenox-Smith 2008 ¹⁹³			X			X

The ITC included two outcomes of interest for the model: rates of remission and withdrawal due to adverse events. The base case network included six treatments (i.e. vortioxetine, agomelatine, venlafaxine, sertraline, bupropion and citalopram), based on four studies: Montgomery 2014²⁶, Kasper 2010¹⁹¹, Rush 2006¹¹ and Lenox-Smith 2008¹⁹³, as shown in Figure B16. Bupropion, although included in the network, is not licensed in the UK and therefore other than being included within this section, is not considered further within this submission. In addition, an alternative network was explored for sensitivity analyses using two additional placebo-controlled trials, Olié and Kasper 2007 and GSK 2009. Expert clinical and health economic opinion was that the patients included within these two trials may differ systematically from patients in active-controlled studies.

Figure B16. Base-case network for the indirect treatment comparison



The base case network used for both outcomes of interest (i.e. rates of remission and withdrawal due to adverse events) included five treatments (i.e. vortioxetine, agomelatine, venlafaxine, sertraline and bupropion) based on three studies: Montgomery 2014 (REVIVE)²⁶, Kasper 2010¹⁹¹ and Rush 2006a (STAR*D)¹¹.

Table B32 summarises the key characteristics of each of the three trials retained for the base-case network, while Table B33 compares the participants' baseline characteristics.

The patient populations of the four studies retained for the base-case network were comparable in age, the means falling within a range of 5 years. In Montgomery 2014, the mean baseline severity score of 28.9 on MADRS corresponds to a score of approximately 21 on the HAM-D₁₇,²⁰⁰ suggesting the symptom severity of the Montgomery 2014 cohort was midway between Rush 2006a and Kasper 2013. Overall, Rush 2006a enrolled a slightly younger and less severely depressed population with a greater proportion of males (see Table B33 below). The population included in Lenox-Smith 2008 was more severely depressed with a mean HAM-D₂₁ of 28.7. In addition, remission rates were only available on the subgroup of patients with HAM-D₂₁ higher than 31. Clinical opinion was that this degree of variability would not be an effect modifier. In each study, the majority of patients were previously treated with SSRIs.

In terms of outcome assessment, remission and withdrawal due to AEs were evaluated after 14 weeks in Rush 2006a and 12 weeks in Lenox-Smith 2008 whereas they were evaluated after 8 weeks in Montgomery 2014 and 6 weeks in Kasper 2010. These differing reporting time points are not expected to be effect modifiers. Supporting this, the Montgomery 2014 results show the relative effect in terms of change from baseline on the MADRS scale between vortioxetine and agomelatine to be roughly constant from week 4 to the end of the study at week 12²⁷. With regards to withdrawals due to AEs, variation in assessment points was not expected by clinical experts to affect relative treatment effects greatly, as most withdrawals due to AEs occur within 2-4 weeks of starting treatment.

Depression symptoms were measured using MADRS in Montgomery 2014 (REVIVE), HAM-D₂₁ in Lenox-Smith 2008 while the other two studies used HAM-D₁₇ (see Table B32 below). Again, clinical opinion and the literature²⁰¹ support that the standard remission cut offs that were applied to calculate remission rates are transferable regardless of scale used.

Table B32. Indirect treatment comparison: summary of study characteristics

Study identifier	Type	Population	Treatments compared, daily dose and FAS <i>N</i>	Primary endpoint	Remission definition	Endpoint assessment
Montgomery 2014 (REVIVE)	RCT	Inadequate response to a previous SSRI	Vortioxetine 10-20mg: N=252 Agomelatine 25-50mg N=241	MADRS	MADRS ≤ 10 with LOCF imputation	8 weeks
Kasper 2010 reanalysis in Kasper 2013	Post-hoc analysis of RCT	"Pre-treated subgroup": patients treated with antidepressant at least once during the year before the inclusion	Agomelatine 25-50mg: N=80 Sertraline 50-100mg: N=96	HAM-D ₁₇ total score	HAM-D ₁₇ ≤ 7 with LOCF imputation	6 weeks
Rush 2006 (STAR*D)	RCT	Patients switch after experiencing lack of efficacy or tolerability problems, previously treated with citalopram	Bupropion SR, dose increasing from 200 to 400mg: 239 patients Sertraline, dose increasing from 50 to 200mg: N=238 Venlafaxine XR dose increasing from 37.5mg to 375mg: N=250	HAM-D ₁₇ total score	HAM-D ₁₇ ≤ 7 Patients with missing remission status at 14 weeks were classified as non-remitters	14 weeks
Lenox-Smith (2008)	RCT	Patients who failed to respond to SSRI (other than citalopram). For remission rates results are only available for the subgroup of patients severely depressed at baseline (HAM-D ₂₁ > 31).	Venlafaxine 75-300mg N=57 Citalopram 20-60mg N=55	HAM-D ₂₁ total score	HAM-D ₂₁ ≤ 7	12 weeks

FAS: full analysis set; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor; MADRS: Montgomery-Åsberg Depression Rating Scale; HAM-D₁₇: Hamilton Depression Rating Scale 17-question version; HAM-D₂₁: Hamilton Depression Rating Scale 21-question version.

Table B33. Indirect treatment comparison: baseline characteristics of participants in included studies

Characteristics	Montgomery 2014 (REVIVE)	Kasper 2010 (pre-treated subgroup)	STAR*D (at baseline of level 2 ^a)	Lenox-Smith 2008
Age, mean $\pm$ sd	46.3 $\pm$ 12.4	44.1 $\pm$ 9.8	41.8 $\pm$ 12.8	NR
Sex, % of female	74.7%	73.4%	58.7%	NR
Previous treatment	SSRI or SNRI (75.8% SSRI)	SSRI 66.7%	Citalopram (100% treated with SSRI)	SSRI other than citalopram (100%)
Severity at baseline on HAM-D total score $\pm$ sd	NA (21) ¹	26.5 $\pm$ 3.0	18.9 $\pm$ 7.3	HAM-D ₂₁ > 31
Severity at baseline on MADRS total score $\pm$ sd	28.9 $\pm$ 4.2	NA (35-36) ²	NA (26) ²	NA

¹ HAM-D was not administered in REVIVE. Carmody (2006)²⁰⁰ describes an exchange rate algorithm between HAM-D₁₇ and MADRS, which implies the italicised HAM-D₁₇ score shown in parentheses.

² MADRS was not administered in these studies. Using the Carmody algorithm referenced above implies the italicised MADRS scores shown in parentheses.

sd: standard deviation; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin noradrenaline reuptake inhibitor; MADRS: Montgomery-Åsberg Depression Rating Scale; HAM-D₂₁: Hamilton Depression Rating Scale 21-question version.

6.7.4.2 Data used in the ITC

Two outcomes were compared in the ITC: efficacy based on remission rates and tolerability based on the rates of withdrawal due to AEs. The two outcomes are described in more detail below with the rationale supporting each. It was not possible to compare the incidence of individual AEs between treatments because of inconsistent reporting between studies.

6.7.4.3 Remission rates

The rationale for the choice of remission as the outcome of interest is provided in Table B46. In the studies in which remission rates were reported, they are defined as the proportions of patients who achieved a depression symptom score below a threshold value on the rating scale used. The studies that reported remission used either HAM-D or MADRS, and remission was defined as a HAM-D score ≤ 7 or a MADRS ≤ 10 which are commonly used definitions²⁰¹.

For the pre-treated subgroup analysis of Kasper (2010) reported in Kasper (2013), remission rates were not provided. To include this study in the network it was therefore necessary to derive remission rates from the reported HAM-D total scores at week 6. This derivation was performed by assuming that HAM-D total scores can be approximated by a parametric distribution. Normal and gamma distributions were selected as the most appropriate functional forms based on exploration of patient-level data from REVIVE. Factors influencing preference between these two distributions were as follows:

Normal distribution: Kasper 2013 states that *t* tests were used to compare the efficacy endpoints, assuming normality of the distribution.

Gamma distribution: When applied to MADRS total score data from REVIVE, a gamma distribution predicted the remission rates observed in REVIVE more closely than the normal distribution. The MADRS scale runs from zero to 60. Similarly, the gamma distribution is constrained to positive values and so overcomes the problem that normal distributions may include negative values.

Further detail on the methods used to derive the remission rates are detailed in Appendix 10.16.1. Remission rates for studies included in the indirect treatment comparisons are presented in Table B34. Differences in remission rates estimated using the normal distribution for agomelatine (27.9%) and sertraline (24.5%) were smaller than those obtained with the gamma distribution: agomelatine (32.3%) and sertraline (27.3%). Consequently, using the Bucher method, the normal distribution provides more conservative results in the indirect comparison for vortioxetine vs. sertraline and any subsequent comparisons through sertraline in the network. Therefore the normal distribution was chosen over the gamma distribution (see full results with gamma distribution in Appendix 10.16.1).

Table B34. Remission rates from studies included in the indirect treatment comparison

Study	Treatment	Total number of patients	Number of remitters (if reported)	Remission rate (reported or derived)	Assessment point
Montgomery 2014 (REVIVE)	VOR	252	102	40.5%	8 weeks
	AGO	241	71	29.5%	
Kasper 2010*	AGO	80†	Not reported	27.9% (Normal)/32.3% (Gamma)	6 weeks
	SER	96†		24.5% (Normal)/27.3% (Gamma)	
Rush 2006a (STAR*D)	SER	238	42	17.6%	14 weeks
	VEN	250	62	24.8%	
	BUP	239	51	21.3%	
Lenox-Smith 2008	VEN	57	21	36.8%	12 weeks
	CIT	55	15	27.3%	

AGO: Agomelatine; BUP: Bupropion; SER: Sertraline; VEN: Venlafaxine; CIT: Citalopram.

* Calculation (for more details see footnote); Norm: Normal estimation; Gam: Gamma estimation

† Kasper 2013 reported in Table 4 that 80% (n=64) of previously-treated patients in the agomelatine arm were responders compared to 75% (n=72) of previously-treated patients in the placebo group. From these data, it was estimated that 80 (i.e. 64/80%) patients were in the AGO arm and 96 (i.e. 72/75%) in the placebo group.

6.7.4.4 Withdrawal rates due to adverse events

Withdrawal due to AEs is considered a clinically relevant endpoint as it provides a summary measure of tolerability. This endpoint was consistently reported across studies, and the reported rates are presented in Table B35.

Table B35. Withdrawal rates due to AEs from studies included in the indirect treatment comparison

Study	Treatment	Total number of patients	Number of withdrawals due to AEs	Withdrawal rate
Montgomery 2014 (REVIVE)	VOR	253	15	5.9%
	AGO	242	23	9.5%
Kasper 2013 (pre-treated subgroup)	AGO	80	Not explicitly reported	2.6%
	SER	96		11.3%
Rush 2006a (STAR*D)	SER	238	50	21.0%
	VEN	250	53	21.2%
	BUP	239	65	27.2%
Lenox-Smith 2008	VEN	200	11	5.5%
	CIT	206	11	5.3%

AGO: Agomelatine; BUP: Bupropion; PBO: Placebo; SER: Sertraline; VEN: Venlafaxine

6.7.5 Methodology of the indirect comparisons

The data were analysed by indirect comparisons implemented both in frequentist and Bayesian frameworks. The Bayesian framework analyses are detailed in Appendix 16, section 10.16.3.

6.7.5.1 Frequentist framework

Meta-analyses based on indirect comparisons were carried out between pairs of treatments of interest if these pairs had not been directly compared in head-to-head trials. Simple adjusted indirect comparisons using the frequentist method of Bucher²⁰² were used to preserve the randomisation of the trials. This approach conformed to guidelines from EUnetHTA²⁰³ and NICE²⁰⁴.

Both outcomes of interest, remission and withdrawal due to AEs, were dichotomous. Risk differences corresponding to the difference between the observed risks (proportions of individuals with the outcome of interest) in the two groups were calculated for each study as a measure of absolute effect of treatment effectiveness and safety, as recommended in the Cochrane Handbook²⁰⁵.

The indirect effect size and its variance were estimated as follows:

$$\hat{\theta}_{AC} = \hat{\theta}_{AB} - \hat{\theta}_{CB}$$
$$var(\hat{\theta}_{AC}) = var(\hat{\theta}_{AB}) + var(\hat{\theta}_{CB})$$

where $\hat{\theta}$ is the rate difference between treatments.

The Bucher method can be applied to risk differences or odds ratios. Although it is more widely applied to odds ratios, an analysis of risk differences was preferred for the reasons described below. Use of odds ratios was found to strongly disadvantage sertraline, venlafaxine XR, bupropion SR and citalopram with respect to estimated adverse event rates. However, remission rate estimates for all therapies were quite comparable by both methods. The risk difference method was selected as it resulted in more conservative estimates.

The indirect comparison assumed that the relative efficacy of a treatment was consistent across trials, i.e. that there was no major difference between the two trials with respect to factors that could have influenced the estimated treatment effect.

The adjusted indirect comparison on rate difference was estimated with the software ITC[®].

6.7.6 Results of the ITC

6.7.6.1 Remission

Table B36 displays the results of the frequentist analysis of remission rates, using the Bucher method.

Table B36. Remission rates estimated by the indirect treatment comparison

	Vortioxetine	Agomel- atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
Agomelatine vs. vortioxetine direct comparison from REVIVE						
Remission rate	40.5%	29.5%	-	-	-	-
Difference vs. vortioxetine	-	-11.0%	-	-	-	-
95% CI	-	[-19.4;-2.6]	-	-	-	-
Sertraline vs. vortioxetine through REVIVE and Kasper 2013						
Remission rate	40.5%	-	26.1%	-	-	-
Difference vs. vortioxetine	-	-	-14.4	-	-	-
95% CI	-	-	[-29.9;1.1]	-	-	-
Venlafaxine XR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Remission rate	40.5%	-	-	33.3%	-	-
Difference vs. vortioxetine	-	-	-	-7.2%	-	-
95% CI	-	-	-	[-24.3;9.9]	-	-
Bupropion SR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Remission rate	40.5%	-	-	-	29.8%	-
Difference vs. vortioxetine	-	-	-	-	-10.7%	-
95% CI	-	-	-	-	[-27.8;6.4]	-
Citalopram vs. vortioxetine through REVIVE, Kasper 2013, STAR*D and Lenox-Smith 2008						
Remission rate	40.5%	-	-	-	-	23.7%
Difference vs. vortioxetine	-	-	-	-	-	-16.8%
95% CI	-	-	-	-	-	[-41.1;7.5]
CI: confidence interval						

6.7.6.2 Withdrawal due to adverse events

Table B37 displays the results of the frequentist analysis on withdrawal rates, using the Bucher method.

Table B37. Rates of withdrawal due to AEs estimated by the indirect treatment comparison

	Vortioxetine	Agomelatine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
Agomelatine vs. vortioxetine direct comparison from REVIVE						
Withdrawal due to AE rate	5.9%	9.5%	-	-	-	-
Difference vs. vortioxetine	-	+3.6%	-	-	-	-
95% CI	-	[-1.1;8.3]	-	-	-	-
Sertraline vs. vortioxetine through REVIVE and Kasper 2013						
Withdrawal due to AE rate	5.9%	-	18.0%	-	-	-
Difference vs. vortioxetine	-	-	+12.1%	-	-	-
95% CI	-	-	[3.1;21.1]	-	-	-
Venlafaxine XR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Withdrawal due to AE rate	5.9%	-	-	18.2%	-	-
Difference vs. vortioxetine	-	-	-	+12.3%	-	-
95% CI	-	-	-	[0.8;23.8]	-	-
Bupropion SR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Withdrawal due to AE rate	5.9%	-	-	-	24.2%	-
Difference vs. vortioxetine	-	-	-	-	+18.3%	-
95% CI	-	-	-	-	[6.4;30.1]	-
Citalopram vs. vortioxetine through REVIVE, Kasper 2013, STAR*D and Lenox-Smith 2008						
Withdrawal due to AE rate	5.9%	-	-	-	-	18.0%
Difference vs. vortioxetine	-	-	-	-	-	+12.1%
95% CI	-	-	-	-	-	[-0.3;24.5]

CI: confidence interval; AE: adverse event.

6.7.7 Statistical assessment of heterogeneity

Statistical assessment of heterogeneity can only be performed when the network includes at least two studies comparing the same treatments head-to-head. Given the very small number of studies, the number of treatments and the fact that each treatment comparison is only informed by one study in the network, it was not feasible to assess statistically the heterogeneity between studies. For similar reasons, it was also not possible to account for factors other than the treatment effects in the model.

6.7.8 Inconsistencies

Not applicable as only indirect evidence is available.

6.7.9 Similarity assumption

Differences between study settings and baseline characteristics were shown in Table B32 and Table B33.

For example, in Kasper 2013, the population was a subgroup of previously-treated patients, making it slightly wider than in the other studies as it is not known with certainty that previous treatment was for the current episode. Baseline characteristics were similar between REVIVE and Kasper 2013 whereas STAR*D appeared to differ in term of sex (fewer female) and severity (less severe patients). Some of these baseline characteristics are missing in Lenox-Smith and patients were more severely depressed (remission rate derived from a subgroup of patients with HAM-D₂₁>31). Clinical experts advised that these differences would not be effect modifiers.

The differences between results estimated from the ITC and those reported in the literature are shown in Table B38 and Table B39.

Table B38. Comparison of ITC estimates with inputs: remission rates

Comparators	Adjusted indirect comparison estimate	Original data inputs (from publications)
Vortioxetine	40.5%	40.5% (REVIVE)
Agomelatine	29.5%	29.5% (REVIVE) 27.9% (Kasper 2013)
Sertraline	26.1%	17.6% (STAR*D) 24.5% (Kasper 2013)
Venlafaxine XR	33.3%	24.8% (STAR*D) 36.8% (Lenox-Smith)
Bupropion SR	29.8%	21.3% (STAR*D)
Citalopram	23.7%	27.3% (Lenox-Smith)

Unadjusted remission rates were lower in the three arms of the STAR*D study than with vortioxetine and agomelatine in REVIVE, despite a longer treatment period in STAR*D.

When considering the rates obtained with the adjusted indirect comparisons, the rates for sertraline, venlafaxine and bupropion are higher and approach those observed in the agomelatine arm of the REVIVE study.

Table B39. Comparison of ITC estimates with inputs: withdrawal rates due to AEs

Comparators	Adjusted indirect comparison estimate	Original data inputs (from publications)
Vortioxetine	5.9%	5.9% (REVIVE)
Agomelatine	9.5%	9.5% (REVIVE) 3.7% (Kasper 2013)
Sertraline	18.0%	21% (STAR*D) 12.2% (Kasper 2013)
Venlafaxine XR	18.2%	21.2% (STAR*D) 5.5% (Lenox-Smith)
Bupropion SR	24.2%	27.2% (STAR*D)
Citalopram	18.0%	5.3% (Lenox-Smith)

Rates of withdrawal due to AEs from STAR*D were greater than in the other studies. The rates of withdrawal due to AEs from the adjusted indirect comparison remained higher in STAR*D than in REVIVE, but the differences were reduced compared to the differences of observed rates. For both remission and drop-out due to adverse events, sensitivity analyses were performed in the cost-effectiveness model to account for uncertainty around these values.

6.7.10 Sensitivity analyses

Several sensitivity analyses were undertaken to assess the robustness of the findings from the Bucher method. Frequentist results for the remission rates were estimated using the inputs re-calculated assuming a gamma distribution. In addition, Bayesian analyses were also conducted for both outcomes on the same networks and also on a slightly different network considering 2 additional studies. These analyses are presented in Appendix section 10.16.3.

6.7.11 Conclusions

These analyses were conducted to add further relevant comparators to the cost-effectiveness evaluation of vortioxetine. The analyses found that vortioxetine is more efficacious and better tolerated than a basket of comparator antidepressants, using a conservative, frequentist approach. A set of sensitivity analyses were performed for both the efficacy and tolerability outcome. First, Bayesian methods were employed, using both the base-case network and an expanded network that included additional studies. Second, a different distributional assumption for deriving remission rates (Appendix 16) was applied. In all sensitivity analyses, the results were either equivalent or more favourable for vortioxetine than was the base-case analysis.

6.8 Non-RCT evidence

A systematic review was conducted that aimed to capture non-RCT evidence for the intervention of interest on the population of interest. Again, the search strategy and databases searched are as described in section 6.1.

6.8.1 Study selection

Two researchers (and a third in the event of disagreements) independently screened all records by title and abstract against the pre-determined inclusion and exclusion eligibility criteria for selection of vortioxetine non-RCTs. These criteria for Population, Intervention(s)/Comparator(s), Outcome(s) and Study design (PICOS) are presented in Table B40.

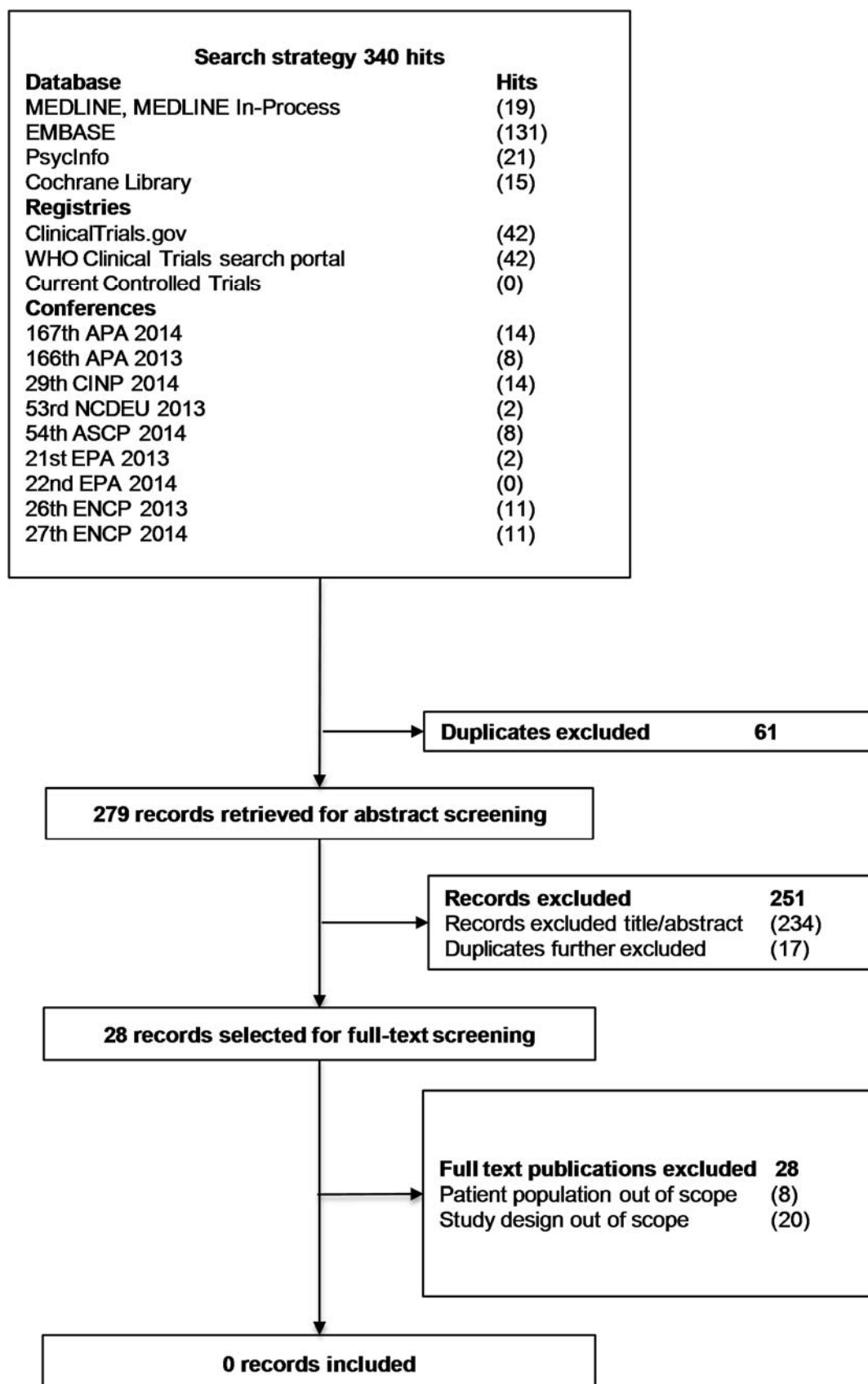
Table B40. Eligibility criteria for selection of non-RCTs

	Inclusion criteria	Exclusion criteria
Population	Adults with MDD who have experienced an inadequate response (in terms of efficacy and safety) to a previous antidepressant for the treatment of an MDE i.e. switch patients.	Patients without MDD/experiencing an MDE. MDD patients but not specifically switch. Paediatric patients.
Intervention	Must include a licensed vortioxetine regimen (5mg, 10mg, 15mg, 20mg tablets once daily).	Any study not containing vortioxetine as an intervention.
Comparators	SSRIs (e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline). TCAs (e.g. clomipramine, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, and amitriptyline). Tricyclic-related antidepressants (for example mianserin and trazodone). SNRIs (e.g. venlafaxine and duloxetine). Other antidepressants (for example mirtazapine, agomelatine, and reboxetine).	No limitations.
Outcomes	Change from baseline severity of depression. Remission of symptoms. Anxiety. Response to treatment (including response rate and time to response). Relapse (including relapse rate and time from remission to relapse). Hospitalisation. Mortality. Adverse effects of treatment (including adverse effects of treatment discontinuation). Health-related quality of life. Disability. Family functioning. Productivity (absenteeism/ presenteeism). Improvements in treatment related side-effects e.g. TESD. Improvement in cognitive functioning. Any other outcome.	No limitations.
Study design	Non-RCTs of any duration.	RCTs. Non-human.

MDD: major depressive disorder; MDE: major depressive episode; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-noradrenaline reuptake inhibitor; TCA: tricyclic antidepressant; RCT: randomised controlled trial.

The search as described in section 6.1 initially identified 297 records and the update added 43 new records (total 340). Following title and abstract screening of these, 28 full-texts were retrieved but none was retained for data extraction. Figure B17 displays the selection process in a PRISMA flow diagram.

Figure B17. PRISMA flow diagram of the selection process for non-RCTs



6.9 Adverse events

6.9.1 Identification of studies

A systematic review was conducted that aimed to capture safety studies for the intervention of interest (vortioxetine) in the population of interest (switch population). Studies that featured safety outcomes as secondary outcomes were not included as per the guidance above. Again, the search strategy and databases searched are as described in section 6.1.

6.9.1.1 Study selection

Two researchers (and a third in the event of disagreements) independently screened all records by title and abstract against the pre-determined inclusion and exclusion eligibility criteria for selection of vortioxetine safety studies. These criteria for Population, Intervention(s)/Comparator(s), Outcome(s) and Study design (PICOS) are presented in Table B41.

Table B41. Eligibility criteria for selection of safety studies

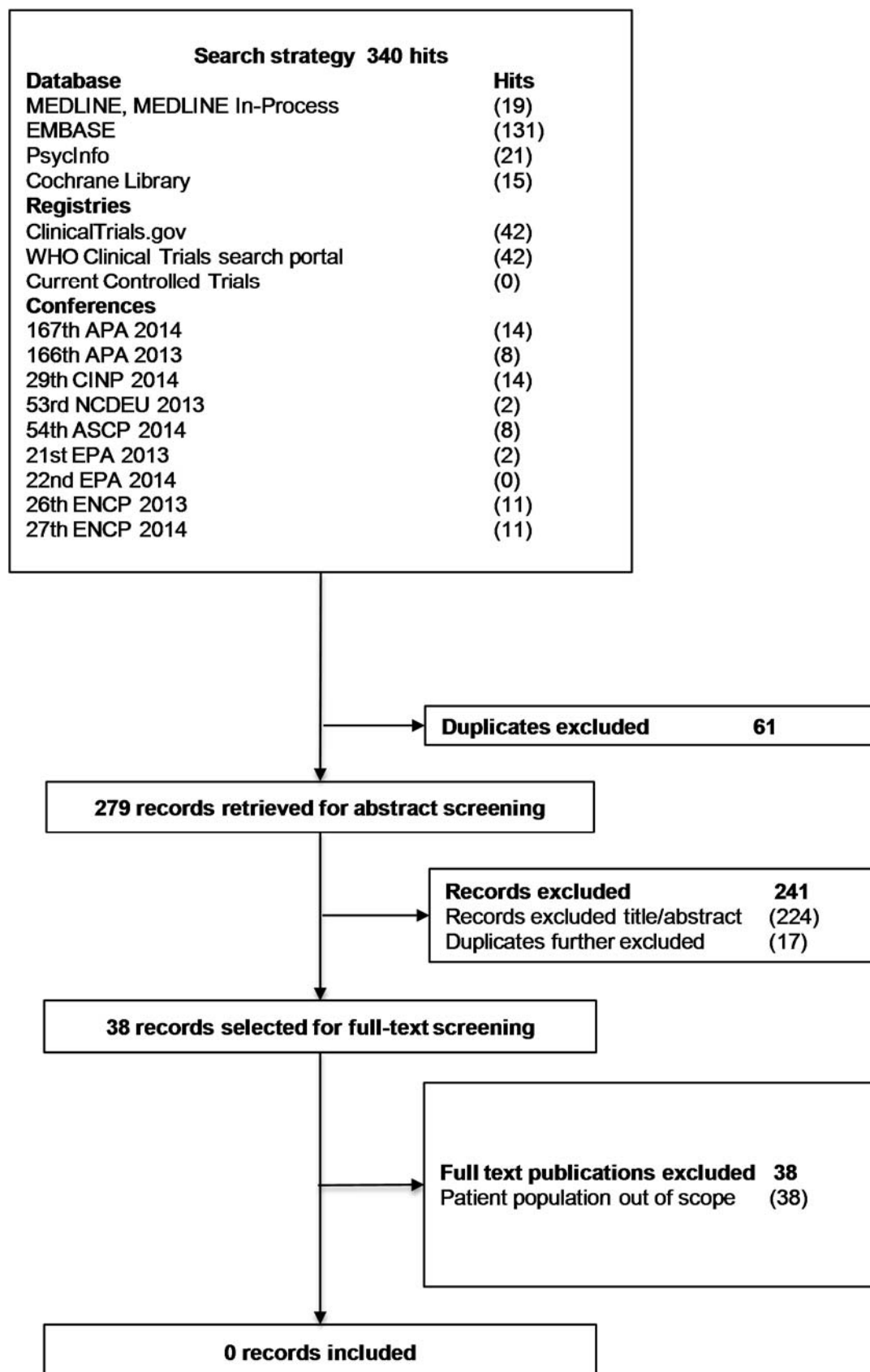
	Inclusion criteria	Exclusion criteria
Population	Adults with MDD who have experienced an inadequate response (in terms of efficacy and safety) to a previous antidepressant for the treatment of an MDE, i.e. switch patients.	Patients without MDD/experiencing an MDE. MDD patients but not specifically switch. Paediatric patients.
Intervention	Must include a licensed vortioxetine regimen (5mg, 10mg, 15mg, 20mg tablets once daily).	Any study not containing vortioxetine as an intervention.
Comparators	SSRIs (e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline). TCAs (e.g. clomipramine, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, and amitriptyline). Tricyclic-related antidepressants (for example mianserin and trazodone). SNRIs (e.g. venlafaxine and duloxetine). Other antidepressants (for example mirtazapine, agomelatine, and reboxetine).	No limitations.
Outcomes	Safety as a primary outcome, e.g.: GI (nausea, diarrhoea, vomiting); Nervous system disorders (dizziness); Skin (pruritus); No. of patients withdrawing due to AEs; Number of participants reporting AEs; Abnormal laboratory results; Body weight changes; Changes in vital signs.	Studies that do not focus on a safety measure as the primary outcome.
Study design	RCTs. Non-RCTs.	Non-human. Reviews. Meta-analyses/pooled analyses. Case studies (sample size not significant). Editorials, notes, comments, letters.

MDD: major depressive disorder; MDE: major depressive episode; RCT: Randomised Controlled Trials; SSRI: Selective-Serotonin Reuptake Inhibitors; TCA: tricyclic antidepressant; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors.

The search described in section 6.1 initially identified 297 records and the update increased the total number of records to 340. Following title and abstract screening of the records, 38

full-texts were retrieved but none was retained for data extraction. Figure B18 displays the selection process in a PRISMA flow diagram.

Figure B18. PRISMA flow diagram of the selection process for safety studies



6.9.1.2 Broadened population scope

As no safety studies were identified that were undertaken specifically within a switch population, the inclusion criteria were broadened to include non-switch populations. Expert clinical advice received by Lundbeck was that unlike efficacy, there is no reason to believe that the safety and tolerability of vortioxetine, or any other antidepressant, would differ by treatment line. The revised eligibility criteria are listed in Table B42.

Table B42. Revised eligibility criteria used in the search for safety studies

	Inclusion criteria	Exclusion criteria
Population	Adults with MDD experiencing an MDE.	Patients without MDD/experiencing an MDE. Paediatric patients.
Intervention	Must include a licensed vortioxetine regimen (5mg, 10mg, 15mg, 20mg tablets once daily).	Any study not containing vortioxetine as an intervention.
Comparators	SSRIs (e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline). TCAs (e.g. clomipramine, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, and amitriptyline). Tricyclic-related antidepressants (for example mianserin and trazodone). SNRIs (e.g. venlafaxine and duloxetine). Other antidepressants (for example mirtazapine, agomelatine, and reboxetine).	No limitations.
Outcomes	Safety as a primary outcome, e.g.: GI (nausea, diarrhoea, vomiting) Nervous system disorders (dizziness) Skin (pruritus) No. of patients withdrawing due to AEs Number of participants reporting AEs Abnormal laboratory results Body weight changes Changes in vital signs	Studies that do not focus on a safety measure as the primary outcome.
Study design	RCTs Non-RCTs	Non-human Reviews Meta-analyses/pooled analyses Case studies (sample size not significant) Editorials, notes, comments, letters

MDD: major depressive disorder; MDE: major depressive episode; RCT: Randomised Controlled Trials; SSRI: Selective-Serotonin Reuptake Inhibitors; TCA: tricyclic antidepressant; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors.

As in the original search, 297 records were identified through the initial review with a further 43 new records identified through the update. Following screening 38 full-texts were retrieved. On screening, 14 records pertaining to 6 studies were included. Figure B19 displays this selection in a PRISMA flow diagram, and Table B43 provides bibliographic details.

Figure B19. PRISMA flow diagram of the revised selection process for safety studies

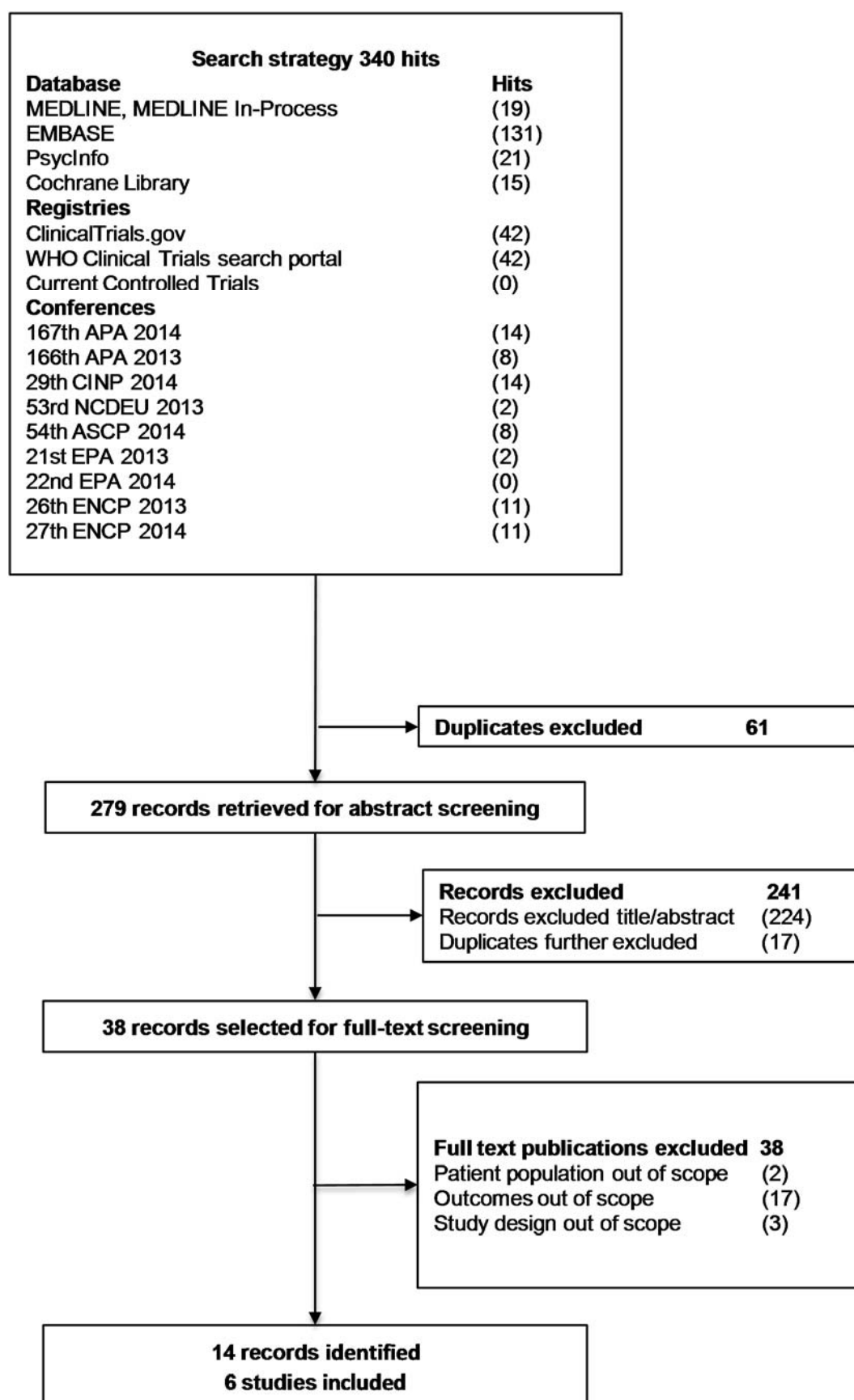


Table B43. Bibliographic details of primary safety studies in adult MDD population

Trial name/ number	Intervention	Population	Primary study reference	Additional references
NCT00694304	Vortioxetine	MDD	Baldwin 2012 ²⁰⁶	ClinicalTrials.gov ¹⁴⁴ ; Baldwin ²⁰⁷
NCT00707980	Vortioxetine	MDD	Alam 2014 ²⁰⁸	ClinicalTrials.gov ¹⁴⁵ ; Alam 2013 ²⁰⁹
NCT00761306	Vortioxetine	MDD	Florea 2012 ²¹⁰	ClinicalTrials.gov ¹⁴⁷
NCT01152996*	Vortioxetine	MDD	Jacobsen 2014 ^{211,212}	ClinicalTrials.gov ¹⁵¹
NCT01323478	Vortioxetine	MDD	Filippov 2013 ²¹³	ClinicalTrials.gov ¹⁵⁶
NCT01395147 *	Vortioxetine	MDD	ClinicalTrials.gov ¹⁵⁸	

* Identified on ClinicalTrials.gov but no publications were found. MDD: major depressive disorder

6.9.2 Details of adverse events

Section 6.9.1 identified the 6 studies of vortioxetine in which safety outcomes were the primary endpoint. These were open-label extensions to short-term efficacy studies and were designed to provide 12-month safety data for regulatory purposes. Pooled data from 5 of these 6 studies provide input parameters for long-term side-effects in the economic model to be described in section 7.

6.9.2.1 Open-label, long-term studies

Long-term tolerability and safety data are available from the “open-label long-term pool”²¹⁴. This pool includes 5 of the 6 open-label, long-term extension studies identified in the revised search described in section 6.9.1 above. These 5 studies, listed by Lundbeck identifier and clinicaltrials.gov identifier in parentheses are: 11492C (NCT00761306), 11984B (NCT00694304), 301 (NCT00707980), 13267B (NCT01323478), 314 (NCT01152996). The sixth trial was conducted in Japan and was excluded from the open-label long-term pool. The pool included a total of 2,587 patients who continued from the short-term studies and received flexible doses of vortioxetine of 2.5 to 20mg/day. Of these patients, 1,391 were exposed for ≥52 weeks²¹⁴. The first 4 of these studies reported in time to provide data for a cut-off date of 26 October 2012 for European regulatory assessment of vortioxetine; study 314 was reported later and was included in the updated safety pool. The sixth study identified by the revised search was Japanese study OCT-001 (one-year extension to CCT-003, NCT01395147). This study included 120 vortioxetine-treated patients and was not included in the open-label long-term pool as it had not been completed.

The incidence of TEAEs was 75% in the vortioxetine total group. The system organ classes (SOCs) with an incidence ≥20% were *gastrointestinal disorders*, *infections and infestations*, and *nervous system disorders*. The incidence of TEAEs in the vortioxetine 15-20mg group was higher (79%) than that in the vortioxetine 2.5-10mg group (71%); the SOC with the highest incidence in both dose groups was *gastrointestinal disorders* (33% in the vortioxetine 2.5-10mg group and 42% in the vortioxetine 15-20mg group).

The TEAEs in the core treatment period with an incidence $\geq 5\%$ in either group are summarised in Table B44. It was not possible to split out the small proportion of patients who received a 2.5mg dose because study 301 and 11984B were flexible dose studies in which patients received a daily dosage of between 2.5mg and 10mg.

Table B44. Incidence of TEAEs of $\geq 5\%$ in the open-label, long-term pool²¹⁴

	Vortioxetine (2.5-10mg)		Vortioxetine (15-20mg)		Vortioxetine (total)	
	n	%	n	%	n	%
Number of patients (APTS)	1,443		1,144		2,587	
Patient-years exposure	1,097		775.4		1,873	
Patients with AEs Preferred term:	1,028	71.2	903	78.9	1,931	74.6
Nausea	252	17.5	277	24.2	529	20.4
Headache	191	13.2	143	12.5	334	12.9
Nasopharyngitis	152	10.5	73	6.4	225	8.7
Diarrhoea	92	6.4	84	7.3	176	6.8
Dizziness	93	6.4	65	5.7	158	6.1
Weight increased	81	5.6	67	5.9	148	5.7
URTI	66	4.6	58	5.1	124	4.8
Vomiting	49	3.4	72	6.3	121	4.7
Constipation	40	2.8	66	5.8	106	4.1
Viral URTI	25	1.7	71	6.2	96	3.7

Source: Lu AA21004 IDB Final ST_AE_5P_C_OL 07FEB2014:15:02:23 SADs Build Number: 14.0.

Studies in the open-label, long-term pool: 11492C, 11984B, 301, 13267B, 314. Preferred terms: MedDRA version.

TEAE: treatment-emergent adverse event. AE: adverse event. APTS: all patients treated set. URTI: upper respiratory tract infection

6.9.3 Overview of safety in relation to the decision problem

As noted in section 6.9.1.2 above clinical expert opinion supports the transferability of tolerability data to all treatment lines.

No short-term safety studies were retrieved through the search. Clinical opinion supports the use of the tolerability data from REVIVE, 318 and the short-term safety pool from the full MDD package (as detailed in Appendix 15) as providing representative data for the use of vortioxetine in switch patients, or any other place within the treatment pathway. This is supported by vortioxetine's tolerability profile as observed in the switch study, being similar to the full MDD short-term safety pool.

As described in this section, five long-term open-labelled extension studies were retrieved through the search. A pooled analysis²¹⁴ was undertaken of these studies which included 2,500 vortioxetine-treated patients with over 1,800 patient-years of exposure (Table B44).

The tolerability profile of an antidepressant is crucial for treatment success as side-effects are commonly cited as the primary reason for non-compliance and treatment discontinuation^{84,90}. Non-compliance or discontinuation is associated with a higher risk of recurrence of depressive disorders with increased morbidity and long-term costs. For these

reasons, the safety and tolerability profile of an antidepressant is a critical aspect of the overall effectiveness of treatment. Vortioxetine's favourable tolerability profile aligned with good efficacy suggests that it would support overall effective treatment within MDD.

6.10 Interpretation of clinical evidence

6.10.1 Principal findings

The mechanism of action of vortioxetine differs from all other classes of antidepressant, including the SSRIs which have become the recommended class for first-line treatment of moderate-to-severe MDEs. While vortioxetine shares the serotonin (5-HT) transport blockade properties of SSRIs and other classes of antidepressant, it also has activity at multiple receptors that modulates neurotransmission in multiple systems. We have seen (section 2.6.3) that patients frequently respond inadequately to initial treatment, necessitating switch to a different antidepressant. By virtue of its multimodal activity, vortioxetine may be particularly suited to the treatment of patients switching from failed initial treatment, which in the UK is usually an SSRI.

Study 14178A (REVIVE)²⁶ compared vortioxetine with another newer-generation antidepressant, agomelatine. The efficacy of agomelatine is known to be comparable^{31,102} to other antidepressants and the statistical analysis plan was based on a non-inferiority hypothesis. Not only was non-inferiority established for the primary endpoint of MADRS total score after 8 weeks of treatment, but vortioxetine was superior to agomelatine (see section 6.5.2.2). Vortioxetine was also superior when MADRS scores were translated into response and remission rates at weeks 8 and 12, and over a range of secondary, socioeconomic outcomes including summary EQ-5D scores. Vortioxetine was at least as well tolerated as agomelatine, an antidepressant that is known to be well tolerated^{87,88}. Fewer patients on vortioxetine withdrew due to AEs and there was a lower incidence of SAEs in the vortioxetine group. Generally, safety and tolerability results were consistent with those seen in studies of vortioxetine in broader MDD populations.

The second trial, TAK318, involved a different type of switch population: patients who were otherwise well-treated with an initial SSRI but who had reported treatment-emergent sexual dysfunction, a well-known side-effect of SSRIs that may interfere with patients' willingness to adhere to their full intended courses of treatment. The comparator, escitalopram, was chosen as it has been associated with lower rates of sexual dysfunction than other SSRIs²¹⁵ and represents a strategy of switching within class, i.e. SSRI to another SSRI. Vortioxetine was superior to escitalopram on the primary endpoint, change in CSFQ-14 total score after 8 weeks of treatment, and on all but one subscale.

Indirect comparisons, necessitated by the lack of head-to-head switch studies other than REVIVE and TAK318, suggest that vortioxetine is more efficacious in terms of remission and withdrawal due to AEs than other frequently-used antidepressants. In the more conservative, frequentist analysis of acute remission rates, vortioxetine was statistically significantly superior to agomelatine (mean difference -11.0%, 95% CI: -19.4% to -2.6%, see also Table B36) the other three comparators. In the frequentist analysis of withdrawals due to AEs, vortioxetine was statistically significantly superior to sertraline and venlafaxine and numerically superior to agomelatine and citalopram (see Table B37).

In sensitivity analysis using a Bayesian mixed-treatment comparison, vortioxetine was the antidepressant most likely to give rise to remission in 68-73% of Bayesian simulations, when compared to agomelatine, sertraline, venlafaxine SR and bupropion. Simulated patients were less likely to withdraw due to adverse events if treated with vortioxetine than with other treatments, and statistically significant so for the comparisons with sertraline, venlafaxine

and bupropion. Simulated patients treated with vortioxetine were the least likely to discontinue because of AEs, and remained on treatment in 93% of simulations.

In conclusion:

- Vortioxetine is effective and generally well-tolerated in a population of adults with MDEs who have switched following inadequate response to initial treatment with an SSRI or SNRI.
- This finding is supported by direct and indirect evidence from well-conducted RCTs.
- Vortioxetine was superior to agomelatine on the clinically relevant outcome of remission rate in a head-to-head comparison and numerically superior to the most commonly used SSRIs and SNRIs in indirect comparison.
- Vortioxetine was numerically superior to citalopram and statistically superior to sertraline and venlafaxine with respect to withdrawal rate due to adverse events, in indirect comparison.

These direct and indirect findings are consistent with pharmacological evidence that vortioxetine may be especially suited to use in switch patients.

6.10.2 Strengths and limitations of the evidence base

6.10.2.1 REVIVE

Given that a large proportion of patients fail to achieve remission on their initial therapy, switch therapy for MDEs is a poorly studied area. REVIVE was a large (501 patient), well-conducted, randomised, double-blind trial, and is the first prospective, randomised, double-blind study to find an advantage of one class of antidepressants over another in inadequate responders. It provides for the first time sound evidence that informs about the management of inadequate response²⁶. The benefits of vortioxetine emerged early and the magnitude of the significant difference seen at 3 or 4 weeks was similar at 8 and 12 weeks, suggesting that these benefits were sustained. The data show that depressive symptomatology improves at least until week 12 and also suggest that useful information concerning treatment may be obtained in studies with follow-up as short as 4 weeks.

The robustness of the finding that vortioxetine was superior to agomelatine on the primary endpoint (MADRS total score after 8 weeks) was confirmed by the consistent demonstration of superiority of vortioxetine on the secondary efficacy analyses and by the significant findings on the overall functioning and HRQoL measures. Differences in EQ-5D index values in favour of vortioxetine reached significance from week 4 and persisted through to the end of the study at week 12. The summary data are underpinned by the reporting of problems on EQ-5D domains, with improvements mainly in anxiety/depression but also pain/discomfort and usual activities (Figure B8). Differences seen in scores on the Sheehan Disability Scale (SDS) and the Depression Family Functioning Scale (DFFS) represent important extrapersonal outcomes favouring vortioxetine that may not be captured by the EQ-5D.

Aside from efficacy considerations, short- and longer-term tolerability are important if patients are to follow their physicians' advice to continue treatment for at least six months after remission to minimise the chance of relapse. In this respect, the comparators were similar in the incidence of adverse events, but fewer patients withdrew because of them in the vortioxetine group at 5.9% vs. 9.5% in the agomelatine group. The possibility that differential rates of dropout could have introduced bias was mitigated by the robustness of the base-case (MMRM) efficacy assessments to sensitivity analyses (LOCF and OC).

The characteristics of the study population were similar to the switch patients in PERFORM, a naturalistic, observational study sponsored by Lundbeck, except that the study population in REVIVE was almost entirely Caucasian.

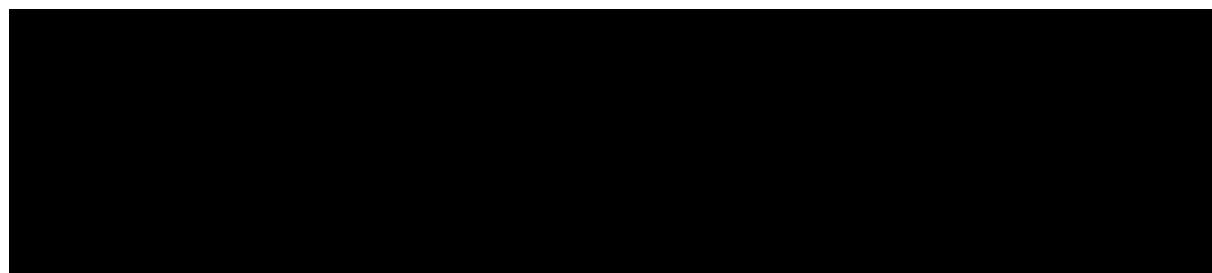
REVIVE reflected clinical practice in that inadequate response was based on physician judgement and patients had to agree to switch, although inadequate response did not include intolerability, which is also a frequent reason for switching in clinical practice. However, as vortioxetine has demonstrated a favourable tolerability profile in both the switch studies and studies in a full MDD population, it is also an appropriate option for patients who switch due to intolerability of their initial treatment. With respect to generalisability to prescribing practice in patients who fail initial treatment, in the trial patients on either an SSRI or SNRI were eligible, whereas market data reveal that the first-line use of SNRIs in the UK is negligible. In the trial, most patients (76%) had received an SSRI, and subgroup analysis showed no difference in results by pre-treatment antidepressant class.

Another limitation of REVIVE relates to the choice of comparator, as agomelatine has minimal use in UK practice. In addition, NICE is unable to recommend the use of agomelatine for the treatment of MDD because no evidence submission was received from the manufacturer. Nevertheless, the choice of agomelatine as an appropriate comparator is supported by its atypical (non-SSRI/SNRI) mode of action and the findings of recent meta-analyses^{31,102} and NICE surveillance¹⁰¹.

Since the intention of treatment is that a patient will continue to take the prescribed antidepressant for as long as necessary to achieve and consolidate remission, the 12 weeks' follow-up of REVIVE is short compared to the recommended duration of treatment but consistent with trials in MDD. Moreover, this shortcoming is mitigated by the findings of relapse-prevention trial (Study 11985A)²¹⁶, which demonstrated 50% fewer patients treated with vortioxetine relapsed vs. placebo (13% vs 26%, $p=0.0013$).

6.10.2.2 TAK318

TAK318 was also a large (447 patients), double-blind, randomised trial. While patients in REVIVE were switched because of lack of efficacy, patients in TAK318 were well-treated on entry to the study and switched because of a treatment-emergent side-effect: sexual dysfunction. The study addressed an important clinical question, because sexual dysfunction (decreasing desire, arousal, orgasm, and satisfaction) in both men and women is experienced by 24% of patients receiving antidepressant monotherapy²¹⁷. The upper age limit was lower at 55 years than REVIVE, which recruited patients up to 75 years old. Unsurprisingly, therefore, TAK318 recruited participants who were, on average, younger than those in REVIVE (39 vs. 46 years). They also had a more even sex balance (60% vs. 75% female) and were more ethnically diverse (80% vs. 99.8% Caucasian). Although the study, which recruited well-treated patients, was not designed to allow conclusions to be drawn about comparative efficacy in achieving remission, it did show that vortioxetine sustained remission as well as escitalopram, while achieving a significantly greater improvement in sexual functioning in comparison to this well-tolerated SSRI, reported to be the most effective antidepressant in its class¹⁰¹.



Another limitation of TAK318 in the context of this STA is that escitalopram is not commonly used in the UK in patients experiencing SSRI-induced sexual dysfunction, even though it has been associated with lower rates of sexual dysfunction than other members of this class²¹⁵. 99 (22%) of the 447 randomised participants withdrew from the study for a variety of reasons (see CONSORT flow diagram in Figure B6). However the dropout rate in TAK318 is similar to other studies in MDD^{106,218}.

6.10.2.3 Indirect treatment comparison

As described earlier in this section, the studies on which the ITC was based were qualified by means of a systematic literature search and review. To ensure the applicability of relative treatment effects to the decision problem, the search was designed to retrieve trials in the 2nd line (switch) population. This review involved careful selection of studies that were sufficiently robust and comparable, while attempting to include all relevant comparators for the study question. The resulting network allows the indirect comparison of the outcomes of interest between vortioxetine, sertraline, venlafaxine and citalopram, and supplements the head-to-head data between vortioxetine and agomelatine. These data provide the necessary inputs to populate the economic model (Section 7).

Due to the scarcity of the data in the switch population defined in the decision problem, the network and associated ITC have limitations. The links between treatments are made through single trials; moreover, comparisons of vortioxetine to other treatments are only possible through multiple indirect comparisons (except for agomelatine). These aspects of the network led to uncertainty in the results, as reflected in the width of the confidence intervals. The number of trials retrieved and included is, however, consistent with previous systematic reviews conducted within the switch population. Lundbeck believes the ITC is founded on the best available data.

There are other aspects which introduce heterogeneity into the network and hence may affect the results. For instance, Kasper (2013) provides the data for agomelatine vs. sertraline and placebo (Kasper 2010, Olié and Kasper 2007, respectively). In this publication, a post-hoc analysis was undertaken which provided the data for the “previously treated” population. This population was defined as patients receiving any antidepressant treatment within the previous 12-month period. This criterion may have allowed patients who were not necessarily switching antidepressants within the current episode to be included in the study. Therefore the population in Kasper 2013 may be slightly wider than those of the other trials. A conclusion on the impact on the estimates of relative effects cannot be drawn. In such a post-hoc analysis, randomisation is not strictly preserved, but expert health economists and statisticians considered this to be a theoretical rather than practical consideration and therefore did not expect it to be an effect modifier.

Another challenge was the difference in outcome measures and their reporting. Some authors reported efficacy as remission rates and others as change from baseline in depression symptom score; Kasper 2013 provided only the latter. A calculation was therefore undertaken to convert the depression symptom scale total scores reported within the trials into remission rates. After consideration of several options in terms of distributional forms, the approach providing the most conservative results for vortioxetine versus other comparators was selected for the base case (normal distribution). Supporting the accuracy of this analysis, the efficacy of agomelatine calculated from Kasper was comparable to that observed in REVIVE and with remission rates of 27.9% and 29.5% respectively.

Furthermore, whilst the scales used to measure remission were different between studies, it is nevertheless generally accepted that the HAM-D and the MADRS are highly correlated¹⁹⁷

and composite endpoints based on both scales have been used in meta-analyses in MDD patients.

It was necessary to accommodate variation in the timing of the primary assessment point, which took place at between 6 and 14 weeks in the included trials. Allowing a range is common practice in data syntheses and was not expected to be an effect modifier with respect to relative effectiveness. Justification is provided by the findings of REVIVE²⁷, in which the difference between vortioxetine and agomelatine in change from baseline of the total MADRS score was almost constant at the week 4, week 8 and week 12 (end of study) assessment points (see Figure B7).

The time-point for reporting withdrawals due to AEs also differed between studies. However, this again was not expected to affect relative treatment effects greatly as most withdrawals due to AEs occur within 2-4 weeks of starting treatment.

Although there were some differences in the baseline characteristics of patients between studies, it is not expected that bias is introduced as the difference between treatments is not affected by these. In the REVIVE study, the interaction between key baseline characteristics and the treatment effect were explored. Within the pre-specified subgroup analyses the following baseline characteristics were tested as dichotomous variables:

- Sex
- Age (≤ 50 , > 50 years) and (< 65 , ≥ 65 years)
- Baseline MADRS (< 30 , ≥ 30)
- Baseline HAM-A (< 20 , ≥ 20)
- Previous SRI treatment (SSRI or SNRI)

None of the interactions between these baseline characteristics and the change from baseline in MADRS was statistically significant, indicating that the treatment effect is not altered by these baseline characteristics. Expert clinical opinion also supported that these factors would not affect relative effects.

Initial antidepressant treatment within the trials was also consistent with UK clinical practice and NICE CG90. The majority of patients in all studies received an SSRI as first line therapy (100% of patients enrolled in STAR*D and Lenox-Smith) reinforcing the external validity of results.

Despite the potential weaknesses within the network, the ITC provides valuable, relevant and applicable data on the relative efficacy and tolerability of vortioxetine versus sertraline, venlafaxine and citalopram, the most widely used SSRIs and SNRI in the UK in the switch population in addition to the comparison to agomelatine. The effect of the uncertainty around the ITC results on the cost-effectiveness of vortioxetine is explored through sensitivity analyses (Section 7.6.1 below).

6.10.3 Relevance of evidence base to decision problem

The evidence presented in section 6.3 above is directly applicable to the population defined in the decision problem: *“adults who are experiencing a moderate-to-severe MDE, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who wish to switch to another antidepressant”*. The systematic reviews undertaken specifically looked to identify data which are relevant and applicable to this specific subgroup of the MDD population

It is uncommon for pharmaceutical companies to commit to head-to-head trials before the completion of regulatory programmes to confirm safety and efficacy. Lundbeck initiated, in

parallel with the regulatory programme for vortioxetine, two such trials to investigate its effectiveness in switch patients: REVIVE and TAK318. These are the trials most relevant to the decision problem with respect to efficacy endpoints: REVIVE provides inputs to the economic evaluation described in Section 7. The open-label, long-term safety extension studies are also relevant in that they provide longer-term pooled data on AEs and withdrawals due to AEs. They complement the short-term AE data from REVIVE, which also together provide inputs to the economic model.

While REVIVE was primarily an efficacy study, TAK318²⁸ was concerned with a common²¹⁷ and troublesome²¹⁹ side-effect of antidepressants, treatment-emergent sexual dysfunction (TESD). TESD is experienced by 24% of patients receiving antidepressant monotherapy²¹⁷ and may manifest as decreasing desire, arousal, orgasm, and satisfaction, in both men and women. It can interfere with patients' willingness to remain on antidepressant treatment over the maintenance phase after initial remission and is therefore relevant to the decision problem.

The indirect treatment comparison was highly relevant to the decision problem in that it allowed estimates of the comparative efficacy and tolerability of vortioxetine in switch from a head-to-head comparison with agomelatine, as provided by REVIVE, to include other antidepressants frequently used in UK switch patients: sertraline, citalopram and venlafaxine.

6.10.4 Factors influencing external validity of evidence base

As previously stated, relative efficacy data for the use of vortioxetine in broad MDD is not seen as transferable to the switch setting (see section 6.1). It is for this reason that REVIVE provides the most externally valid efficacy evidence to support the decision problem. TAK318 also provides relevant evidence but in a subgroup of switch patients: those who are well-controlled but experiencing a specific side-effect, TESD. As for tolerability, clinical expert opinion advised that the transferability of data from the broad to switch populations was acceptable.

With respect to dosage used in the trials of vortioxetine, the flexible dosing of vortioxetine (10-20mg per day) reflects the posology in the SmPC for adult patients. The only evidence that is discrepant from the SmPC posology is for the AE data from the pooling of five long-term safety extension studies. A small proportion of the pooled patients were in studies (301 and 11984B) that included a 2.5mg per day dose of vortioxetine. The flexible-dose study design makes it difficult to split out the 2.5mg dose but as the proportion of patients receiving this dose was small it is not expected to affect the results.

The pragmatic design of REVIVE is likely to have enhanced its external validity. Eligibility of patients was based on factors similar to those that pertain in clinical practice. As discussed by the authors of the primary publication²⁶, the relevant population of inadequate responders was ensured by including patients nonpartially or partially responsive to a single treatment course of one of six commonly prescribed SSRIs/SNRIs optimised with respect to duration and dose. The patients also wished to change their current treatment and were considered by the investigators to be candidates for a switch. A direct switch was chosen to reflect normal clinical practice. Certain characteristics of the REVIVE (ethnic composition, exact definitions of reasons for switching and prior treatment) were discussed in section 6.10.2.1 above, but these did not constitute major concerns for external validity in the opinion of clinical experts.

EQ-5D utility data were collected in REVIVE and valued using the UK tariff. The data analysed by health state were in close agreement with those from a prospective cohort

study¹⁸ of French primary care patients, suggesting that the REVIVE study is externally valid in terms of HRQoL as well as clinical outcomes.

The baseline characteristics of patients included in the ITC were comparable to the UK PERFORM cohort and represented UK MDD demography well, in the opinion of clinical experts. Ethnicity was the only unrepresentative characteristic; the REVIVE cohort was 100% Caucasian. This factor does not lessen the external validity of the study or results of the ITC, as the efficacy of vortioxetine did not differ by race in subgroup analyses of the full MDD package.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

A detailed search strategy is provided in Appendix 10.

A systematic literature review was conducted in order to identify existing economic evaluations evaluating vortioxetine (Brintellix®; Lu AA21004; 508233-74-7) pertinent to the decision problem investigating the cost-effectiveness of vortioxetine in adults experiencing an inadequate response to a previous SSRI or SNRI for the treatment of an MDE.

Vortioxetine and its alternative names were included in a search strategy that incorporated disease terms consistent with the searches in section 6. Population related searches included, but were not limited to, a switch population as this was expected to further reduce the search results as full MDD models may consider more than one treatment line.

In addition to these terms, database-specific search filters were added to capture cost-effectiveness analyses based upon the validated filter terms published by the Centre for Reviews and Dissemination²²⁰.

The searches were limited to human studies, not restricted by language or geographical scope published since 2000. This cut-off was applied in order to capture the data the manufacturer filed for the patent for vortioxetine (2001). Searches were conducted on 29 May 2014 in MEDLINE, MEDLINE In-Process, Embase, EconLit, PsycInfo, the Health Technology Assessment (HTA) database, the National Health Service's Economic Evaluations Database (NHSEED), and the Cochrane Database of Systematic Reviews (CDSR), as displayed in Appendix 10 (section 10.10.1).

Screening was performed by two researchers independently and according to pre-set criteria for Population, Intervention(s), Outcome(s) and Study design (PIOS). Upon disagreement on the relevance of an abstract between the two reviewers, a third reviewer would assist to attain a consensus decision, as recommended in the CRD guidelines for systematic reviews. The criteria were defined by the decision problem and are presented below:

- The population for inclusion was adults with major depressive disorder or experiencing major depressive episodes.
- The intervention of interest was vortioxetine. Evaluations without a vortioxetine-based regimen were excluded. Outcomes of interest were the results from economic evaluations (including cost-utility, cost-benefit, cost-effectiveness, cost-consequence and cost-minimisation analyses). Results should be presented as incremental ratios in a cost per event, cost per QALY or cost-benefit format.
- Study designs for inclusion were economic evaluations and reviews of economic evaluations (to source the original studies). Resource use studies were also flagged separately within the search because these would be useful for the model.

7.1.2 Description of identified studies

Twenty-eight potentially relevant publications were identified from the systematic review, of which 26 were excluded on the basis of title or abstract. After a full-text review of the remaining two studies, both were excluded as no cost-effectiveness analysis was reported (Table B45). The absence of relevant publications was expected as vortioxetine has been

developed only recently. The flow diagram in Figure B20 details the study selection process, which was conducted in accordance with PRISMA guidelines^{221,222}.

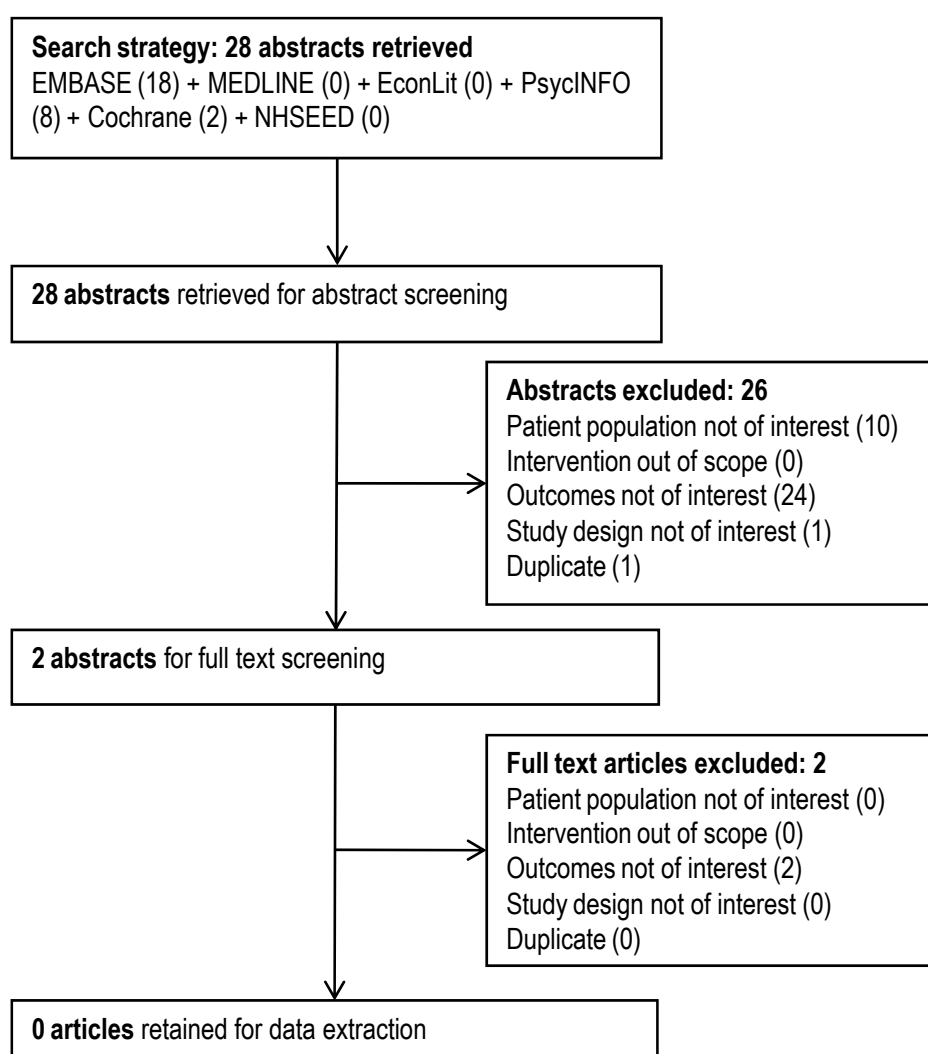
Table B45. Cost-effectiveness articles excluded following initial screening

Study details	Reason for exclusion
Chamberlin, 2014 ²²³	Outcomes out of scope: no CEA
Lincoln, 2014 ²²⁴	Outcomes out of scope: no CEA

7.1.3 Quality assessment

No suitable studies were identified on which quality assessment could be performed.

Figure B20. PRISMA flow diagram of the selection process for cost-effectiveness studies



7.2 De novo analysis

7.2.1 Patient groups

As discussed in previous sections, substantial proportions of patients either fail to respond adequately to an initial antidepressant or experience intolerable side-effects, either of which event is likely to lead to the decision to switch to an alternative antidepressant (see Figure

A9). Little clinical evidence, nor economic evidence, exists concerning the optimal choice of antidepressant switch treatment. However, CG90 recommends use of a “*newer generation, better-tolerated antidepressant*” when switch is required (see Figure A7), and clinical opinion supports the rationale for a trial of an agent with differing pharmacological and side-effect profile to the initial prescription. Vortioxetine meets these criteria, being newly marketed, offering distinct, multimodal mechanisms of action and having demonstrated a favourable side-effect as well as efficacy profile, as described earlier in this submission. Therefore, the patient group considered in the present economic evaluation consists of patients as described in the decision problem, as follows:

“Adult patients with moderate-to-severe MDD who are experiencing an MDE, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to alternative antidepressant”

This population is referred to as the “**switch population**”.

The switch population is more restricted than the licensed indication described in the SmPC (see section 1.3), in that it excludes patients receiving their first antidepressant within the current episode. This restriction has important implications for the choice of clinical evidence to support the economic evaluation. As described in section 6, only trials of vortioxetine in a switch population are considered to provide relevant effectiveness evidence. Although vortioxetine has been extensively studied in adults with MDD, there are only two trials in pre-specified switch populations. One of these (Study TAK318) concerns well-treated patients who switched following emergence of one specific side-effect of initial treatment, i.e. sexual dysfunction. The other one (study 14178A, REVIVE), studied patients who switched as a result of inadequate efficacy to initial treatment with SSRIs or SNRIs. Therefore, REVIVE provides the main source of comparative evidence for efficacy and tolerability of vortioxetine versus agomelatine in the submitted model. The ITC (see Table B36 and Table B37 in section 6.7.6) allow the inclusion of additional antidepressants in the set of data to populate the model.

7.2.2 Diagrammatical representation

A diagrammatical representation of the model is provided in Figure B21 and Figure B22. The model is a decision tree with a Markov component to model subsequent treatment switches to third and later lines. The decision tree describes the possible pathways patients may follow on entry to the model (Figure B21). The tree includes an **acute phase** of treatment of 8 weeks (months 0-2), a **maintenance phase** of 6 months (months 2-8) and a **recovery phase** (months 8-12). The amount of time patients spend in the tree is variable and depends on whether treatment is successful in each phase. If treatment in all three stages is successful, with remission being achieved and sustained to recovery at the 12-month model horizon, the entire 12 months is spent in the tree. However, the model also includes events in which treatment is not successful. These lead to a further switch, i.e. to third-line treatment. During the acute phase, the modelled events leading to switch are withdrawal due to short-term side-effects and failure to achieve remission. Patients not completing the acute phase successfully leave the decision tree and enter a Markov model with a 2-month cycle length. These patients leave the tree early and enter the Markov model. The specific reasons and sequences of events determine the time at which these patients are assumed to leave the tree. Similarly, during the maintenance phase switching treatment is modelled.

Figure B21. Decision tree for modelled events before possible switch to third line

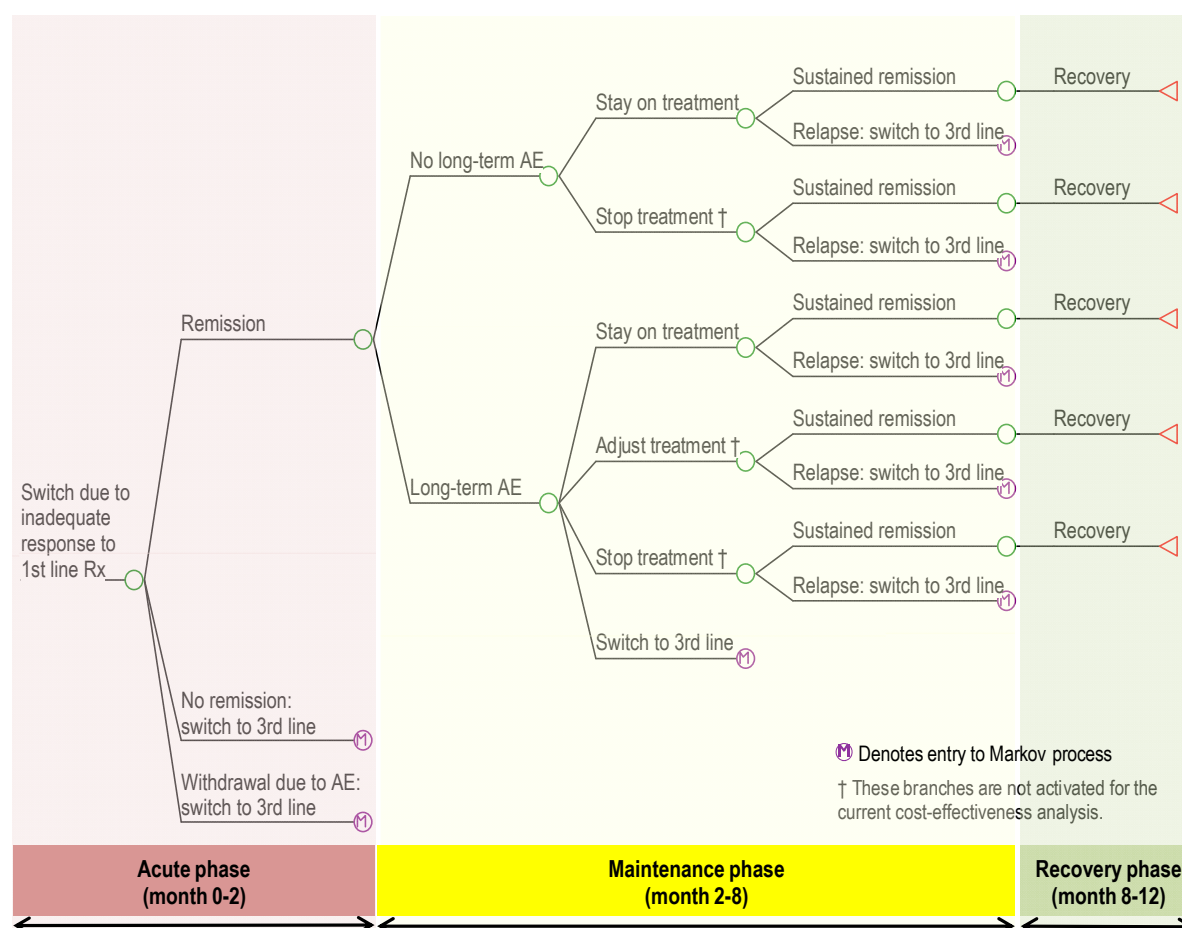
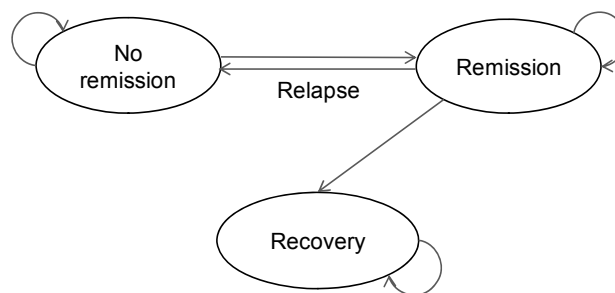


Figure B22. Markov state transition diagram for modelled events following switch to third line

7.2.3 Correspondence to clinical pathway

The structure of the economic evaluation is intended to be consistent with the clinical pathways described by NICE CG90, particularly those for switching, as summarised in section 2.5.1 and Figure A5, subject to the points noted below. The clinical starting point is inadequate response (lack of efficacy or intolerability) to an initial antidepressant in adult patients who wish to switch (the portion of Figure A5 shown in red). The relationship between the model, the clinical course of MDEs and CG90/NICE Pathways is more fully explained in section 7.2.5.

The model structure was validated by UK health economists and clinicians (expert psychiatrists, GPs and pharmacists). It differs in some respects from the economic model included in CG90. The main differences between the two models are the modelling of the acute phase, the inclusion of further lines of therapy and the addition of adverse events with the latter two addressing limitations recognised by CG90. In Table B46 the rationale is detailed for the differences in model structure.

Table B46. Rationale for differences between submission model and CG90 model

Model specification	NICE CG90	Submission model	Rationale for difference
Health state(s) modelled after acute phase	Response (symptom reduction of >50%)	Remission (HAM-D total score <7; MADRS < 10)	While response is a valid initial treatment objective, remission is the consensus treatment goal for most patients, and is the most frequently used efficacy outcome in other CEAs ³⁴⁻³⁶ . We understand that the choice of response as the CG90 model's efficacy outcome was in part dictated by the data reported in the Cipriani review. Clinical opinion suggests that for a small proportion of patients (those difficult to treat or very severe) response may be considered a more realistic treatment goal and such patients may not be switched at 8 weeks if they have achieved response but not remission. The impact of assuming no switch at 8 weeks given response but no remission is explored in a sensitivity analysis to the base case CEA (section 7.6).
Spontaneous response	Assumed that 20% of patients would spontaneously respond	No spontaneous response is modelled	Spontaneous response is expected to be captured within clinical trial reported results. There is also no evidence for differential spontaneous response between treatments, therefore no impact on incremental cost and QALY calculation was expected.
Further lines of therapy	For patients who did not complete initial therapy, no specific treatments were considered after discontinuation	For patients who do not complete initial therapy, further lines of therapy are considered.	Treatment switching is common in depression due to inadequate response (lack of efficacy and/or tolerability). CG90 recognised that a limitation of its associated model was that this aspect of the condition was not incorporated.
Adverse events	No AEs were specifically modelled	Common treatment-emergent AEs are modelled	AEs associated with antidepressant treatment are widely recognised as troublesome for patients. It is recognised in CG90 that adverse events are associated with treatment discontinuation, poor adherence and HRQoL. The utility impact of AEs has been modelled in line with NICE requirements to capture all aspects of HRQoL associated with treatment.

7.2.4 Events, health states and transitions

The events and health states in the model were defined to correspond to conventionally-defined clinical outcomes associated with MDEs and their treatment. Specific events and health states are shown in **bold** and *italic text*.

7.2.4.1 Clinical starting point

Depression is the health state at model entry and represents the baseline state of trial cohorts who experienced inadequate response to initial treatment in the current MDE who are switching to a different antidepressant.

7.2.4.2 Side-effects and tolerability

The model includes short-term and long-term treatment side-effects. **Short-term side-effects** corresponded to AEs recorded in clinical trials during the first 8 weeks of treatment before remission was assessed. Short-term side-effects modelled are those most frequently reported with antidepressants. The range was validated according to clinical guidelines^{10,90} and Cochrane reviews of antidepressants^{10,90,215,225}.

- Diarrhoea
- Dizziness
- Dry mouth
- Headache
- Insomnia
- Nausea
- Sexual dysfunction
- Somnolence
- Sweating

Long-term side-effects are modelled between 2 and 8 months for patients who are on treatment and in remission, and correspond to long-term AEs recorded in clinical trials. These AEs include:

- Insomnia
- Sexual dysfunction
- Weight gain

7.2.4.3 Effectiveness

The definitions of the modelled health states **remission** and **recovery** correspond to consensus definitions^{57,59}. Remission is accepted as an important measure of effectiveness, as it represents a resolution of symptoms to below the criterion for a diagnosis of an MDE, and is the most-frequently used effectiveness outcome in recent economic evaluations³⁴⁻³⁶. In clinical trials, remission is defined by a score on the threshold of normality using a standardised instrument¹⁸⁶. In the model, **remission** is the health state corresponding to the remission of symptoms assessed after 8 weeks of treatment. At this point, patients may be in remission or not in remission (due to lack of efficacy or intolerable side-effects). If they are not in remission, patients remain in the acute phase and switch to a third line of therapy.

During the maintenance phase, patients who achieved remission were at risk of **relapse** for the next 6 months. The model includes a **recovery** state for subjects who maintained remission for 6 months. Patients who do not maintain remission (i.e. relapse) occupy the **no remission** state and move to a further line of treatment.

Patients in remission are assumed to remain on treatment for 6 months after remission has been achieved in the acute phase (i.e. 8 months for those who remit and recover after second-line therapy with no further switching) unless the patient experiences a long-term side-effect (insomnia, sexual dysfunction and weight gain), which may interfere with treatment continuation; in case of such long-term side-effects patients may switch to a third line of therapy (as in the acute phase). A proportion of patients who do not encounter long-term side-effects may also decide to stop treatment.

Patients who switch to third-line treatment, whether in the acute phase or the maintenance phase following remission, enter the recursive, Markov part of the model. Here, in a given cycle patients may either remain not in remission or achieve remission. In the following cycles, patients who have achieved remission may sustain remission for up to 6 months after achieving this health state or relapse. Once patients have sustained remission, they then move to **recovery** which is modelled after month 8 until month 12.

Table B47 displays the initial state and the duration spent in the different treatment phases based on possible pathways through the model. For example, if at 5 months a patient relapsed after being in remission, the 5 months would have consisted of two months in the acute phase followed by 3 months in the maintenance phase. Due to relapse the patient would then switch to another line of treatment and the remaining time horizon for this patient would be 7 months. As stated above, utilities and costs associated with switch to third and subsequent lines (up to line 5) of therapy were calculated using a Markov approach. If, for example, a patient switched due to a short-term adverse event the modelled pathway would be as follows; one month of the cost and utilities related to switch occur during the acute phase and the remaining arise in 11 months from the Markov part of the model (2 months of acute phase and 6 months of maintenance phase in case of a successful treatment). Following the maintenance phase, patients are modelled to enter the recovery state, when they are assumed to receive no further treatment.

Table B47. Disposition of 12-month time horizon according to events in the acute stage of the model

Pathway	On initial therapy (2 nd line): Time (months) spent in				Health state at start of 3 rd line treatment	After switch to 3 rd line: Time (months) spent in			Total time horizon (months)
	<i>Acute phase</i>	<i>Maint- enance phase</i>	<i>Recov- ery</i>	Total in tree		<i>Acute phase</i>	<i>Mainten- ance phase</i>	Total in Markov model	
<i>Remission</i> at 8 weeks:									
Sustained remission	2	6	4	12	n/a	n/a	n/a	n/a	12
Relapse	2	3	-	5	<i>No remission</i>	2	5	7	12
Switch (long-term AEs)	2	1	-	3	<i>Remission</i>	n/a	6	9	12
<i>No remission</i> at 8 weeks:									
Switch (lack of efficacy)	1	NA	-	1	<i>No remission</i>	2	6	11	12
Switch (short-term AEs)	1	NA	-	1	<i>No remission</i>	2	6	11	12

Note: ***Bold italic*** text denotes model phases and health states. AEs: adverse events.

7.2.5 Context of the model

The model reflects the episodic nature of MDD. As discussed in section 2.1, although patients with MDD may experience repeated episodes (i.e. MDEs) interspersed with periods

in which they are symptom-free or subclinical, the present model is intended to represent the course of a single episode only, because its purpose is to analyse the cost-effectiveness of antidepressants for the switch treatment of a single MDE. The time horizon of 12 months is appropriate for this purpose, as patients who recover from an episode normally do so within that period.

As described in section 2.1, treatment of an MDE involves a sequential set of objectives: initial response, remission contingent on response and, finally, recovery contingent on remission⁵⁷⁻⁵⁹. The section of CG90 informing the *Pathways* diagram specifies that patients should be reviewed every 2-3 weeks for the first 3 months for continuing response. In the model, remission is assessed at 8 weeks, which corresponds to the 8-week assessment visit in clinical trials of vortioxetine, and appears fully consistent with the intent of CG90. The final goal of treatment is to consolidate remission by continuing treatment until the patient is considered to have achieved full recovery. Recovery is assessed in the model at the end of the 12-month time horizon, again consistent with CG90 and with “*Continuation and relapse prevention*” in the NICE *Pathways* diagram.

These transitions between health states and the possibility of side-effects are accompanied by fluctuations in HRQoL experienced by patients. The model captures the trajectory of patients’ HRQoL as utility values, as discussed in section 7.4.2 below.

7.2.6 Key features and assumptions

Other key features of the model are summarised in Table B48.

Table B48. Key features of the cost-effectiveness analysis

Factor	Chosen values	Justification
Time horizon	12 months	Coincides with clinical evidence for single MDE, consistent with other models. No evidence available to support extrapolation to recurrent MDEs or longer-term outcomes, or for mortality differences.
Cycle length	2 months	No data to support shorter cycles.
Half-cycle correction	Yes	This is applied in the calculation of the Markov utilities in the switch model. A half-cycle correction is used when it is not known when the transitions occur within the cycle. Therefore it is assumed that on average they will occur about half-way through the cycle.
Outcome measure	QALYs	NICE reference case.
Discount of 3.5% for utilities and costs	Not applicable	Time horizon of one year only.
Perspective	NHS/PSS	NICE reference case.
N.B. 1 month is taken as equivalent to 4 weeks. MDE: major depressive episode.		

A number of simplifying assumptions were necessarily made where lack of data precluded a more detailed representation of the clinical pathway.

1. While the possibility of suicide attempts is a concern for clinicians treating MDD, no attempt is made to model suicide attempts. No differences between active drug and placebo in the risk of attempted or actual suicide were seen in pooled analyses of trials of venlafaxine ER and citalopram²²⁶, and no differences were expected between modelled comparators.

2. As per CG90, initial clinical response is normally assessed approximately 2-3 weeks after treatment initiation, to allow dosage adjustment or early switching in the event of lack of response or intolerable side-effects. The model does not incorporate initial response because remission is considered to be the primary clinical outcome of interest. Moreover, the summarised level of reporting of clinical trials of comparators does not allow back-calculation of conditional probabilities of remission at 8 weeks contingent on prior events such as response. Therefore, the data available did not allow such a model structure incorporating both response and remission. However, a sensitivity analysis was designed to approximate the effect of a proportion of patients who respond but do not achieve full remission at 8 weeks to remain on initial switch treatment.
3. Dosage titration is not explicitly modelled but is accounted for by use of average dosages reported in publications of clinical trials included in the ITC, all of which allowed dosage to be optimised.
4. Where remission occurs with antidepressant treatment, clinical opinion suggests it is usually achieved within 6-12 weeks. In the model, remission is assessed at 8 weeks, based on expert clinical opinion.
5. Remission is assumed to be independent of the occurrence of short-term adverse events.
6. Switch contingent on short-term side-effects is assumed to occur at week 4 after treatment initiation. Associated disutilities are applied for 3 weeks in the base case, but are reduced to 1 week in a sensitivity analysis. These assumptions were informed by clinical expert opinion. Literature and clinical opinion indicate that long-term side-effects can lead to treatment switching, which were reflected in the model. These events were modelled to occur during the maintenance phase and were assumed to trigger switch after one month in the maintenance phase.
7. Premature stopping of treatment (other than due to intolerable AEs) is not modelled, as it was not expected to differ by treatment, nor was any evidence was available for between-treatment differences.
8. Patients who do not relapse after 6 months on maintenance treatment are defined as in recovery. They stop treatment and, as a simplifying assumption, are considered to be at no risk of recurrence between that point (a minimum of 8 months) and the 12-month time horizon.
9. Switch to a third, fourth and fifth line of therapy is modelled as a standardised, blended pathway representing clinical practice. The efficacy assumption is specific to treatment line. No attempt was made to vary the pathway according to treatment arm or the nature of the event leading to switch.
10. While depression is typically a recurrent condition, insufficient information is available to infer differential relapse rates between vortioxetine and the comparators, and rates are assumed to be equivalent⁵.
11. A patient experiencing an AE is assumed to have a probability of 30% of consulting a GP in the base case, based on clinical expert opinion reflecting the variability of types of AEs and severity. This value is varied in sensitivity analyses.
12. Costs of drugs used in the acute phase are taken from the WHO DDD, while in the maintenance phase they are based on the average end-of-study dosage reported in the trials included in the ITC.

7.2.7 Concordance of modelled interventions with marketing authorisation

The interventions compared are vortioxetine, sertraline (an SSRI), citalopram (an SSRI), venlafaxine (an SNRI) and agomelatine (a melatonergic-acting agent). All interventions are compared at dosages consistent with the clinical evidence used to derive inputs for effectiveness and side-effects. The dosages were also consistent with the marketing authorisations of all comparators except citalopram, for which the study¹⁹³ providing clinical evidence used an average dosage of 51mg per day, while the UK marketing authorisation is for a maximum dosage of 40mg per day. This discrepancy does not materially affect the

relevance of the trial to the decision problem, because dose response is flat and only acute-phase withdrawals due to adverse event rates were taken from this study; short- and long-term adverse event rates were sourced from alternative sources.

7.2.8 Clinical continuation rules

No clinical continuation rules are specified within the SmPC. In clinical practice, patients receiving antidepressants are given approximately 8 weeks to achieve remission; if this is not achieved an alternative antidepressant is offered. The model reflects this practice by incorporating an assessment point at 8 weeks and contingent pathways including further switch (see section 7.2.2 above).

7.3 Clinical parameters and variables

7.3.1 Clinical data sources

The main clinical data source for vortioxetine is a head-to-head phase IIIb study, 14178A (REVIVE), which compared the efficacy of vortioxetine vs. agomelatine in patients who switched due to lack of efficacy of an SSRI/SNRI. REVIVE provided the vortioxetine data on remission rates and discontinuation rates due to AEs for the population of interest in the model, i.e. those who switch due to inadequate response to previous treatment. Health state utilities (EQ-5D, UK tariff) during the acute phase were also derived from this study.

An ITC (as detailed in Section 6.7) provided comparative data for acute phase remission rates and withdrawals due to AEs for the following antidepressants in the switch population:

- Vortioxetine
- Agomelatine
- Sertraline
- Venlafaxine
- Citalopram

Clinical trials investigating long-term exposure to vortioxetine listed in section 6.9.2.1 were used to derive the probabilities of long-term adverse events with vortioxetine treatment. The remaining model inputs for the basket of comparators were obtained from the literature (see Table B49). Where possible, these were treatment-specific.

For subsequent treatment lines (lines 3 to 5), STAR*D (Rush 2006¹¹) was the main source of data on remission and relapse rates. This trial evaluated the outcome of four successive steps of antidepressant treatment in depressed patients recruited in primary and psychiatric care centres. This source was validated by expert clinical opinion.

Relapse rates after remission on antidepressants were obtained from Limosin 2004²²⁷, which recruited 476 depressed outpatients and examined their treatment outcome. 51 patients (14.2%) experienced a relapse whereas 308 patients responded to maintenance treatment over a four- to six-month period. The relapse rate was very close to the value reported in the relapse prevention study for vortioxetine (13.2%). Due to lack of published data, relapse rates were not treatment-specific in the model. In subsequent treatment lines relapse rates were derived from STAR*D. These were specific to the number of treatment lines, at 25.0% for line 3 and 42.6% for line 4. The values for line 4 was assumed for line 5, which was not studied in STAR*D.

7.3.1.1 Effectiveness outcome: remission

The principal model input for effectiveness in the acute phase was remission. The studies in the ITC that reported remission used either HAM-D or MADRS, and remission was defined as a HAM-D score ≤ 7 or a MADRS ≤ 10 , which are commonly accepted definitions^{201,228-230}. These cut-offs between HAM-D and MADRS for remission are equivalent¹⁹⁷.

7.3.1.2 Tolerability

Short-term AE data for vortioxetine and agomelatine were taken from Study 14178A (REVIVE). Corresponding probabilities for sertraline, citalopram and venlafaxine were taken from Cochrane reviews. Drug-specific Cochrane reviews provided comprehensive data on the tolerability of sertraline and citalopram (Cipriani 2010²²⁵ and Cipriani 2012¹⁶⁵). As no review was available for venlafaxine, the results for all venlafaxine arms in the above reviews associated with escitalopram, sertraline, duloxetine and citalopram were pooled in a similar manner.

For **long-term** adverse events, data for vortioxetine were taken from the long-term safety pool analysed by health state²¹⁴. For comparators, a single source was preferred insofar as possible.

For insomnia, no single source was identified. A relapse prevention trial of agomelatine (Goodwin 2009)²³¹ provided the probability of insomnia for the agomelatine arm, while values for sertraline, venlafaxine and citalopram were taken from Bet 2013²³², which investigated the side-effects of long-term use of antidepressants. Data specific to venlafaxine are provided in this study while for SSRIs only a pooled SSRI value was reported and this was applied to sertraline and citalopram.

Although Serretti 2009²¹⁵ provides data on sexual dysfunction for all the comparators considered, the studies included in this meta-analysis of TESD elicited responses that were prompted. The reported rates are much higher than would be expected from spontaneous reporting. Therefore, this source was rejected in favour of sexual dysfunction data from Bet 2013²³², except for agomelatine, where corresponding data were taken from Goodwin 2009²³¹.

With respect to weight gain, a single source of data²³³ was identified for sertraline, citalopram and venlafaxine. However, the values reported are inconsistent with the opinion of experts, who preferred the pooled SSRI and venlafaxine data reported in Bet 2013²³². Goodwin 2009²³¹ provided the corresponding data source for agomelatine.

Table B49. Summary of primary sources of model parameters

Parameter		Clinical trials (individual and syntheses)			Literature
		14178A (REVIVE) ²⁷	Pooled vortioxetine clinical data ²¹⁴	Indirect comparison	
Remission	Initial treatment	√		√	
	After switch to ≥ 3rd line				Rush 2006 (STAR*D) ¹¹
Relapse	Active treatment				Limosin 2004 ²²⁷
	Treatment 3rd line, 4th line and later				Rush 2006 (STAR*D) ¹¹
Side-effects	Short-term	√		√	Cipriani 2010 ²²⁵ , Cipriani 2012 ^{108,109,165}
	Long-term		√		Goodwin 2009 ²³¹ ; Bet 2013 ²³²
Resource use					Byford 2011 ²³⁴ , Taylor 2013 ²³⁵ , PERFORM) ^{19,20,236} NICE guidelines ¹⁰
Utility values		√			Sapin 2004 ¹⁸
Adverse event disutility values					Sullivan 2004 ²³⁷

7.3.2 Transition probabilities

Effectiveness in the model is determined by the two following parameters:

- A probability of remission after 8 weeks of antidepressant treatment (the **acute phase**)
- During 6 months of treatment after remission (the **maintenance phase**), a probability of relapse

Patients who relapse during the maintenance phase (assumed to be halfway through the maintenance phase) can switch to third-line treatment. These patients are then assessed for remission status 2 months after starting third-line treatment. The probability of relapse is governed by whether the patient is on or off treatment and is line- rather than treatment-dependent for lines 3, 4 or 5.

7.3.3 Variability of transition probabilities over time

As previously discussed, STAR*D provides evidence that remission (and response) rates diminish over successive lines of treatment¹¹, as shown in Figure A9. Hence, the model assumes the declining transition probabilities of remission observed in STAR*D¹¹ (see Table B50).

Table B50. Probability assumptions for remission rates after switching to third- and fourth-line treatment

Treatment line	Patients starting line	Patients achieving remission	Patients relapsing (probabilities calculated)
	N	n (%)	
Third line	390	53 (13.7%)	25%
Fourth line	123	16 (13.0%)	45.6%
Fifth line	N/A	Not reported in STAR*D. Assumed equivalent remission rate to 4 th line.	

Source: Rush 2006¹¹

In subsequent treatment lines, remission values vary for line three and four. However, no remission data are available in STAR*D for fifth line, which is therefore assumed to be equivalent to fourth line. STAR*D reports relapse in subsequent treatment lines as rates. These were converted to probabilities for the two month cycle length. As with remission, the values for relapse differ between third and fourth line, while the values for fourth and fifth line are assumed to be equivalent.

7.3.4 Intermediate outcomes

The efficacy outcome of **remission** rate at 8 weeks (i.e. at the end of the **acute phase**) is an intermediate outcome. It is linked to the outcomes of **remission** in the maintenance phase and the final outcome of **recovery**.

As described elsewhere in section 7, remission at 8 weeks is informed by the rates for each comparator taken from the ITC reported in section 6.7. The evidence from the ITC is derived from short-term trials and does not provide data to determine whether or not remission is sustained through the maintenance phase. Relapse data applied in the maintenance phase were derived from a separate study, Rush 2006¹¹, as described in section 7.3.3. Also, patients could experience long-term adverse events, which could lead to a further switch of treatment.

7.3.5 Clinical expert assessment of values

7.3.5.1 Approach used

The validity, internal and external, as well as the applicability of the evidence presented in the context of this submission, has been assessed, commented on, directed and validated by multiple UK experts including psychiatrists, GPs, mental health pharmacists and health economists. Three advisory board meetings prior to and during the development of this submission and the participation of external advisors is summarised in Table B51.

Table B51. Participation of experts in advisory board meetings

Role	Advisory Board 1	Advisory Board 2	Advisory Board 3
Health economist	3	2	3
GP or GP with mental health interest	3	2	-
Psychiatrist	3	2	1
Pharmacist with mental health interest	-	1	-

Along with review of the full dossier by health economists, the following specific aspects of the submission were discussed in depth, improved and validated through interactions with

health economists, psychiatrists and GPs. This included the structure and parameters of the cost-effectiveness model. In the main, experts were aligned in the approach taken. Key discussion points have been detailed below.

7.3.5.2 Modelling of effectiveness

Expert discussions of the approach to the ITC and potential impact on outcomes are discussed in section 6.7.

7.3.5.3 Modelling of adverse events

As part of the model validation process all aspects of the application of adverse events were covered. Initially, the adverse events included within the model were verified as being the most prevalent and troublesome for patients. Please see also certain assumptions listed section 7.2.6 above that relate to AEs.

Rates

The sources for the rates of adverse events were agreed as being the most comprehensive and relevant and the rates were checked to ensure alignment with that seen in clinical practice. All sources were validated as providing estimates which were reflective bar one. Initially, Uguz (2014)²³³ was presented as the source for weight gain. Clinical opinion did not support the rates detailed within this source as they were thought to be too high for products such as venlafaxine when compared to what is seen in clinical practice. It was thought that the small patient numbers in Uguz may have contributed to the discrepancies. An alternative source, Bet (2013)²³², was verified with clinical experts and considered more representative of rates seen in clinical practice. The single rate reported by Bet for SSRIs was considered reasonable as the experts believed rates for citalopram and sertraline were similar.

An issue raised by experts was the under-reporting, both in clinical practice and in clinical trials, of TESD. They expressed the opinion that, given the benefits of vortioxetine on this endpoint, the analysis would probably underestimate its advantages over other products.

Additional consultations

Clinical advice was sought to quantify the proportion of patients who, on experiencing an adverse event, would seek an additional consultation. It was confirmed that around 30% of patients would consult, almost always with a GP. This assumption was used as the base case.

With respect to the management of side-effects, patients are advised that most adverse events will subside within a few weeks and that they should take over-the-counter medication (such as pain killers for headache) in the meantime. Prescribing of remedies for side-effects is rare. If the side-effect is intolerable, patients are offered the opportunity to switch to an alternative antidepressant.

Treatment switching

The clinical experts agreed that the practice of treatment switching due to adverse events for a proportion of patients with short- and long-term adverse events should be incorporated in the model. To reflect differing side-effect profiles between antidepressants, incorporating withdrawals due to adverse event rates as reported in short-term trials was agreed as appropriate for short-term adverse events. With regards to long-term adverse events, clinical expert opinion was used to define the proportion of patients who switch due to

experiencing TEDS, weight gain or insomnia. This proportion was estimated to be 25%, and was the base case model assumption.

Disutilities: duration of application

The length of time over which disutility is applied to a short-term adverse event was based on the average length of time a patient would experience the AE. The clinical experts advised an average duration of 3 weeks across all short-term AEs; this duration became the base-case model assumption.

As for long-term adverse events, the model incorporated the advice that the corresponding disutility values should be applied for the full duration of the maintenance phase (unless the patient switches treatment).

7.3.5.4 Model structural assumptions

With respect to endpoint selection, remission was considered the criterion for clinical success for most patients. However, response would be considered a success for some patients, particularly those with more severe MDEs or who have a history of being difficult to treat. The experts assisted in specifying a sensitivity analysis to explore the impact of an alternative endpoint on the CEA, in which the remission rate for all treatments at initial switch was increased by 20%. This addition captured the increased proportion of patients who would stay on their initial switch treatment in spite of not achieving remission and the associated effects on utility and cost accrual, as well as the continued exposure to the risk of AEs from initial switch treatment.

In the absence of more formal evidence, advice was taken on the choice of treatment at third, fourth line and fifth line along with appropriate assumptions for efficacy rates and costs. As the choice of third and subsequent lines of treatment depends on the treatments prescribed at the beginning of the MDE and at initial switch (i.e. second-line), the clinicians recommended modelling these later lines as a blend of antidepressants. The advisory group recommended basing remission rates at lines 3, 4 and 5 on the corresponding treatment steps reported in STAR*D (Rush 2006)¹¹, and applying the cost of the cheapest antidepressant (citalopram) to each of these lines as a conservative assumption. Assessing the impact of varying the treatment choice was recommended as a sensitivity analysis.

7.3.6 Summary of selected values

All parameter inputs in the cost-utility analysis, including mean values, ranges (distributions) and sources, along with cross-references to other parts of the submission, are listed in Table B52 to Table B55 inclusive.

Table B52. Model parameter inputs: effectiveness

Event	Treatment	Probability	Distribution	Comment	Source
Remission after 8 weeks	Vortioxetine	40.5%	Beta (α : 102, β : 151)	95% CI assumes beta distribution	See ITC (section 6.7.6.1)
	Agomelatine	29.5%			
	Difference from vortioxetine	-11.0%	Normal (95% CI: -19.4%, -2.6%,)		
	Sertraline	26.1%			Distribution derived from 95% CI around risk difference between vortioxetine and each comparator
	Difference from vortioxetine	-14.4%	Normal (95% CI: -29.9%, -1.1%, 29.9%)		
	Venlafaxine	33.3%			
	Difference from vortioxetine	-7.2%	Normal (95% CI: -24.3%, 9.9%)		
	Citalopram	23.7%			
	Difference from vortioxetine	-16.8%	Normal (95% CI: -41.1%, 7.5%)		
	Treatment 3 rd line	13.7%			STAR*D
Relapse after 6 months	Treatment 4 th line	13.0%		Not included in sensitivity analysis	
	Treatment 5 th line	13.0%			Assumed equivalent to 4 th line
	Active treatment	14.2%	Beta (α : 51; β : 308)		Limosin 2004
	Treatment 3 rd line	25.0%	Beta (α : 8.74; β : 26)	95% CI assumes beta distribution	STAR*D
	Treatment 4 th and 5 th line	42.6%	Beta (α : 6.39; β : 9)		Assumed equivalent to 4 th line)

References to sources: STAR*D: Rush 2006¹¹, Limosin 2004²²⁷. 1 month is assumed equivalent to 4 weeks. CI: confidence interval.

Table B53. Model parameter inputs: withdrawal due to side-effects

Event	Treatment	Probability	Distribution	Comment	Source
Discontinuation due to side-effects at 2 months	Vortioxetine	5.9%	Beta (α : 15; β : 238)		See ITC (section 6.7.6.2)
	Agomelatine	9.5%			
	Difference vs. agomelatine	3.6%	Normal (95% CI: -1.1%, 8.3%)		
	Sertraline	18.0%			Distribution derived from 95% CI around risk difference between vortioxetine and each comparator
	Difference vs. sertraline	12.1%	Normal (95% CI: 3.1%, 21.1%)		
	Venlafaxine	18.2%			
	Difference vs. Venlafaxine	12.3%	Normal (95% CI: 0.8%, 23.8%)		
	Citalopram	18.0%			
	Difference vs. citalopram	12.1%	Normal (95% CI: -0.3%, 24.5%)		

1 month is assumed equivalent to 4 weeks. ITC: indirect treatment comparison.

Table B54. Model parameter inputs: short-term side-effects (acute phase)

Side-effect	Treatment	Probability	Distribution	Source
Sexual dysfunction	Vortioxetine	0.4%	Beta (α : 1; β : 252)	14178A (REVIVE)
	Agomelatine	0.0%	Beta (α : 0; β : 242)	14178A (REVIVE)
	Sertraline	10.6%	Beta (α : 131; β : 1,100)	Cipriani 2010
	Venlafaxine	14.4%	Beta (α :22; β :131)	Pooled Cochrane reviews
	Citalopram	6.2%	Beta (α :57; β :856)	Cipriani 2012
Dry mouth	Vortioxetine	4.7%	Beta (α :12; β :241)	14178A (REVIVE)
	Agomelatine	3.3%	Beta (α :8; β :234)	14178A (REVIVE)
	Sertraline	14.5%	Beta (α :305; β :1,805)	Cipriani 2010
	Venlafaxine	23.0%	Beta (α :148; β :495)	Pooled Cochrane reviews
	Citalopram	6.7%	Beta (α :92; β :1,286)	Cipriani 2012
Nausea	Vortioxetine	16.2%	Beta (α :41; β :212)	14178A (REVIVE)
	Agomelatine	9.1%	Beta (α :22; β :220)	14178A (REVIVE)
	Sertraline	26.2%	Beta (α :693; β :1,955)	Cipriani 2010
	Venlafaxine	41.0%	Beta (α :345; β :496)	Cipriani 2010
	Citalopram	11.0%	Beta (α :172; β :1,393)	Cipriani 2012
Sweating	Vortioxetine	2.4%	Beta (α :6; β :247)	14178A (REVIVE)
	Agomelatine	2.1%	Beta (α :5; β :237)	14178A (REVIVE)
	Sertraline	13.3%	Beta (α :234; β :1,520)	Cipriani 2010
	Venlafaxine	12.9%	Beta (α :105; β :711)	Pooled Cochrane reviews
	Citalopram	6.5%	Beta (α :53; β :762)	Cipriani 2012
Somnolence	Vortioxetine	4.0%	Beta (α :10; β :243)	14178A (REVIVE)
	Agomelatine	7.9%	Beta (α :19; β :223)	14178A (REVIVE)
	Sertraline	9.1%	Beta (α :188; β :1,867)	Cipriani 2010
	Venlafaxine	8.6%	Beta (α :70; β :746)	Pooled Cochrane reviews
	Citalopram	6.8%	Beta (α :70; β :952)	Cipriani 2012
Headache	Vortioxetine	10.3%	Beta (α :26; β :227)	14178A (REVIVE)
	Agomelatine	13.2%	Beta (α :32; β :210)	14178A (REVIVE)
	Sertraline	26.1%	Beta (α :684; β :1,939)	Cipriani 2010
	Venlafaxine	21.6%	Beta (α :221; β :801)	Pooled Cochrane reviews
	Citalopram	10.8%	Beta (α :155; β :1,274)	Cipriani 2012
Diarrhoea	Vortioxetine	3.2%	Beta (α :8; β :245)	14178A (REVIVE)
	Agomelatine	3.3%	Beta (α :8; β :234)	14178A (REVIVE)
	Sertraline	20.1%	Beta (α :493; β :1,955)	Cipriani 2010
	Venlafaxine	8.9%	Beta (α :80; β :814)	Pooled Cochrane reviews
	Citalopram	6.7%	Beta (α :88; β :1,218)	Cipriani 2012
Insomnia	Vortioxetine	7.1%	Beta (α :18; β :235)	14178A (REVIVE)
	Agomelatine	2.9%	Beta (α :7; β :235)	14178A (REVIVE)
	Sertraline	18.1%	Beta (α :402; β :1,819)	Cipriani 2010
	Venlafaxine	18.0%	Beta (α :144; β :658)	Cipriani 2010
	Citalopram	7.5%	Beta (α :115; β :1,427)	Cipriani 2012
Dizziness	Vortioxetine	7.1%	Beta (α :18; β :235)	14178A (REVIVE)
	Agomelatine	11.6%	Beta (α :28; β :214)	14178A (REVIVE)
	Sertraline	10.4%	Beta (α :184; β :1,586)	Cipriani 2010
	Venlafaxine	13.2%	Beta (α :116; β :760)	Pooled Cochrane reviews
	Citalopram	4.6%	Beta (α :39; β :812)	Cipriani 2012

References to sources: 14178A (REVIVE)^{132,134}; Cipriani 2010²²⁵; Cipriani 2012¹⁶⁵. Pooled results from the sertraline²²⁵, escitalopram¹⁰⁸, duloxetine¹⁰⁹ and citalopram¹⁶⁵ Cochrane reviews.

Table B55. Model parameter inputs: long-term side-effects (maintenance phase)

Side-effect	Treatment	Probability	Distribution	Source
Sexual dysfunction	Vortioxetine	1.6%	Beta (α :12; β :755)	Pooled long-term extension studies
	Agomelatine	0.0%	Beta (α :0; β :165)	Goodwin 2009
	Sertraline	23.0%	Beta (α :134; β :450)	Bet 2013
	Venlafaxine	31.0%	Beta (α :45; β :100)	Bet 2013
	Citalopram	23.0%	Beta (α :134; β :450)	Bet 2013
Insomnia	Vortioxetine	3.5%	Beta (α :27; β :740)	Pooled long-term extension studies
	Agomelatine	1.8%	Beta (α :3; β :162)	Goodwin 2009
	Sertraline	7.0%	Beta (α :41; β :543)	Bet 2013
	Venlafaxine	10.0%	Beta (α :15; β :130)	Bet 2013
	Citalopram	7.0%	Beta (α :41; β :543)	Bet 2013
Weight gain	Vortioxetine	2.9%	Beta (α :22; β :745)	Pooled long-term extension studies
	Agomelatine	0.0%	Beta (α :0; β :0)	Goodwin 2009
	Sertraline	19.0%	Beta (α :111; β :473)	Bet 2013
	Venlafaxine	17.0%	Beta (α :25; β :120)	Bet 2013
	Citalopram	19.0%	Beta (α :111; β :473)	Bet 2013

Sources. Pooled long-term extension studies: Lundbeck data on file²³⁸ Goodwin 2009²³¹, Bet 2013²³²,

7.3.7 Extrapolation

Rates of remission in the maintenance phase are estimated by applying rates for withdrawals due to adverse events and relapse rates specific to the line of therapy to the proportions of patients achieving remission in the acute phase, as detailed in Table B1. There was no extrapolation of any clinical outcomes or costs beyond the 12-month model horizon described above.

7.3.8 List of assumptions

Please refer to section 7.2.6 and 7.3.5.

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Impact of MDD/MDEs on patients' health-related quality of life.

Although people with depression typically feel sad, hopeless and lose interest in things they used to enjoy, depression may manifest as a wide array of psychological and physical symptoms^{54,239}. While they tend to vary between patients, depression symptoms severely affect patients' HRQoL. In a survey²⁴⁰ of patients suffering from MDD the following aspects were reported as being the most prominent:

- Crying spells
- Easy to anger or impatient
- Mood swings/emotional
- Fatigue or lack of energy
- Insomnia
- Low motivation
- Procrastination
- Lack of focus
- Memory problems

As described in the overview of MDD in section 2.1, a recent English survey by Roberts¹⁷ found that the mean EQ-5D utility for depression, at 0.54, was the lowest of all mental and physical health problems. The baseline EQ-5D data collected by Lundbeck in the REVIVE study (see Figure B8) are concordant with Roberts' findings. A study by Sapin¹⁸, which provided the health state utility data in the NICE CG90 model, reported a baseline depression EQ-5D score of 0.33. Moreover, both REVIVE and Sapin show that, prior to treatment, it is anxiety/depression for which the greatest proportions of respondents report problems (at level 2 or 3). In both studies, a majority also reported problems with usual activities and with pain and discomfort, while approximately 18-28% reported problems on the mobility and the self-care domains.

Further effects of MDEs on quality of life are reviewed in section 2.1.7.

7.4.2 HRQoL change over the course of an MDE

The utility trajectory of MDD is notable for the rapid swings that may occur contingent on the onset of an MDE and the outcomes of treatment. As described in section 2.1.3, five recognisable and measurable events characterise the potential course of an MDE: response, remission, recovery, relapse and recurrence^{34,60}. The most severe impact on HRQoL occurs with the onset of an MDE, particularly at the beginning of the acute phase before any response to treatment is apparent, and gradually lessening if the patient responds until remission has been achieved. This acute phase is variable but typically lasts from 6-12 weeks. In the study by Sapin¹⁸ referred to above, mean utility improved from the pre-treatment value of 0.33 to 0.85 after remission assessed at 8 weeks of treatment, which is comparable to the post-treatment values seen in REVIVE (see Table B15). The utility impact of antidepressant side-effects and sources of evidence are discussed later in this section.

7.4.3 HRQoL data derived from clinical trials

HRQoL data were collected alongside Study 14178A (REVIVE), one of the two trials of vortioxetine identified in section 6 that support the decision problem, and which is the principal source of outcome data for vortioxetine in the model presented here.

The assessment of HRQoL and functioning in REVIVE consisted of the administration of a battery of validated patient-reported outcome (PRO) questionnaires, consisting of the Sheehan Disability Scale (SDS), the EuroQoL EQ-5D, the Work Limitations Questionnaire (WLQ) and the Depression and Family Functioning Scale (DFFS). The purpose of doing so was to gain an understanding of the effects of the study treatments across a broad range of relevant domains beyond the standard evaluation of efficacy, safety and tolerability. This section, however, is concerned with HRQoL to generate single-index utility values for the calculation of QALYs. The purpose of including EQ-5D in REVIVE was twofold:

1. To compare the study treatments (vortioxetine and agomelatine) in terms of changes in utility score from baseline at assessment points (the "between-treatment analysis")
2. To elicit utility values for defined health states, irrespective of randomised treatment assignment (the "health state analysis").

The first of these analyses has been reported in section 6.5.2.3 along with the other trial outcomes specified in the REVIVE statistical analysis plan, and is not repeated here. Here we focus on the health state analysis, which was not part of the main trial SAP as it was conceived separately to provide health state utilities for use in modelling.

The method of elicitation and valuation was reported in section 6.5.2.3: study participants completed the EQ-5D profile questionnaire at baseline and at Week 4, 8 and 12

assessments, and their responses were scored on a summary index, using the UK tariff (Dolan 1997)¹⁸⁵. The only difference between the analyses was in the grouping of subjects. In the health state analysis, the analysis sets were treated as a single cohort and not reported by randomised treatment assignment. Utility values were reported for the all patients treated set (APTS) at baseline and for the full analysis set (FAS) at the post-baseline assessment of interest, which was 8 weeks to correspond with the model specification. At 8 weeks, the full cohort was divided according to remission status. Remission was defined as MADRS total score ≤ 10 : see **Error! Reference source not found.** This analysis took no account of treatment assignment.

Table B56. Definition and results of analyses of REVIVE to generate utility values for model

Health state	Patient profile	Analysis set	N	Utility value	
				Mean	se
<i>Depression</i>	At study entry, i.e. switch following inadequate response to initial SSRI/SNRI	APTS	495	0.54	0.01
<i>Remission</i>	In remission at 8 weeks (MADRS total score ≤ 10)	FAS (all patients in APTS with a valid baseline assessment and at least one valid post-baseline assessment of MADRS)	493	0.85	0.01
<i>No remission</i>	Not in remission at 8 weeks (MADRS total score > 10)			0.62	0.02

Source: Lundbeck data on file²⁴¹. se: standard error; APTS: all patients treated set; FAS: full analysis set, MADRS: Montgomery and Åsberg Depression Rating Scale; SSRI: Selective serotonin reuptake inhibitor; SNRI: Serotonin-noradrenaline reuptake inhibitor. MADRS: Montgomery-Åsberg Depression Rating Scale.

The above analysis is fully consistent with the NICE Reference Case, in that the preferred instrument, EQ-5D, was administered and scored using the relevant tariff for the UK. Therefore, Lundbeck believes the utility values reported above are appropriate for use in the model presented in this submission and are consistent with the population of interest. The utility values of health states derived from REVIVE are also in line with values reported in the literature^{17,18}.

7.4.4 Mapping

No mapping was required.

7.4.5 Systematic search for HRQoL data

7.4.5.1 Study identification

A detailed search strategy is provided in Appendix 12.

Lundbeck is aware of the 2008 systematic literature review reported in NICE CG90¹⁰, which identified HRQoL data. This review included 3 studies^{18,242,243} reporting EQ-5D data valued using the UK population tariff, including one by Sapin¹⁸ that the authors of CG90 considered the most suitable source of utility data for the guideline economic model; the data reported within this study are also suitable to populate the health states of the model used within this STA. Given this prior work, Lundbeck considered that a search for HRQoL studies published since 29 May 2008 would be sufficient to supplement the CG90 search results with any more recently published work.

Databases searched were as follows: Embase, MEDLINE, MEDLINE In-Process, EconLit, PsycINFO, Cochrane, NHSEED and HTA. The searches were limited to human studies but were not limited by language. Search strategies are displayed by database in Appendix 12 (section 10.12.4).

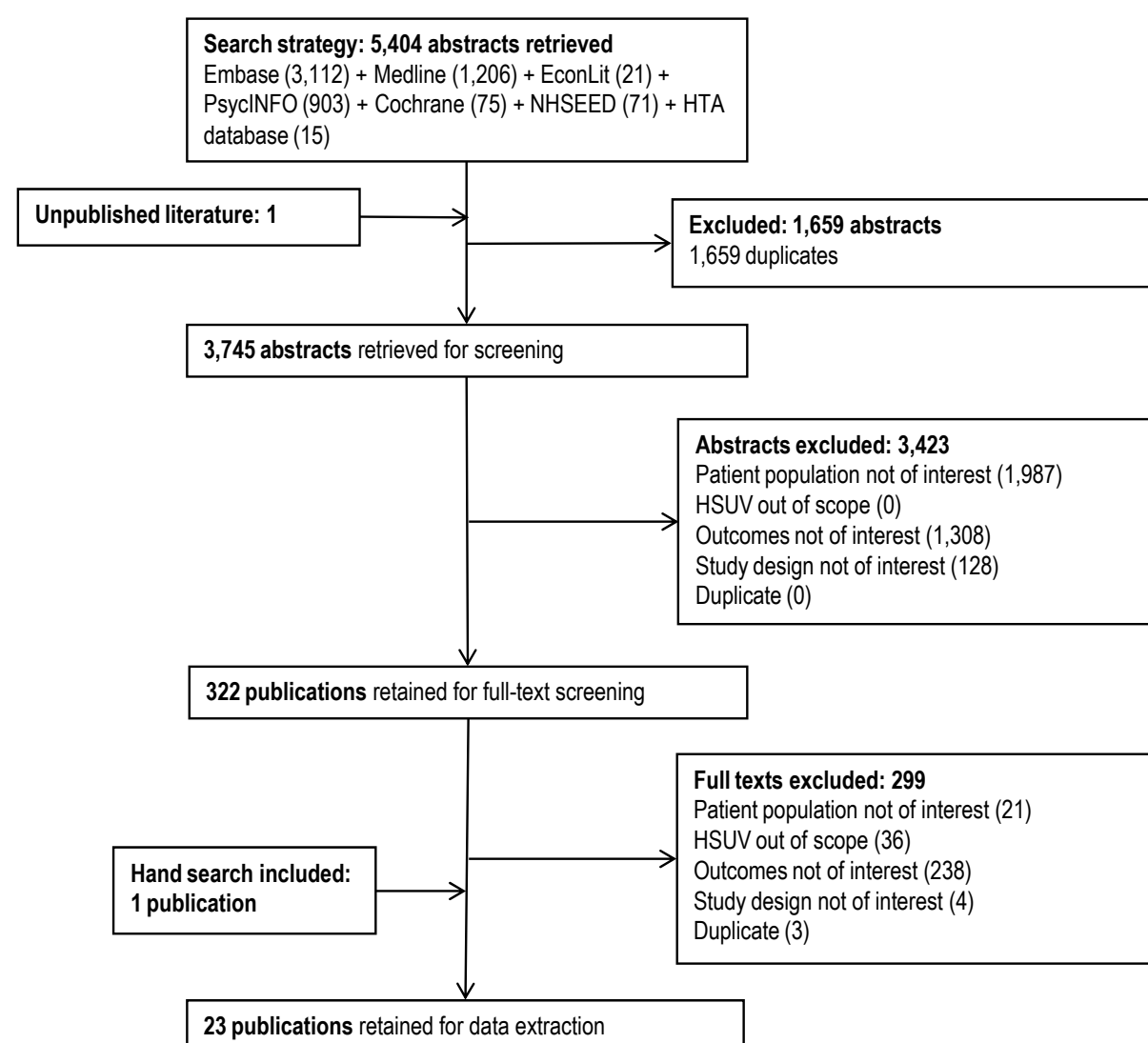
NICE Decision Support Unit 9 document (DSU9) states: “...*the scope may be narrowed to focus on EQ-5D if relevant and plentiful EQ-5D data is known to be available.*” Given the findings of the CG90 search it was deemed appropriate to focus on identifying more recently published sources of EQ-5D data to populate the model health states. As no existing search filter for HRQoL has been validated²⁴⁴, supplementary terms to EQ-5D synonyms were added to increase the sensitivity of the filter. Population and disease terms used in the clinical and cost-effectiveness searches were chosen, though the terms were not limited to a switch population. These population terms were then combined with our customised HRQoL search filter.

To validate the search strategy, the results were cross-checked with the HRQoL references considered relevant in NICE CG90. Seven of eight studies were retrieved^{18,242,243,245-248}; the only missing study²⁴⁹ concerned the consistency of computer-aided utility scoring, which reported SF-12 rather than EQ-5D data. The actual search was performed with an earliest date cut-off of 2008 to limit results to work published since the NICE CG90 search. A total of 5,404 abstracts were retrieved. All EQ-5D studies from 2008 onwards that were identified in a systematic review by Mohiuddin and Payne (2014)²⁵⁰ were also identified in our search, further validating the search strategy.

7.4.5.2 Study selection

The study inclusion/exclusion criteria were not only intended to identify HRQoL studies in patients with MDD or experiencing an MDE, but also to assign utility values to the health states of the proposed economic model, as per the DSU TSD9 guidance²⁵¹. Therefore, all studies that reported data potentially useful for this purpose were retained. It was not stipulated that a single publication had to provide data for each and every health state. The criteria for the abstract selection and full-text publication selection were based on the relevance to the decision problem of the study's population, health states, outcomes and study design. These criteria are detailed in Appendix 12 (Section 10.12.6). The review process was equivalent to that described for the cost-effectiveness study review (see Section 7.1.1).

Of the identified 5,404 abstracts, 1,659 were excluded as duplicates and a further 3,423 excluded based upon title and abstract screening, predominantly due to inappropriate patient population or reported outcomes (Figure B23). Hand searching of the bibliographies of all identified systematic reviews identified one additional publication²⁵², which was excluded on examination of the full text. Some conference abstracts referred to posters not publicly available, in which instances the posters were requested from the authors. Following a full-text screen of 322 retrieved publications, 23 that reported HRQoL studies were retained for data extraction. A summary of the data extracted is provided in Appendix 12 (section 10.12.8).

Figure B23. PRISMA flow diagram of the selection process for HRQoL studies

7.4.6 Description of identified studies

Details of the 23 publications in which HRQoL was measured and reported using EQ-5D and considered potentially suitable sources of utility estimates for the *de novo* model are presented in Appendix 12 (section 10.12.8). Only those that report utility data of potential value for populating the economic model are discussed here.

7.4.6.1 Health state utilities

Following the precedent set by NICE of using a single source of utility data (Sapin)¹⁸ for the guideline model, it was considered desirable to consider only studies that could provide all the utility values required to populate the maintenance phase health states within the current model (i.e. remission, no remission, recovery). Data were required only for the maintenance phase. For the acute phase, health state utility data from REVIVE were used as it was also the source of clinical inputs for vortioxetine and agomelatine.

Through the systematic review, four additional potential sources of utility values for the maintenance phase health states were identified: a poster published by Soini (2011)²⁵³ and manuscripts authored by Mann (2009)²⁵⁴, Winter (2011)²⁵⁵ and PERFORM²³⁶. An overview

of each of these and a rationale and summary of appropriateness for use in the cost-utility analysis are provided below.

Soini (2011)²⁵³

This reference was a conference abstract²⁵³ of a Finnish cost-utility analysis comparing agomelatine, venlafaxine and placebo. It provides values for patients who are 'well', in 'remission', and with 'depression', which correspond to the Markov states in the modelled analysis. The related poster contains little detail on the utility elicitation methods. The totality of the information provided is as follows:

"Finnish EQ-5D utilities ... were estimated from a representative one year survey data (Health 2000) of 298 subjects with MDD and 5,707 subjects without MDD."

The poster presentation has not been followed by a manuscript. The lead author was repeatedly contacted to request additional information but no response has been received.

Mann (2009)²⁵⁴

This study²⁵⁴ compared the use of EQ-5D and SF-6D in a UK sample of 114 patients with MDD, and reported utility scores at baseline and after 3 months of treatment, stratified according to four levels of severity defined by PHQ-9 score. Utilities for health states "depression" and "no depression" at 3 months were also reported.

Winter (2011)²⁵⁵

The Winter publication studied elderly patients with Alzheimer dementia or vascular dementia and assessed the impact of having depression or not on their quality of life. The study population was unsuitable because of the above comorbidities.

PERFORM^{19,256}

Two of the records from the 23 retained publications report utility data from the Lundbeck-sponsored PERFORM study^{19,256}, a two-year, prospective, observational study of patients diagnosed with MDD in 5 European countries: UK, Spain, Sweden, France and Germany. PERFORM is an ongoing study, but it has already generated posters reporting interim data. These data include EQ-5D utility values at baseline for switch versus non-switch (initiating) UK patients¹⁹ and for UK patients by severity of depression, as defined by PDQ-5 score²⁵⁶. EQ-5D was administered only among the UK participants. PERFORM was therefore considered a potentially useful source of model data. At the time of conducting the economic evaluation for this submission, interim data were available for 2 months' follow-up.

Sapin (2004)¹⁸

The study by Sapin was not identified by the present search due to its date of publication. This study is discussed here because it was the source used to populate the CG90 model, and hence was our default choice for the present model unless any preferable, more recent studies could be identified.

The study enrolled 250 patients with a DSM-IV diagnosis of MDD within French primary care. Patient assessments included MADRS, CGI, SF-36 and EQ-5D. Utility scores at baseline and 8 weeks of treatment were reported. The 8-week scores were stratified by depression, response – no remission, and remission.

7.4.6.2 Disutilities associated with side-effects

As side-effects associated with antidepressant treatment adversely affect patients' HRQoL, identification of data to quantify the disutility of adverse events was also an objective of this review.

Sullivan (2004)²³⁷

Before this review, the study by Sullivan had already been identified through reviews of economic models in MDD. Sullivan provided disutility values for a range of treatment-emergent adverse events derived directly from an EQ-5D analysis of the US Medical Expenditure Panel Survey (MEPS) for year 2000, using the UK scoring algorithm. MEPS is recognised as being a nationally representative survey of the civilian non-institutionalised US population. The well-reported analysis has been used as a source of disutility values associated with side-effects in several published models²⁵⁷⁻²⁶¹.

Soini 2011²⁵³

The only other publication reporting disutilities associated with TEAEs identified in the systematic review for HRQoL data was the Soini 2011 poster presentation²⁵³. The reporting was insufficient to draw conclusions on the analyses undertaken, as reported in section 7.4.6.1.

7.4.7 Differences between the values reported in literature and from REVIVE.

As detailed in Section 7.4.3, REVIVE provides EQ-5D data up to 12 weeks, which has been analysed by health state for use in the economic model. The utility values that were derived from EQ-5D responses at the 8-week assessment point were compared with the 2-month data from PERFORM, the 8-week data from Sapin (2004) and the 3-month data from Mann (2009). As Table B57 shows, the utility values are, in the main, consistent. The only slightly anomalous result is the baseline depression EQ-5D score from Sapin, which is lower than that seen in other trials. The baseline MADRS score of the populations may contribute to this as the mean MADRS total score was 32.7 whereas in REVIVE it was 29.1. As Table B57 shows, the utility values are remarkably similar.

Table B57. Comparison of utility values between potential sources

Health state	REVIVE		PERFORM		Sapin (2004)		Mann (2009)	
	Utility value	Assessment point	Utility value	Assessment point	Utility value	Assessment point	Utility value	Assessment point
<i>Depression</i>	0.54	Baseline	0.54	Baseline	0.33	Baseline	0.516	Baseline
<i>Remission</i>	0.85	8 weeks	0.82	2 months	0.85*	8 weeks	0.759	3 months
<i>No remission</i>	0.62	8 weeks	0.58	2 months	0.58**	8 weeks	0.506	3 months

*EQ-5D score for 'responders remitters' ; ** EQ-5D score for non-responders
REVIVE²⁴¹; PERFORM^{19,256}; Sapin (2004)¹⁸; Mann (2009)²⁵⁴

7.4.8 Impact of side-effects on HRQoL

Side-effects of antidepressant treatment, as discussed in section 2.6.2.2, are widely recognised to impact on the immediate HRQoL of a patient with depression. Side-effects of antidepressant treatment frequently occur and may be sufficiently troublesome to affect a patient's HRQoL directly or indirectly, the latter as a consequence of reduced adherence or treatment discontinuation¹⁰. In line with NICE recommendations, the utility impact of side-effects was included in the model.

Clinical expert advice suggests that side-effects can be split into two categories: short-term and long-term. Those that are short-term persist on average for 3 weeks and sometimes lead to discontinuation of treatment. Long-term effects, such as sexual dysfunction and insomnia, are seen to persist from treatment commencement (although weight gain occurs gradually). These side-effects are acknowledged by clinical experts as being the key drivers for treatment cessation in the maintenance phase.

7.4.9 Quality-of-life data used in cost-effectiveness analysis

7.4.9.1 Acute phase

As EQ-5D utility data stratified by health states corresponding to the acute phase health states of the *de novo* model were available from REVIVE, this trial was considered to be an appropriate source. The assessment points at baseline and 8 weeks in REVIVE correspond exactly to the 8-week acute phase of the model, and the opportunity to source utility as well as clinical efficacy data from a single study would enhance the model's internal consistency.

Consideration was also given to the data from Sapin¹⁸, partly for consistency with the CG90 model. It was considered important to attempt to match baseline severity between the sources of utility and efficacy data. Sapin reported a baseline mean MADRS score of 32.7, whereas in REVIVE²⁷ the corresponding score was 29.1. Sapin also reported baseline severity as CGI-S scores expressed as named categories. The mean and median scores can be inferred as approximately 5, corresponding to the category "markedly ill". In REVIVE, the mean baseline CGI-S score was 4.4. These differences suggest the population of the Sapin study had more severe symptoms at baseline, which may explain the lower baseline utility value of 0.33 in that study, as compared to 0.54 in REVIVE²⁴¹.

Otherwise, the scores corresponding to remission and no remission were in close agreement between REVIVE and Sapin, so the use of REVIVE would therefore be conservative in terms of utility gain. These factors led to the overall conclusion in favour of REVIVE as the source of acute phase utility values.

7.4.9.2 Maintenance phase

The Sapin publication was, however, considered the most appropriate source of maintenance phase health state utility values. Although the study was conducted in France, the country demographics are similar to those of the UK and the responses were valued using the EQ-5D UK tariff¹⁸⁵. This was the utility data source used in CG90.

Mann (2009)²⁵⁴ also provided potentially useful utility data for the maintenance phase, collected alongside a UK clinical trial of a collaborative care intervention in general practice. Data are reported at baseline and after 3 months' treatment. The 3-month value for "depression" could be applied to the **no remission** health state after relapse, and the value for "remission" to **remission** and **recovery**. However, as the study was small (n=114), Sapin was preferred as the base case source for maintenance phase health state utility values, while Mann provided data for a sensitivity analysis.

7.4.9.3 Disutilities associated with adverse events

In view of its prior use in other models to provide a single source of disutility data for individual side-effects of antidepressant treatment, the Sullivan publication²³⁷ was selected as the most appropriate source. Soini 2011²⁵³ was disqualified because of insufficient reporting.

Weight gain, an adverse event recorded with sufficient frequency in clinical trials to require inclusion in the model, was not included in the set of utility values provided by Sullivan. Expert advice suggested that the disutility reported as 'other' in Sullivan was not appropriate for use in the model as it was not specific to weight gain and did not take into account the amount of weight change a patient experienced. To address this concern, experts suggested that reviewing the link between body weight and utilities would be more appropriate. A published literature review (Dennett 2008²⁶²) was identified, which reviewed the impact of body weight on patient utilities at different body mass index (BMI) categories in patients with and without type 2 diabetes. From this review, Dixon 2004²⁶³ was considered the most appropriate source for the model, as it reported a UK-based study of a large number (13,152) of hospital inpatients and outpatients in the Health Outcomes Data Repository, and reported a change in EQ-5D utility score of per one unit change in BMI rather than per BMI category. In the study, for each unit increase in BMI, utility decreased by 0.0168 in people with a BMI >25kg/m².

To use this published value, a calculation of change from baseline BMI was required. Baseline BMI was calculated from the REVIVE population. The CSR reported the average height and weight of patients at study entry, from which the mean BMI at baseline was calculated as 27.01kg/m². As this value was >25kg/m², it was appropriate to apply the BMI disutility reported by Dixon to each unit of increase. To calculate this change from baseline it was assumed that each reported adverse event of weight gain must have been at least a 7% weight increase. This value was applied to the baseline weight reported in REVIVE, giving a mean BMI of 28.9kg/m², a change of 1.89 units. The disutility value of 0.032 (rounded) was therefore applied to patients experiencing the adverse event of weight gain. The calculation is shown in Table B58.

Table B58. Calculation of disutility value for weight gain

Number of patients	495
Mean height at baseline (cm)	167.18
Mean weight at baseline (Kg)	75.50
BMI calculated from height and weight (kg/m ²)	27.01334
7% weight increase (Kg)	5.285
Weight plus 7% (Kg)	80.785
BMI if 7% weight gain (Kg/m ²)	28.90428
Change in BMI from baseline (Kg/m ²)	1.890934
Utility change per BMI unit	0.0168
Utility change per weight gain adverse event	0.031768

BMI: body mass index.

7.4.9.4 Summary of utility values used in model

Given the selection of sources of utility values, the actual values used as model parameter inputs are listed in Table B59.

Table B59. Model parameter inputs: utility values

Event	Input utility value	Distribution	Comment	Source	
Acute phase					
Depression at baseline	0.54			} REVIVE	
Remission	0.85	Beta (α :1.083; β :191)			
No remission	0.62	Beta (α :365; β :223)	Weighted average of non-responders and responding non-remitters at 8 weeks		
Maintenance phase					
Remission	0.85	Beta (α :8; β :1)		} Sapin 2004	
Relapse	0.58	Beta (α :25; β :18)			
Recovery	0.85				
Disutilities of side-effects					
Sexual dysfunction	0.049		} Directly reported by Sullivan	} Sullivan 2004	
Headache	0.115				
Diarrhoea	0.044		} Lundbeck applied Sullivan value reported for drowsiness*		
Somnolence	0.085				
Nausea	0.065		Sullivan assumed average of GI AEs		
Insomnia	0.129		Sullivan assumed equivalent utility to anxiety		
Dry mouth	0†		} No data available	} Dixon 2004, REVIVE CSR	
Dizziness	0†				
Sweating	0†				
Weight gain	0.032		Calculation (see below)		

Sources: REVIVE²⁴¹; Sapin 2004¹⁸; Sullivan 2004²³⁷; Dixon 2004²⁶³; REVIVE CSR²⁷.

*Drowsiness is normally considered less severe than somnolence, therefore utility estimate for somnolence may be conservative. †As no utility values were available, no utility decrement was assumed for these AEs in the base-case of the economic evaluation.

7.4.10 Clinical expert assessment

Please see section 7.3.5.

7.4.11 Patient experience in terms of HRQoL

Please refer to sections 2.1.6, 2.1.7 and 7.4.1.

7.4.12 Excluded health effects

Response has not been explicitly modelled separately from remission in the base case, as explained in section 7.2.6.

7.4.13 Baseline quality of life

All patients were assumed to be in the health state **depression** at the clinical starting point and were assigned the utility value for this state.

7.4.14 HRQoL trajectory

HRQoL is assumed to remain constant over time within a health state. As a patient moves between health states and experiences treatment emergent adverse events their utility score changes.

7.4.15 Amendments to HRQoL data

There have been no amendments to the HRQoL data described in sections 7.4.3 to 7.4.8.

7.5 Resource identification, measurement and valuation

7.5.1 NHS costs

The treatment of MDD is principally undertaken in primary care and therefore falls within the responsibilities of general practice contracts as a common mental illness. Normally, only patients with risk to life, severe self-neglect, treatment-resistant, recurrent, atypical and psychotic depression would be referred to secondary specialist mental health services. Typically, specialist mental health services are agreed on fixed contract terms between CCGs and Mental Health trusts. It is therefore not possible to cost using either the Payment by Results (PbR) or Reference Costs. Although mental health PbR clusters were mandated for use from April 2012, a national tariff has not yet been specified. The currently recommended clusters are detailed in the NHS document *Mental Health Payment by Results Guidance for 2013-14*.

Many HRGs identify mental health problems as complicating factors in care, though depression is not specified.

7.5.2 Costing conventions

See above. Reference costs and PbR tariffs are not appropriate for the costing of the resource items considered in this economic evaluation as the majority of care is provided in primary care. Also, there is no agreed national tariff for PbR at this point.

7.5.3 Resource identification, measurement and valuation studies

The systematic review identifying HRQoL data (see Appendix 12) was used as the basis for identification of the resource use data. As resource use data may not be transferable between healthcare systems, it was stipulated that only UK data would be eligible.

The ongoing PERFORM study^{19,20,236} has been referred to in section 7.4.6 in the context of its potential use as a source of HRQoL data for modelling. As with the HRQoL data, some UK healthcare resource utilisation (HCRU) data were available as an unpublished, internal document from an interim analysis of 226 patients in England who had completed 2 months of follow-up. Of these patients, only 39 were starting switch treatment; the remainder were starting initial treatment for an MDE. It was therefore necessary to use the full data set to populate the model in view of the small numbers for the switch subgroup. Hence, this interim dataset provides resource use by health state for 2 months of follow-up, corresponding to the **acute phase** of the model.

Byford (2011)²³⁴ reports on a naturalistic, longitudinal study using data for years 2001 and 2006 from the General Practice Research Database (GPRD), which is representative of the UK population. The records of 88,935 patients aged ≥18 years, diagnosed with depression and in receipt of at least two antidepressant prescriptions (for amitriptyline, citalopram, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine) in the first 3 months after the

index prescription were included. The main outcome measures were health service use and cost over the 12-month study period, by remission status. This study was considered to be an appropriate source to populate the model (see Table B60).

The PERFORM study^{19,20,236} was used to calculate the absenteeism rate by health state (Table B61).

Table B60. Model parameter inputs: healthcare resource utilisation

Resource	No. of visits	Distribution	Patients with ≥ 1 visit (%)	Distribution	Source
GP consultations					
Remission 0-8 weeks	2.50	Gamma ($\alpha:61.47$; $\beta:0.04$)	100.0%	Uniform ($\alpha:75$; $\beta:100$)	PERFORM
No remission 0-8 weeks	2.80	Gamma ($\alpha:61.47$; $\beta:0.05$)	100.0%	Uniform ($\alpha:75$; $\beta:100$)	PERFORM
Remission after 8 weeks	2.15	Gamma ($\alpha:61.47$; $\beta:0.03$)	100.0%	Uniform ($\alpha:75$; $\beta:100$)	Byford 2011
Relapse after 8 weeks	2.89	Gamma ($\alpha:61.47$; $\beta:0.05$)	100.0%	Uniform ($\alpha:75$; $\beta:100$)	Byford 2011
Psychiatrist consultations					
Remission 0-8 weeks	0.00	-	0.0%	Beta ($\alpha:0$; $\beta:0$)	PERFORM
No remission 0-8 weeks	1.00	Gamma ($\alpha:61.47$; $\beta:0.02$)	1.3%	Beta ($\alpha:2$; $\beta:152$)	PERFORM
Remission after 8 weeks	0.23	Gamma ($\alpha:61.47$; $\beta:0.00$)	2.9%	Beta ($\alpha:60$; $\beta:1,997$)	Byford 2011
Relapse after 8 weeks	0.23	Gamma ($\alpha:61.47$; $\beta:0.00$)	5.0%	Beta ($\alpha:58$; $\beta:1,109$)	Byford 2011
Psychotherapy or counselling					
Remission 0-8 weeks	1.20	Gamma ($\alpha:9.00$; $\beta:0.13$)	12.7%	Beta ($\alpha:9$; $\beta:62$)	PERFORM
No remission 0-8 weeks	2.10	Gamma ($\alpha:1.96$; $\beta:1.07$)	18.8%	Beta ($\alpha:29$; $\beta:125$)	PERFORM
Remission after 8 weeks	0.0	-	0.2%	Beta ($\alpha:61$; $\beta:30609$)	Byford 2011
Relapse after 8 weeks	0.0	-	0.2%	Beta ($\alpha:61$; $\beta:30609$)	Byford 2011
Psychiatric ward admissions					
Remission 0-8 weeks	0.0	-	0.0%	Beta ($\alpha:0$; $\beta:0$)	PERFORM
No remission 0-8 weeks	0.0	-	0.0%	Beta ($\alpha:0$; $\beta:154$)	PERFORM
Remission after 8 weeks	0.22	Gamma ($\alpha:61.47$; $\beta:0.00$)	5.2%	Beta ($\alpha:58$; $\beta:1,061$)	Byford 2011
Relapse after 8 weeks	0.23	Gamma ($\alpha:61.47$; $\beta:0.00$)	5.7%	Beta ($\alpha:58$; $\beta:958$)	Byford 2011
General ward admissions					
Remission 0-8 weeks	0.0	-	0.0%	Beta ($\alpha:0$; $\beta:0$)	PERFORM
No remission 0-8 weeks	1.0	Gamma ($\alpha:0.35$; $\beta:2.89$)	0.5%	Beta ($\alpha:1$; $\beta:153$)	PERFORM
Remission after 8 weeks	0.0	-	0.0%	Beta ($\alpha:0$; $\beta:0$)	Assumed equivalent to acute phase
Relapse after 8 weeks	1.0	Gamma ($\alpha:61.47$; $\beta:0.02$)	0.51%	Beta ($\alpha:61$; $\beta:11924$)	Assumed equivalent to acute phase
Accident & Emergency visits					
Remission 0-8 weeks	0.0	-	0.0%	Beta ($\alpha:0$; $\beta:0$)	PERFORM
No remission 0-8 weeks	0.0	-	0.0%	Beta ($\alpha:0$; $\beta:154$)	PERFORM
Remission after 8 weeks	0.22	Gamma ($\alpha:61.47$; $\beta:0.00$)	3.1%	Beta ($\alpha:60$; $\beta:1,861$)	Byford 2011
Relapse after 8 weeks	0.25	Gamma ($\alpha:61.47$; $\beta:0.00$)	3.3%	Beta ($\alpha:59$; $\beta:1,741$)	Byford 2011

References to sources: Byford 2011²³⁴, PERFORM^{19,20,236}.**Table B61. Model parameter inputs: absenteeism effects**

Event	Number of days absent	Distribution	% of patients with ≥ 1 day absent	Distribution	Source
Absenteeism					
Remission 0-8 weeks	28.60	Gamma ($\alpha:61.47$; $\beta:0.47$)	15.49%	Beta ($\alpha:52$; $\beta:2820$)	PERFORM
No remission 0-8 weeks	41.60	Gamma ($\alpha:61.47$; $\beta:0.68$)	28.57%	Beta ($\alpha:44$; $\beta:109$)	
Remission after 8 weeks	0.39	Gamma ($\alpha:61.47$; $\beta:0.01$)	7.57%	Beta ($\alpha:57$; $\beta:693$)	
Relapse after 8 weeks	9.50	Gamma ($\alpha:61.47$; $\beta:0.15$)	22.75%	Beta ($\alpha:47$; $\beta:160$)	

References to sources: PERFORM^{19,20,236}.

7.5.4 Clinical expert assessment

Please see section 7.3.5.

7.5.5 Cost of each treatment

Table B62 provides unit costs for vortioxetine, for each of the modelled comparators and for the antidepressants assumed to be used in the event of further switches. The medication costs were taken from MIMS²⁶⁴.

Antidepressants are titrated during the first weeks of treatment until the optimal dose is reached. The drug costs inputted into the model are separated into a daily cost for the first 8 weeks acute treatment and then for a maintenance phase. The dose used in the maintenance phase is calculated from the end of study dose in the studies used in the indirect comparison. Where more than one end of study dose is available the mean dosage is used (e.g. venlafaxine ER has an end of study dose of 193.6mg in STAR*D and 191mg in Lenox-Smith, so a dosage of 192.3mg is used in the cost calculation for maintenance dose). For the acute phase where the drug is titrated no details are given in the published studies of the average dosage during titration. Therefore the World Health Organisation Defined Daily Dose (DDD) is used to calculate the cost during the acute phase.

Table B62. Model parameter inputs: unit costs of vortioxetine and other antidepressants

INN and pharmaceutical form	Brand name*	Dosage unit	Pack size	Basic NHS cost per pack	Dose in acute phase	Dose in maintenance phase	Daily cost in acute phase	Daily cost in maintenance phase
Vortioxetine tablets	Brintellix	5mg	28	£27.72	10mg	16.47mg	£0.99	£0.99
		10mg	28	£27.72				
		20mg	28	£27.72				
Agomelatine tablets excluding (including) LFT**	Valdoxan	25mg	28	£30.00	25mg	42.93mg	£1.07 (£1.46)	£1.84 (£2.10)
		50mg	NA	£60.00				
Sertraline tablets		50mg	28	£1.75	50mg	135.5mg	£0.06	£0.10
		100mg	28	£2.15				
Venlafaxine modified-release tablets	VenlaBlue XL	37.5mg	28	£ 5.25	100mg	192.3mg	£0.24	£0.46
	VenlaBlue XR	75mg	28	£6.95				
	VenlaBlue XR	150mg	28	£9.95				
	Venlalic XL	225mg	30	£33.60				
Citalopram tablets		10mg	28	£0.91	20mg	51mg	£0.04	£0.06
		20mg	28	£1.10				
		40mg	28	£1.28				

*Prices from MIMS December 2014. Drug costs are calculated using the lowest cost format when several formats are available (i.e. the lowest cost generic available). n/a: not available.

** The SmPC for agomelatine stipulates that liver function tests (LFT) are required at specific intervals. Therefore the total drug cost includes the costs associated with monitoring liver function during the acute and maintenance phases and the drug acquisition cost. Three LFTs during the acute phase and 2 in the maintenance phase are assumed. The costs are estimated as the cost of an LFT from the NHS Reference Cost 2012-2013 (£3 - DAPS05 Haematology) and 5 minutes of nurse time for each test based on Curtis 2013²⁶⁵ (£52 per hour of patient-related work including qualifications – Unit Costs of Health & Social Care 2013 p.184). The cost-effectiveness analyses use the cost including LFT.

7.5.6 Health state costs

Resource utilisation for the **acute phase** was taken from PERFORM^{19,20,236} and for the **maintenance phase** from Byford²³⁴. Table B63 below gives weighted average costs for each modelled health state. Information on number of visits or utilisations of each resource item and percentage of patients with at least one visit or utilisation were applied to each health state. Corresponding unit costs were taken from Unit Costs of Health & Social Care 2013 (Curtis 2013)²⁶⁵ and NHS Reference Costs. Any non-2013 costs were expressed at 2013 levels, using the Hospital and Community Health Services (HCHS) inflator.

Table B63. Model parameter inputs: health state contingent costs

Resource item Health state/event	No. of visits every 2 months	% of patients with ≥1 visit	Unit cost	Weighted average cost	Source
Consultations					
GP consultation			£45.00		Curtis 2013 - GP visit lasting 11.7 min including direct care staff costs with qualification costs
Remission 0-8 weeks	2.5	100%		£112.50	PERFORM
No remission 0-8 weeks	2.8	100%		£126.00	PERFORM

Resource item Health state/event	No. of visits every 2 months	% of patients with ≥1 visit	Unit cost	Weighted average cost	Source
Remission after 8 weeks	2.15	100%		£96.60	Byford 2011
Relapse after 8 weeks	2.89	100%		£130.05	Byford 2011
Treatment change/switch/stop	1		£46.00	£46.00	Assumption
Psychiatrist consultation			£125.00		Curtis 2013 - weighted average of all community contacts
Remission 0-8 weeks	0	0.0%		£0.00	PERFORM
No remission 0-8 weeks	1	1.3%		£1.62	PERFORM
Remission after 8 weeks	0.230	2.9%		£0.83	Byford 2011
Relapse after 8 weeks	0.233	5.0%		£1.46	Byford 2011
Psychotherapy or counselling			£145.00		NHS Reference Costs 2012/13: Outpatient attendance cost for psychotherapy (Code 713: Total - outpatient attendances)
Remission 0-8 weeks	1.2	12.68%		£22.06	PERFORM
No remission 0-8 weeks	2.1	18.83%		£57.34	PERFORM
Remission after 8 weeks	0	0.20%		£0.00	Not stated
Relapse after 8 weeks	0	0.20%		£0.00	Not stated
Hospital inpatient admissions					
Psychiatric ward			£342.00		Curtis 2013: Mental health care clusters (admitted).
Remission 0-8 weeks	0	0.0%		£0.00	PERFORM
No remission 0-8 weeks	0	0.0%		£0.00	PERFORM
Remission after 8 weeks	0.22	5.2%		£3.99	Byford 2011
Relapse after 8 weeks	0.23	5.7%		£4.56	Byford 2011
General ward			£697.00		Curtis 2013: Weighted average of all stays - day cases HRG data
Remission 0-8 weeks	0	0.0%		£0.00	PERFORM
No remission 0-8 weeks	1	0.5%		£3.56	PERFORM
Remission after 8 weeks	0	0.0%		£0.00	Assumed equivalent to acute phase
Relapse after 8 weeks	1	0.5%		£3.56	Assumed equivalent to acute phase
Hospital outpatient visits					
A&E visits			£177.00		Curtis 2013: Weighted average of attendances - See and treat and refer
Remission 0-8 weeks	0	0.0%		£0.00	PERFORM
No remission 0-8 weeks	0	0.0%		£0.00	PERFORM
Remission after 8 weeks	0.22	3.1%		£1.18	Byford 2011
Relapse after 8 weeks	0.25	3.3%		£1.48	Byford 2011

Curtis 2013²⁶⁵ (Unit Costs of Health & Social Care 2013). Sources: Byford 2011²³⁴, PERFORM^{19,20,236}.

7.5.7 Adverse event costs

In addition to the health state-contingent costs reported in Table B63, patients incurred cost tolls for adverse events in the model. Information on the management and treatment of adverse events was based on investigation of NICE guidelines and the literature^{10,235}.

Although guidelines including those from the British Association for Psychopharmacology⁸⁹ recommend the use of some pharmacological therapies to help patients deal with their adverse events, clinical opinion suggested that in reality this rarely occurs. Therefore, a conservative approach was taken and it is assumed that no treatments are prescribed to help manage TEAEs.

With regards to the number of patients who present to their GP regarding TEAEs, clinical consensus was that around one-third of patients will schedule an additional appointment concerning these. Therefore, it has been assumed that 30% of patients experiencing an adverse event return to their GP for an additional appointment.

Table B64 gives the costs of managing adverse events, given the units of each type of health care resource utilised and the unit costs of each.

Table B64. Model parameter inputs: adverse event contingent costs

Short term adverse events	No. of visits	Unit cost (£)	Total cost (£)	Source
GP visit for all AEs	0.3	45.00	13.50	Unit Costs of Health & Social Care 2013 - GP visit lasting 11.7 minutes including direct care staff costs with qualification costs

Unit Costs of Health & Social Care 2013²⁶⁵

7.5.8 Productivity costs

As described in section 2.1.9, depression has an impact on workplace productivity. This impact is included alongside healthcare costs in an alternative analysis. Productivity costs were estimated by the human capital approach, in which the value of an individual's absenteeism is assumed to be equivalent to the duration of absence multiplied by the national average wage. No attempt was made to estimate the productivity impact for people remaining at work but operating at an impaired level of performance, nor were personal and social services (PSS) costs and indirect effects on patients' families or carers estimated. Hence, this alternative analysis is described hereafter as analysis from a partial societal perspective.

Table B65 provides the calculation for the cost of absenteeism. Data on the number of days lost due to illness and the percentage of patients with at least one absent day were collected from PERFORM, based on reported sick leaves (as previously shown in Table B61). These health-state contingent weighted mean absence data were multiplied by the national average wage to estimate mean costs for patients in remission and not in remission. It was assumed that absenteeism associated with remission and relapse after 8 weeks was the same as remission and no remission, respectively, in the acute treatment phase before 8 weeks.

Table B65. Model parameter inputs: costs of absenteeism

Event	Daily wage	Calculation	Mean cost	Source	Comment
Absenteeism					
Remission 0-8 weeks		15.49% x 28.6 days x £113.70	£504		(Overall UK population)
No remission 0-8 weeks		28.57% x 41.6 days x £113.70	£1,351		
Remission after 8 weeks	£113.70	7.57% x 0.39 days x £113.70	£3	PERFORM; ASHE 2013 (revised) Table 1 - All Employees / Table 1.5a hourly pay - Gross	Assumption
Relapse after 8 weeks		22.75% x 9.5 days x £113.70	£246		Assumption. Not used in switch

Sources: PERFORM. Data on file²³⁶; Annual Survey of Hours and Earnings (ASHE)²⁶⁶.

7.6 Sensitivity analysis

To assess the sensitivity of the economic analysis to alternative assumptions, several sensitivity analyses were carried out:

- To evaluate the impact of the uncertainty around single parameters on the results individually and in combination
- To evaluate the impact of selecting alternative data sources

Analyses conducted included:

- One way deterministic sensitivity analysis (DSA)
- Scenario analysis
- Probabilistic sensitivity analysis (PSA)
- Threshold analysis

7.6.1 Structural assumptions

The sensitivity of the base-case results to a number of alternative analytic perspectives, structural assumptions, and sources of parameter inputs was tested in scenario analyses. These scenarios are listed in Table B66.

Table B66. Structural and other assumptions tested in scenario analyses

Assumptions	Base case	Alternative assumption(s)	
Analytic perspective	NHS and PSS	Partial societal (includes cost of absenteeism but not presenteeism)	-
Structural			
Management of MDE after long-term AEs	75% of patients remain on current treatment and 25% switch to 3rd line	50% of patients remain on current treatment, 50% switch to 3rd line treatment	All patients remain on current treatment
Consultations following an AE (in addition to standard monitoring)	30% of patients consult GP	No patients consult GP	All patients consult GP
Cost of subsequent treatment lines (3+)	Equivalent to citalopram (£0.06/day)	£10 per day for all subsequent treatment lines	-
Outcome scenarios			
Methodology of data synthesis in ITC: Acute phase remission and withdrawal due to AEs	Values from ITC using frequentist framework	Values from Bayesian mixed treatment comparison	-
Probability of remission at 8 weeks	Remission rates from ITC (frequentist)	Include additional 20% of patients into the “remitters” cohort following 2 nd line treatment to represent responders who have not achieved remission but may continue treatment	-
Relapse rates	Rate does not vary between comparators (14.2%)	More aggressive assumption: rate does not vary between comparators, but increased rates assumed in CG90 model used (55%)	More conservative assumption: rate does not vary between comparators; use alternative rate from relapse prevention study (13.2%)
Utility and disutility scenarios			
Range of short-term AEs with disutilities applied	Included: sexual dysfunction, nausea, somnolence, headache, diarrhoea, insomnia and weight gain. Excluded: AEs not reported explicitly in Sullivan ²³⁷ (dizziness, dry mouth and sweating)	Apply disutility reported in Sullivan for “other” AEs to dizziness, dry mouth and sweating.	No disutilities applied to any short-term AEs
Duration of impact of short-term AEs on utility	3 weeks	1 week	-
Source of maintenance phase health state utility values	Sapin 2004 ¹⁸	Mann 2009 ²⁵⁴	-
Others			

Rates of weight gain	Pooled rate for SSRIs and rate for venlafaxine from Bet 2013 ²³² ; agomelatine from Goodwin 2009 ²³¹	Individual rates for citalopram, sertraline, venlafaxine from Uguz ²³³ ; agomelatine from Goodwin 2009 ²³¹	-
Reduce cost of venlafaxine to immediate release (IR) cost	Lowest cost formulation of venlafaxine XR used, as clinical studies in ITC use XR formulation	A proportion of UK patients use venlafaxine IR, which has a lower acquisition cost. Costs reduced to IR formulation*, no change in efficacy inputs.	

*Venlafaxine IR cost: £2.59 per pack of 56 75mg tablets, taken from MIMS Dec 2014. Acute phase cost £0.06 per day, maintenance phase cost £0.12 per day. ITC: indirect treatment comparison; AE: adverse event.

7.6.2 Deterministic sensitivity analysis

DSAs were conducted to illustrate the extent to which the results were affected by a change in a single parameter or model assumption with all others being held constant. Table B67 lists the parameters that were varied and their alternative values. All distributions used for the parameters were linked to PSA.

Table B67. Deterministic sensitivity analysis: efficacy parameters

Parameter	Base case	Minimum value	Maximum value	Comment
Remission at 8 weeks for vortioxetine (based on the difference between vortioxetine vs. agomelatine)	40.5%	34.5%	46.6%	REVIVE
Withdrawal due to AEs at 8 weeks for vortioxetine (based on the difference between vortioxetine vs. agomelatine)	5.9%	3.37%	9.15%	REVIVE
Relapse rates on vortioxetine maintenance treatment	14.2%	10.8%	18.0%	Based on beta distribution used for the PSA
Relapse rates after premature stop on vortioxetine	24.8%	20.1%	30.0%	Based on beta distribution used for the PSA
Relapse rates after switch to 3rd line	25.0%	12.3%	40.3%	Based on beta distribution used for the PSA
Relapse rates after switch to 4th line	42.6%	19.7%	67.3%	Based on beta distribution used for the PSA

AEs: adverse events; PSA: probabilistic sensitivity analysis.

Table B68. Deterministic sensitivity analysis: short-term side-effects parameters (acute phase)

Side-effect	Treatment	Probability	95% CI	
			Lower bound	Upper bound
Sexual dysfunction	Vortioxetine	0.4%	0.0%	1.5%
	Agomelatine	0.0%	0.0%	0.0%
	Sertraline	10.6%	9.0%	12.4%
	Venlafaxine	14.4%	9.3%	20.3%
	Citalopram	6.2%	4.8%	7.9%
Dry mouth	Vortioxetine	4.7%	2.5%	7.7%
	Agomelatine	3.3%	1.4%	5.9%
	Sertraline	14.5%	13.0%	16.0%
	Venlafaxine	23.0%	19.8%	26.3%
	Citalopram	6.7%	5.4%	8.1%
Nausea	Vortioxetine	16.2%	11.9%	21.0%
	Agomelatine	9.1%	5.8%	13.0%
	Sertraline	26.2%	24.5%	27.9%
	Venlafaxine	41.0%	37.7%	44.4%
	Citalopram	11.0%	9.5%	12.6%
Sweating	Vortioxetine	2.4%	0.9%	4.6%
	Agomelatine	2.1%	0.7%	4.2%
	Sertraline	13.3%	11.8%	15.0%
	Venlafaxine	12.9%	10.7%	15.2%
	Citalopram	6.5%	4.9%	8.3%
Somnolence	Vortioxetine	4.0%	1.9%	6.7%
	Agomelatine	7.9%	4.8%	11.5%
	Sertraline	9.1%	7.9%	10.4%
	Venlafaxine	8.6%	6.8%	10.6%
	Citalopram	6.8%	5.4%	8.5%
Headache	Vortioxetine	10.3%	6.9%	14.3%
	Agomelatine	13.2%	9.3%	17.8%
	Sertraline	26.1%	24.4%	27.8%
	Venlafaxine	21.6%	19.2%	24.2%

Side-effect	Treatment	Probability	95% CI	
			Lower bound	Upper bound
Diarrhoea	Citalopram	10.8%	9.3%	12.5%
	Vortioxetine	3.2%	1.4%	5.6%
	Agomelatine	3.3%	1.4%	5.9%
	Sertraline	20.1%	18.6%	21.8%
	Venlafaxine	8.9%	7.2%	10.9%
	Citalopram	6.7%	5.4%	8.2%
Insomnia	Vortioxetine	7.1%	4.3%	10.6%
	Agomelatine	2.9%	1.2%	5.3%
	Sertraline	18.1%	16.5%	19.7%
	Venlafaxine	18.0%	15.4%	20.7%
	Citalopram	7.5%	6.2%	8.8%
Dizziness	Vortioxetine	7.1%	4.3%	10.6%
	Agomelatine	11.6%	7.9%	15.9%
	Sertraline	10.4%	9.0%	11.9%
	Venlafaxine	13.2%	11.1%	15.6%
	Citalopram	4.6%	3.3%	6.1%

Table B69. Deterministic sensitivity analysis: long-term side-effects parameters (maintenance phase)

Side-effect	Treatment	Probability	95% confidence interval	
			Lower bound	Upper bound
Sexual dysfunction	Vortioxetine	1.6%	0.8%	2.6%
	Agomelatine	0.0%	0.0%	0.0%
	Sertraline	23.0%	19.6%	26.4%
	Venlafaxine	31.0%	23.8%	38.8%
	Citalopram	23.0%	19.6%	26.4%
Insomnia	Vortioxetine	3.5%	2.3%	4.9%
	Agomelatine	1.8%	0.4%	4.3%
	Sertraline	7.0%	5.1%	9.2%
	Venlafaxine	10.0%	5.9%	15.8%
	Citalopram	7.0%	5.1%	9.2%
Weight gain	Vortioxetine	2.9%	1.8%	4.2%
	Agomelatine	0.0%	0.0%	0.0%
	Sertraline	19.0%	15.9%	22.3%
	Venlafaxine	17.0%	11.6%	23.8%
	Citalopram	19.0%	15.9%	22.3%

Table B70. Deterministic sensitivity analysis: resource use parameters

Parameter	Base case	95% confidence interval	
		Lower bound	Upper bound
Consultations			
Mean number of GP consultations			
Acute phase remission	2.50	1.91	3.16
Acute phase no remission	2.80	2.14	3.54
Maintenance phase remission	2.15	1.64	2.72
Maintenance phase relapse	2.89	2.21	3.66
% of patients with at least one GP consultation			
Acute phase remission	100%	75%	100%
Acute phase no remission	100%	75%	100%
Maintenance phase remission	100%	75%	100%
Maintenance phase relapse	100%	75%	100%
Mean number of psychiatrist consultations			
Acute phase remission	0.00	0.00	0.00
Acute phase no remission	1.00	0.77	1.27
Maintenance phase remission	0.23	0.18	0.29
Maintenance phase relapse	0.23	0.18	0.30
% of patients with at least one psychiatrist consultation			
Acute phase remission	0.0%	0.0%	0.0%
Acute phase no remission	1.3%	0.2%	3.6%
Maintenance phase remission	2.9%	2.2%	3.7%
Maintenance phase relapse	5.0%	3.8%	6.3%
Mean number of psychotherapy or counselling consultations			
Acute phase remission	1.20	0.55	2.10
Acute phase no remission	2.10	0.25	5.90
Maintenance phase remission	0.00	0.00	0.00
Maintenance phase relapse	0.00	0.00	0.00
% of patients with at least one psychotherapy consultation			
Acute phase remission	12.7%	6.1%	21.3%
Acute phase no remission	18.8%	13.1%	25.4%
Maintenance phase remission	0.2%	0.2%	0.3%
Maintenance phase relapse	0.2%	0.2%	0.3%
Hospital inpatient admissions			
Mean number of admissions to psychiatric ward			
Acute phase remission	0.00	0.00	0.00
Acute phase no remission	0.00	0.00	0.00
Maintenance phase remission	0.22	0.17	0.28
Maintenance phase relapse	0.23	0.18	0.30
% of patients with at least one psychiatric admission			
Acute phase remission	0.0%	0.0%	0.0%
Acute phase no remission	0.0%	0.0%	0.0%

Parameter	Base case	95% confidence interval	
		Lower bound	Upper bound
Maintenance phase remission	5.2%	4.0%	6.6%
Maintenance phase relapse	5.7%	4.4%	7.2%
Mean number of admissions to general ward			
Acute phase remission	0.00	0.00	0.00
Acute phase no remission	1.00	0.00	5.94
Maintenance phase remission	0.00	0.00	0.00
Maintenance phase relapse	1.00	0.77	1.27
% of patients with at least one general ward admission			
Acute phase remission	0.0%	0.0%	0.0%
Acute phase no remission	0.5%	0.0%	2.4%
Maintenance phase remission	0.0%	0.0%	0.0%
Maintenance phase relapse	0.5%	0.4%	0.6%
Hospital outpatient visits			
Mean number of A&E visits			
Acute phase remission	0.00	0.00	0.00
Acute phase no remission	0.00	0.00	0.00
Maintenance phase remission	0.22	0.16	0.27
Maintenance phase relapse	0.25	0.19	0.32
% of patients with at least one A&E visit			
Acute phase remission	0.0%	0.0%	0.0%
Acute phase no remission	0.0%	0.0%	0.0%
Maintenance phase remission	3.1%	2.4%	3.9%
Maintenance phase relapse	3.3%	2.5%	4.2%

Table B71. Deterministic sensitivity analysis: absenteeism parameters

Absenteeism	Base case	95% CI	
		Lower	Upper
% of patients at least one absent day remission 8 weeks	15.5%	11.8%	19.6%
Number of absenteeism days at remission 8 weeks	28.60	21.90	36.18
% of patients at least one absent day no remission 8 weeks	28.6%	21.7%	36.0%
Number of absenteeism days at no remission 8 weeks	41.60	31.86	52.63
% of patients at least one absent day remission after 8 weeks	7.6%	5.8%	9.6%
Number of absenteeism days remission after 8 weeks	0.39	0.30	0.49
% of patients at least one absent day relapse after 8 weeks	22.8%	17.3%	28.7%
Number of absenteeism days relapse after 8 weeks	9.50	7.27	12.02

Table B72. Deterministic sensitivity analysis: health state utility values

	Base case	95% CI	
		Lower bound	Upper bound
Acute phase (0-8 weeks)			
Remission	0.85	0.83	0.87
No remission	0.62	0.58	0.66
Maintenance phase (2-8 months)			
Remission	0.85	0.58	0.99
No remission	0.58	0.43	0.72

7.6.3 Probabilistic sensitivity analyses

Probabilistic sensitivity analyses (PSAs) were conducted for each model input that was considered to be a random variable and for which a probability distribution and associated parameters could be defined. The differences in rates of remission and differences in withdrawal rates due to AEs at 8 weeks were assumed to be normally distributed. Relapse rates, AEs, proportions of patients with at least one utilisation of a resource item, and utility values were assumed to follow beta distributions. The numbers of utilisations for each resource item were assumed to follow a gamma distribution. All model inputs that were included in PSA and associated distributional assumptions are shown in Table B52 to Table B55.

7.7 Results

7.7.1 Clinical outcomes from the model

Please see clinical outcomes reported in Table B73.

7.7.2 Markov traces

The cohort enters the model initially into a decision tree. According to contingent events, they may remain in the tree or enter the Markov process. There are three routes into the Markov process: switch due to lack of efficacy, switch due to adverse events and switch due to long-term adverse events. In Appendix 18 the Markov traces including the transition matrix, Markov utilities and Markov costs of vortioxetine and each comparator are presented for switch due to lack of efficacy as an example.

7.7.3 Accrual of QALYs over time

QALYs are calculated by rolling the tree for each of the potential pathways. In the acute phase, all pathways have QALYs calculated based on one month of depression at baseline and one month of utility associated with the relevant health state. The formulas in the maintenance phase are adjusted to reflect its six-month duration. As the impact of AEs is modelled as disutilities, the associated QALYs lost to each AE occurrence are subtracted from the overall QALYs of the pathway. In the Markov component of the model, QALYs are calculated by multiplying the probability of being in each health state by the utility of that health state. Half-cycle corrections are applied as the timing of transitions within a cycle are not known. Appendix 18 provides an example of the Markov traces associated with QALYs accrued in the event of switch due to lack of efficacy.

7.7.4 Accrual of QALYs for each clinical outcome.

As Table B73 shows, the expected number of QALYs accrued per patient was greatest for vortioxetine, at 0.694. As the modelled time horizon was 12 months, this value corresponds to a mean utility of 0.694 over the same period. Agomelatine had the next greatest expected number of QALYs (0.676), followed by venlafaxine (0.675). The two SSRIs, sertraline and citalopram had the least expected QALYs, at 0.664 each. The differences between these values were driven by the treatment-specific joint effects of remission rate in the acute phase, adverse events in both phases and AE-related withdrawals. These variables determined the differences between treatments in the proportions of the cohort that maintained remission and entered the recovery state in the maintenance phase, and the length of time spent in these states of relatively greater utility.

Table B73. Model outputs by clinical outcomes, for each comparator

Outcome	Vortioxetine	Agomelatine	Sertraline	Venlafaxine	Citalopram
Expected QALYs per patient	0.694	0.676	0.664	0.675	0.664
Percentage of patients in remission at 8 weeks	40.5%	29.5%	26.1%	33.3%	23.7%
Percentage of patients achieving recovery	39.7%	31.2%	27.7%	33.0%	25.9%
Percentage of patients in recovery after initial treatment	34.1%	25.2%	20.0%	25.1%	18.2%
Percentage of patients who relapse on initial treatment	5.6%	4.2%	3.3%	4.2%	3.0%
Percentage of patients who relapse after initial remission	13.9%	14.1%	12.7%	12.5%	12.7%
Percentage of patients who switch	65.9%	74.8%	80.0%	74.9%	81.8%
Mean number of months spent in remission and recovery states	5.27	4.41	4.26	4.86	4.07

7.7.5 Disaggregation of QALYs and costs by health state

For vortioxetine and each of its four comparators (agomelatine, sertraline, venlafaxine and citalopram) Table B74-Table B77, respectively, show the total QALYs accrued during the acute and maintenance phases of the model broken down by the outcomes within each phase. Each table also reports incremental values between vortioxetine and the respective comparator in absolute terms and the percentage of total incremental QALYs.

Table B74. Breakdown of QALYs accrued by health state: vortioxetine vs. agomelatine

	Vortioxetine QALYs	Agomelatine QALYs	Incremental QALYs	% of total incremental QALYs
Acute phase	0.102	0.100	0.002	10.8%
Depression at baseline	0.045	0.045	0.000	0.0%
Remission at 8 weeks	0.029	0.021	0.008	44.0%
No remission at 8 weeks	0.031	0.036	-0.006	-32.1%
Short-term adverse events	-0.002	-0.002	0.000	-1.1%
Maintenance phase	0.591	0.576	0.016	89.2%
Remission 2-8 months	0.145	0.107	0.038	215.7%
Relapse 2-8 months	0.008	0.006	0.002	12.0%
Recovery 8-12 months	0.097	0.071	0.025	142.0%
Switch	0.342	0.391	-0.049	-279.0%
Long-term adverse events	0.000	0.000	0.000	-1.5%
Total	0.694	0.676	0.018	100.0%

Table B75. Breakdown of QALYs accrued by health state: vortioxetine vs. sertraline

	Vortioxetine QALYs	Sertraline QALYs	Incremental QALYs	% of total incremental QALYs
Acute phase	0.102	0.096	0.006	20.4%
Depression at baseline	0.045	0.045	0.000	0.0%
Remission at 8 weeks	0.029	0.018	0.010	34.8%
No remission at 8 weeks	0.031	0.038	-0.007	-25.4%
Short-term adverse events	-0.002	-0.005	0.003	11.0%
Maintenance phase	0.591	0.568	0.023	79.6%
Remission 2-8 months	0.145	0.087	0.058	198.5%
Relapse 2-8 months	0.008	0.005	0.003	11.5%
Recovery 8-12 months	0.097	0.057	0.040	135.5%
Switch	0.342	0.421	-0.079	-270.6%
Long-term adverse events	0.000	-0.002	0.001	4.7%
Total	0.694	0.664	0.029	100.0%

Table B76. Breakdown of QALYs accrued by health state: vortioxetine vs. venlafaxine

	Vortioxetine QALYs	Venlafaxine QALYs	Incremental QALYs	% of total incremental QALYs
Acute phase	0.102	0.098	0.005	24.6%
Depression at baseline	0.045	0.045	0.000	0.0%
Remission at 8 weeks	0.029	0.024	0.005	27.0%
No remission at 8 weeks	0.031	0.034	-0.004	-19.7%
Short-term adverse events	-0.002	-0.005	0.003	17.3%
Maintenance phase	0.591	0.577	0.014	75.4%
Remission 2-8 months	0.145	0.110	0.036	189.8%
Relapse 2-8 months	0.008	0.006	0.002	11.4%
Recovery 8-12 months	0.097	0.071	0.025	134.7%
Switch	0.342	0.393	-0.052	-273.6%
Long-term adverse events	0.000	-0.003	0.002	13.1%
Total	0.694	0.675	0.019	100.0%

Table B77. Breakdown of QALYs accrued by health state: vortioxetine vs. citalopram

	Vortioxetine QALYs	Citalopram QALYs	Incremental QALYs	% of total incremental QALYs
Acute phase	0.102	0.099	0.003	11.6%
Depression at baseline	0.045	0.045	0.000	0.0%
Remission at 8 weeks	0.029	0.017	0.012	39.4%
No remission at 8 weeks	0.031	0.039	-0.009	-28.8%
Short-term adverse events	-0.002	-0.002	0.000	0.9%
Maintenance phase	0.591	0.565	0.027	88.4%
Remission 2-8 months	0.145	0.079	0.066	219.7%
Relapse 2-8 months	0.008	0.004	0.004	12.6%
Recovery 8-12 months	0.097	0.052	0.045	149.1%
Switch	0.342	0.431	-0.090	-297.0%
Long-term adverse events	0.000	-0.002	0.001	4.1%
Total	0.694	0.664	0.030	100.0%

In similar fashion to the previous four tables, Table B78 to Table B81 present a breakdown of the total costs accrued during the acute and maintenance phases of the model and the cost categories within each phase, for each comparator to vortioxetine. Each table also reports incremental values in absolute terms.

Table B78. Breakdown of costs accrued by category: vortioxetine vs. agomelatine

	Vortioxetine	Agomelatine	Incremental
Overall costs	£971	£1,082	-£111
Drug costs before switch*	£101	£149	-£49
Consultation costs before switch	£221	£187	£34
Hospitalisation costs before switch	£7	£6	£1
Switch costs	£635	£733	-£98
Adverse event costs	£8	£7	£1
Acute phase costs	£239	£264	-£25
Drug costs*	£39	£53	-£14
Consultation costs	£110	£105	£5
Hospitalisation costs	£1	£1	-£0
Switch costs	£82	£97	-£15
Adverse event costs	£7	£7	£0
Maintenance phase costs	£732	£818	-£86
Drug costs*	£62	£96	-£35
Consultation costs	£111	£82	£29
Hospitalisation costs	£6	£4	£2
Switch costs	£553	£635	-£83
Adverse event costs	£0	£0	£0

*Includes cost of liver function monitoring

Table B79. Breakdown of costs accrued by category: vortioxetine vs. sertraline

	Vortioxetine	Sertraline	Incremental
Overall costs	£971	£977	-£6
Drug costs before switch*	£101	£6	£94
Consultation costs before switch	£221	£170	£50
Hospitalisation costs before switch	£7	£5	£2
Switch costs	£635	£774	-£139
Adverse event costs	£8	£22	-£14

	Vortioxetine	Sertraline	Incremental
Acute phase costs	£239	£229	£10
Drug costs*	£39	£2	£37
Consultation costs	£110	£103	£6
Hospitalisation costs	£1	£1	-£0
Switch costs	£82	£102	-£20
Adverse event costs	£7	£20	-£13
Maintenance phase costs	£732	£748	-£16
Drug costs*	£62	£4	£58
Consultation costs	£111	£67	£44
Hospitalisation costs	£6	£4	£2
Switch costs	£553	£671	-£119
Adverse event costs	£0	£2	-£1

Table B80. Breakdown of costs accrued by category: vortioxetine vs. venlafaxine

	Vortioxetine	Venlafaxine	Incremental
Overall costs	£971	£964	£7
Drug costs before switch*	£101	£30	£70
Consultation costs before switch	£221	£191	£30
Hospitalisation costs before switch	£7	£6	£1
Switch costs	£635	£713	-£78
Adverse event costs	£8	£24	-£17
Acute phase costs	£239	£231	£9
Drug costs*	£39	£9	£30
Consultation costs	£110	£106	£3
Hospitalisation costs	£1	£1	-£0
Switch costs	£82	£92	-£10
Adverse event costs	£7	£22	-£14
Maintenance phase costs	£732	£733	-£2
Drug costs*	£62	£21	£40
Consultation costs	£111	£84	£27
Hospitalisation costs	£6	£4	£1
Switch costs	£553	£621	-£68
Adverse event costs	£0	£3	-£2

Table B81. Breakdown of costs accrued by category: vortioxetine vs. citalopram

	Vortioxetine	Citalopram	Incremental
Overall costs	£971	£976	-£5
Drug costs before switch*	£101	£3	£97
Consultation costs before switch	£221	£163	£58
Hospitalisation costs before switch	£7	£5	£2
Switch costs	£635	£795	-£160
Adverse event costs	£8	£11	-£3
Acute phase costs	£239	£220	£20
Drug costs*	£39	£1	£38
Consultation costs	£110	£102	£7
Hospitalisation costs	£1	£1	-£0
Switch costs	£82	£105	-£23
Adverse event costs	£7	£9	-£2
Maintenance phase costs	£732	£757	-£25
Drug costs*	£62	£2	£60
Consultation costs	£111	£61	£50
Hospitalisation costs	£6	£3	£3
Switch costs	£553	£689	-£137
Adverse event costs	£0	£2	-£1

7.7.6 Base-case analysis

The results of the base-case analysis are presented in Table B82 as an incremental cost-utility analysis in accordance with NICE guidance²⁰⁴. The comparator that resulted in the lowest expected costs was venlafaxine, followed by vortioxetine, citalopram, sertraline and agomelatine, in ascending order. Citalopram, sertraline and agomelatine, being more expensive and less effective than at least one comparator, were eliminated by dominance, leaving venlafaxine and vortioxetine to form a cost-effectiveness frontier. Vortioxetine was more expensive and more effective than venlafaxine, and the ICER between the two was £378 per QALY gained.

Table B82. Results of the base-case analysis

Comparators	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Venlafaxine	£964	0.675	-	-	-
Vortioxetine	£971	0.694	£7	0.019	£378
Citalopram	£976	0.664	£5	-0.030	Dominated
Sertraline	£977	0.664	£0	-0.001	Dominated
Agomelatine	£1,082	0.676	£105	0.012	Dominated*

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

*Dominated by extended dominance. Costs for 2014.

7.7.7 Sensitivity analyses

The impact of varying key parameters within plausible ranges was explored. Incremental values between vortioxetine and each comparator are presented as tornado diagrams (Figure B24 to Figure B31). The tornado charts present incremental costs and incremental QALYs separately; there are no tornado charts of ICERs because where negative values occur (in the case of dominance) they are ambiguous. Tables presenting a breakdown of incremental and absolute costs, QALYs and ICERs for vortioxetine versus each comparator are available in Appendix 19.

Hereafter, all pairwise analyses between vortioxetine and a single comparator are presented in ascending order of expected total cost of each comparator in the base-case results, i.e. venlafaxine, citalopram, sertraline, agomelatine.

Figure B24. Sensitivity analysis of incremental costs: vortioxetine vs. venlafaxine

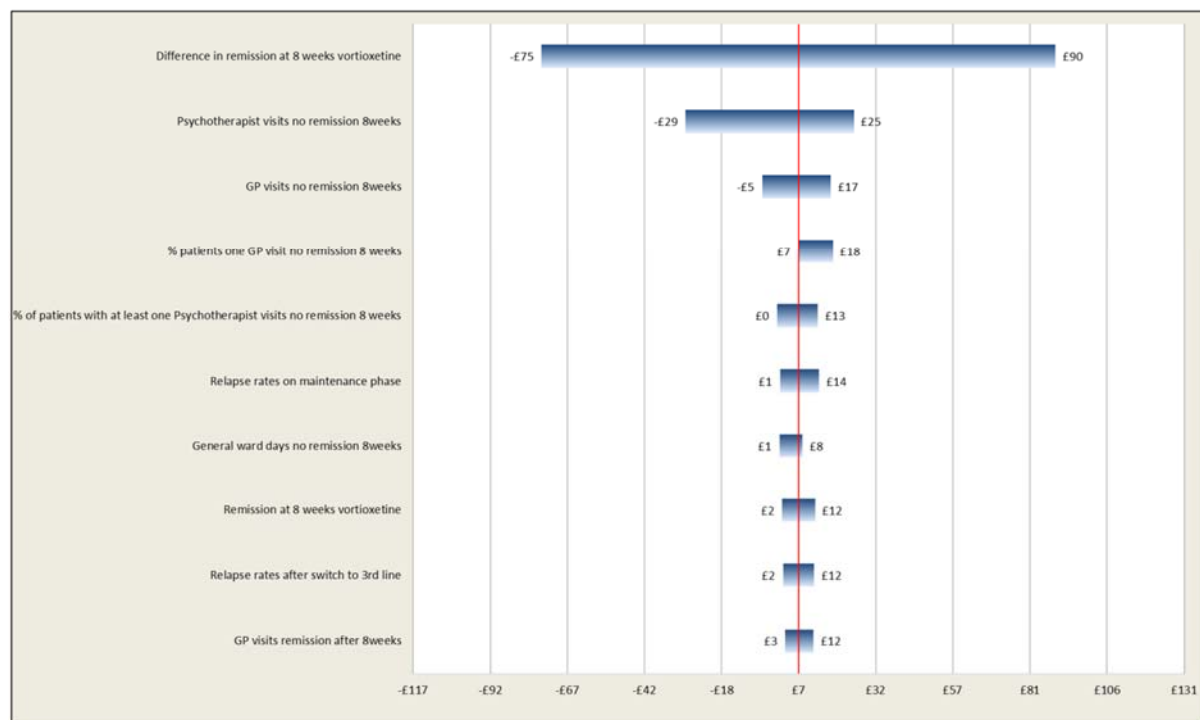


Figure B25. Sensitivity analysis of incremental QALYs: vortioxetine vs. venlafaxine

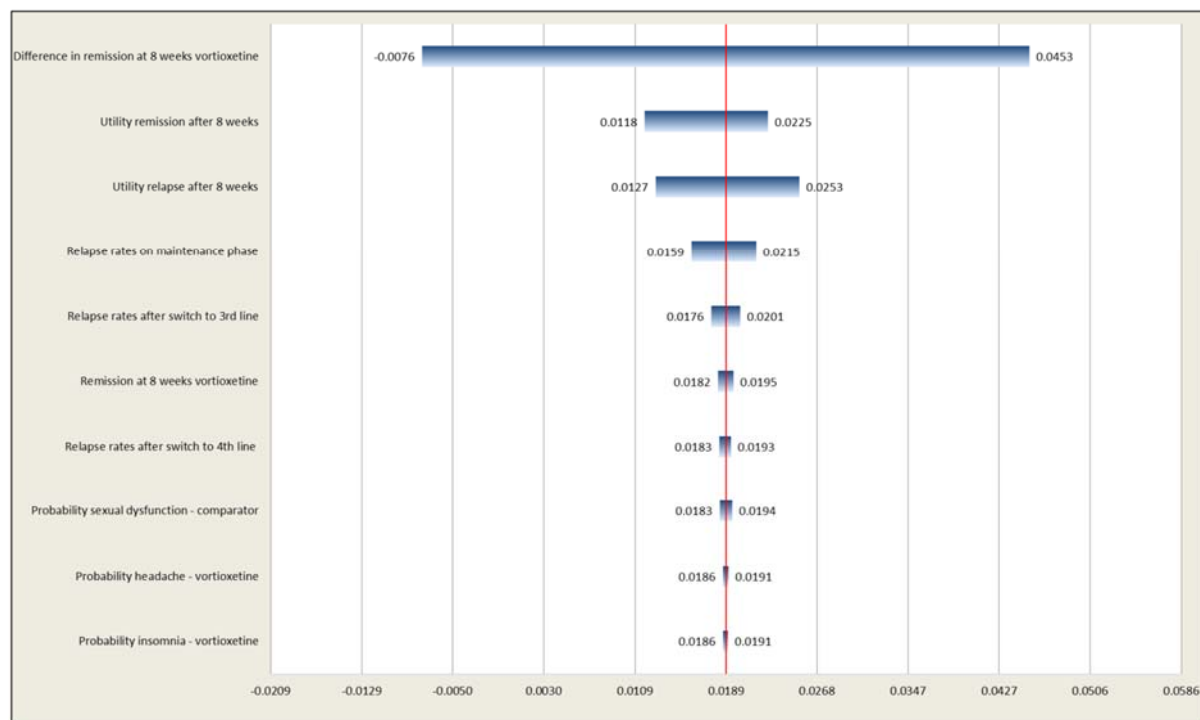


Figure B26. Sensitivity analysis of incremental costs: vortioxetine vs. citalopram

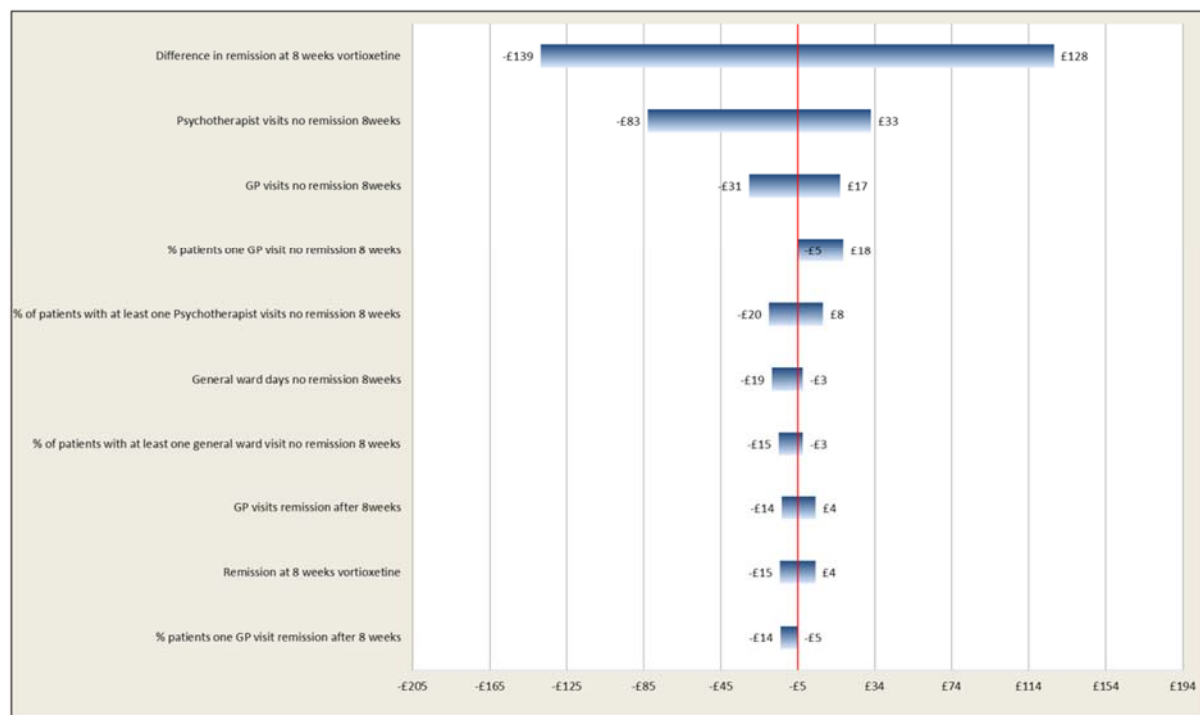


Figure B27. Sensitivity analysis of incremental QALYs: vortioxetine vs. citalopram

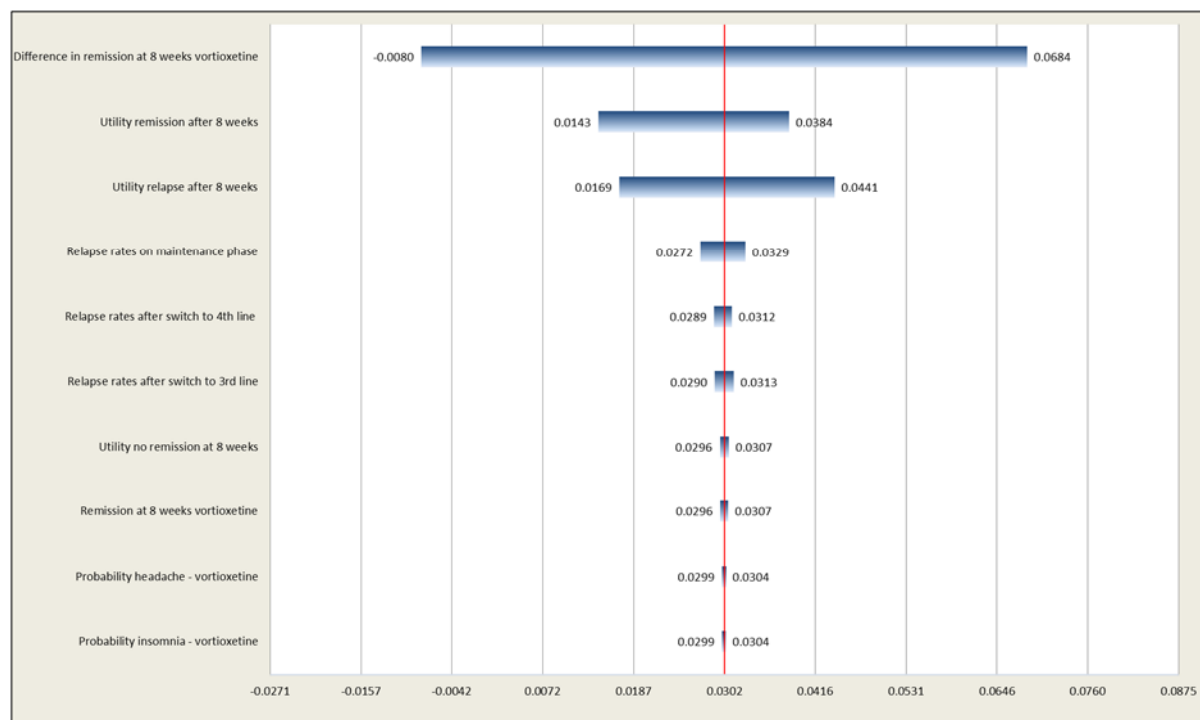


Figure B28. Sensitivity analysis of incremental costs: vortioxetine vs. sertraline

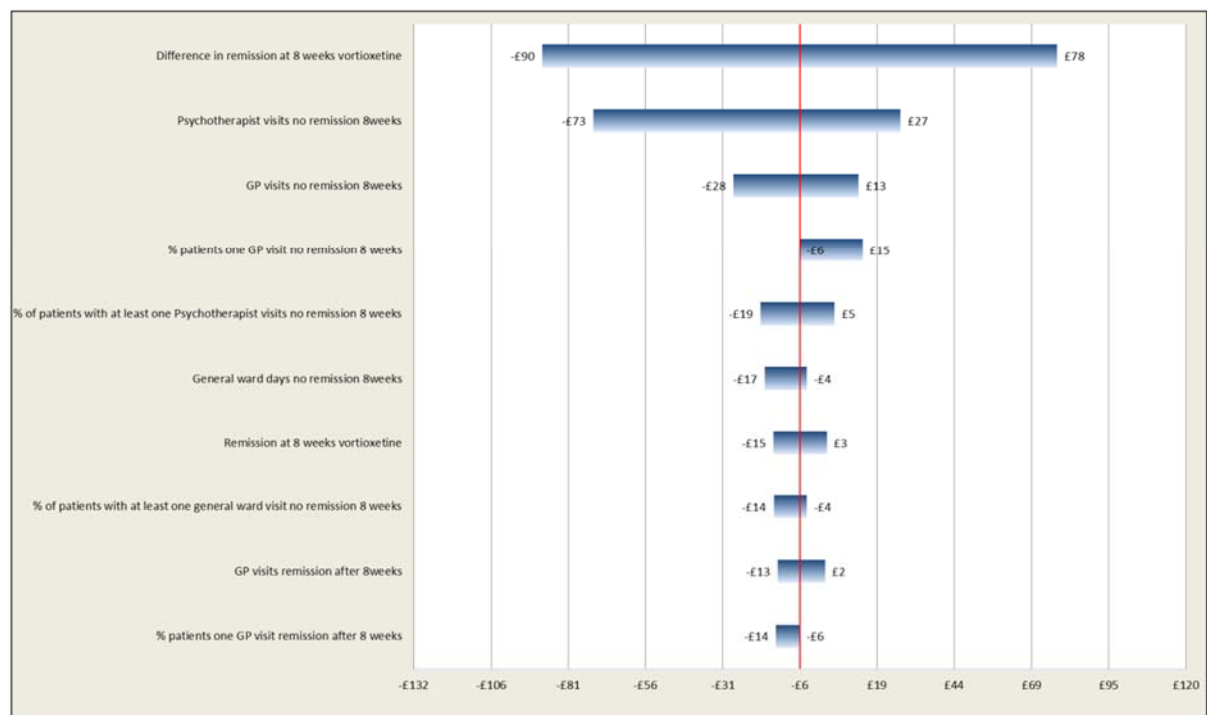


Figure B29. Sensitivity analysis of incremental QALYs: vortioxetine vs. sertraline

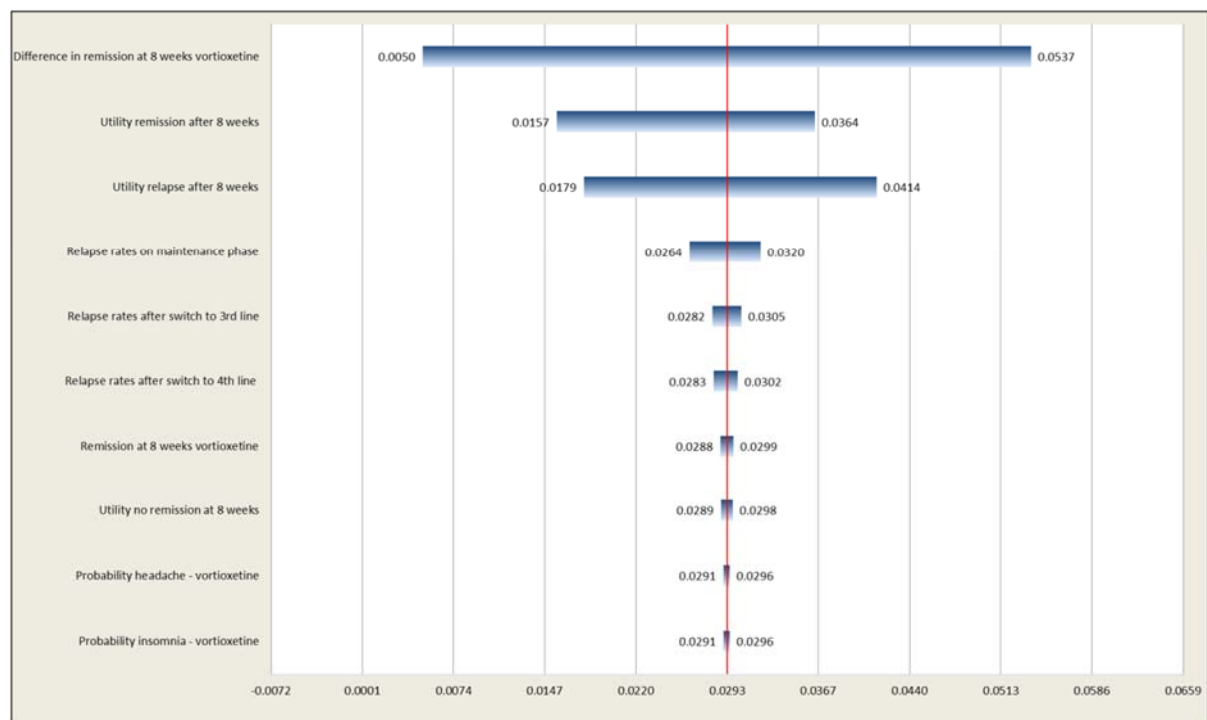


Figure B30. Sensitivity analysis of incremental costs: vortioxetine vs. agomelatine

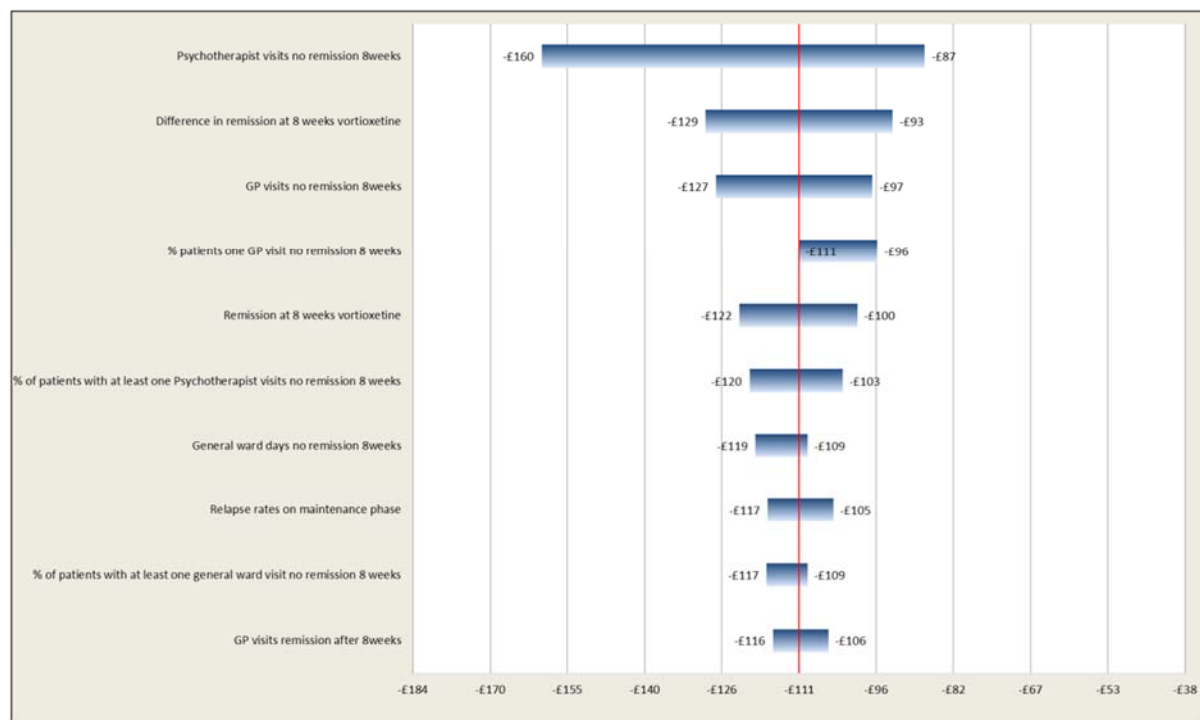
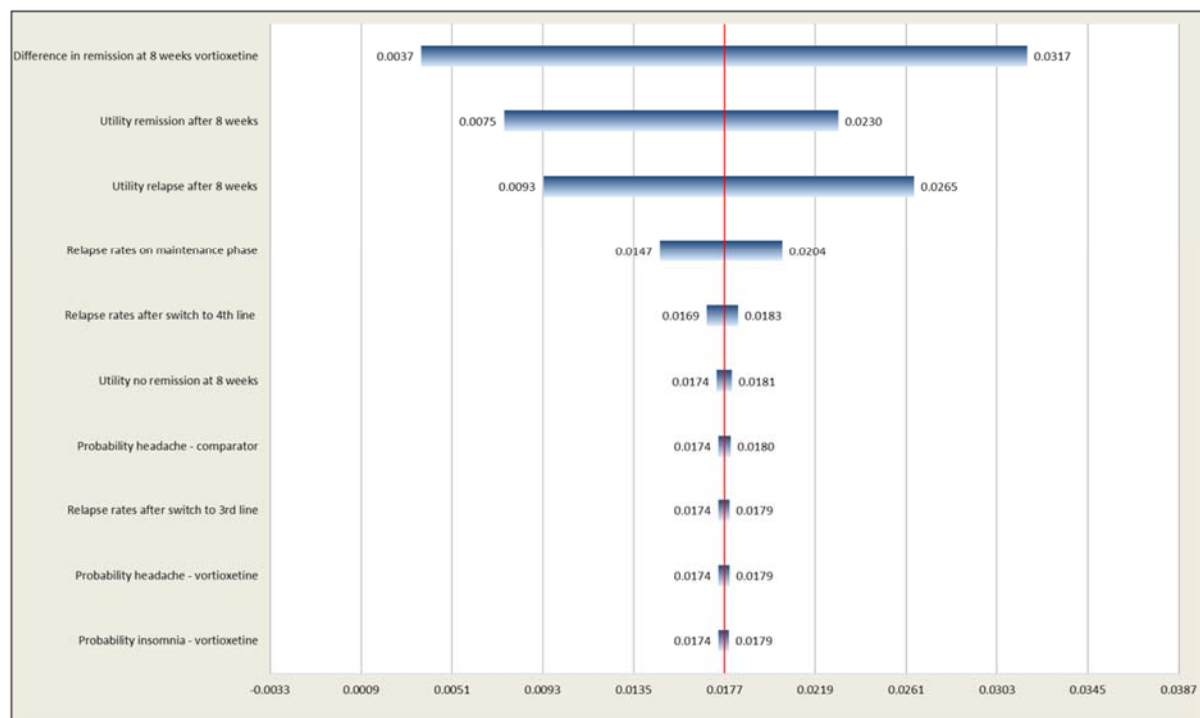


Figure B31. Sensitivity analysis of incremental QALYs: vortioxetine vs. agomelatine



7.7.8 Probabilistic sensitivity analysis

Scatter plots of simulated ICERs between vortioxetine and each comparator, and an associated cost-effectiveness acceptability curve, are presented in Figure B32 to Figure B39. Finally, a multiple cost-effectiveness acceptability curve is presented in Figure B40. The results are interpreted in section 7.7.10.2 below.

Figure B32. Scatter plot of PSA: vortioxetine vs. venlafaxine

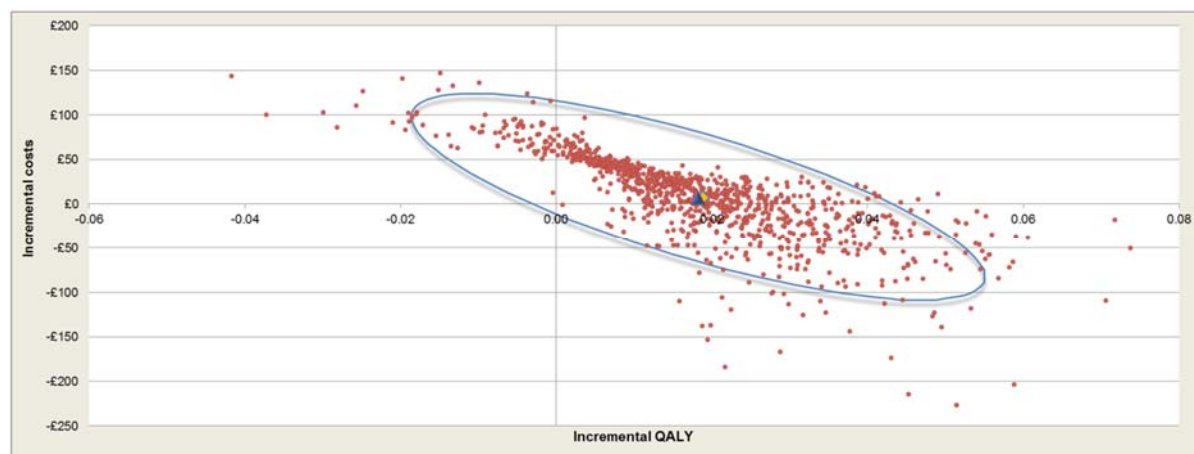


Figure B33. Cost-effectiveness acceptability curve: vortioxetine vs. venlafaxine

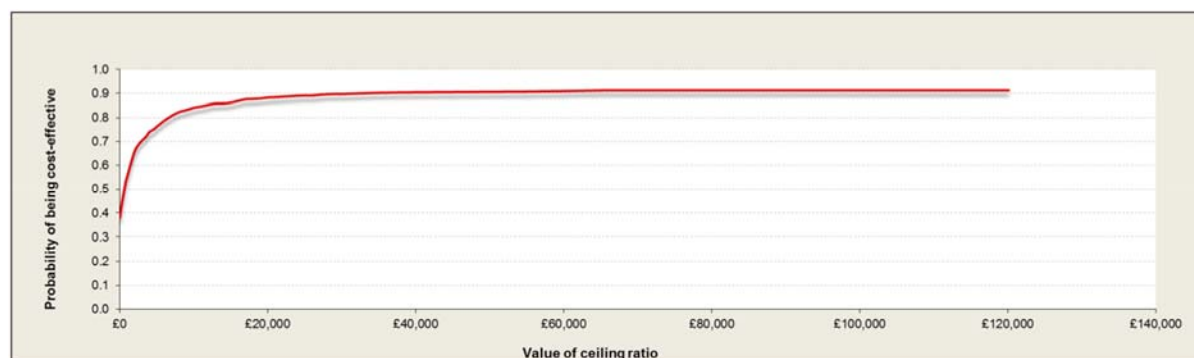


Figure B34. Scatter plot of PSA: vortioxetine vs. citalopram

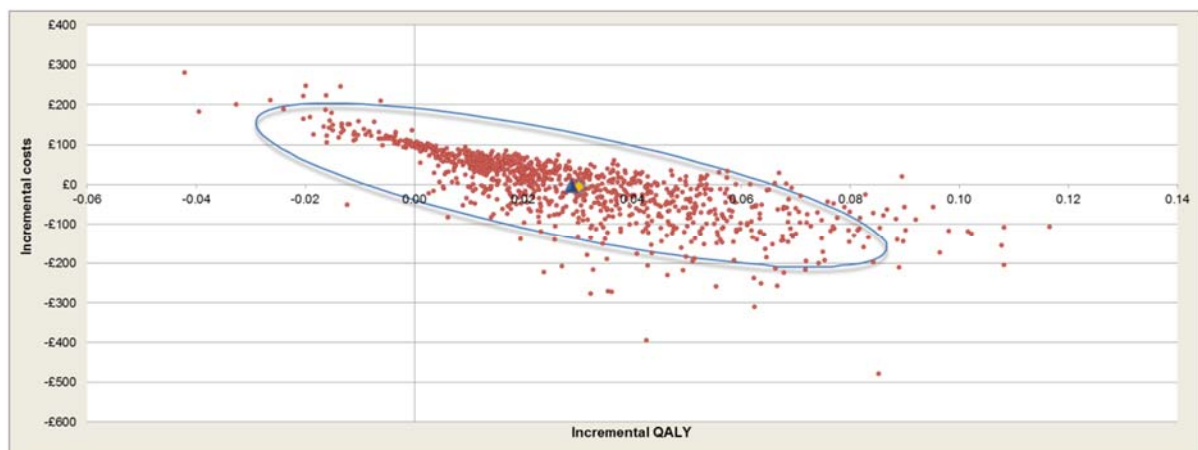


Figure B35. Cost-effectiveness acceptability curve: vortioxetine vs. citalopram

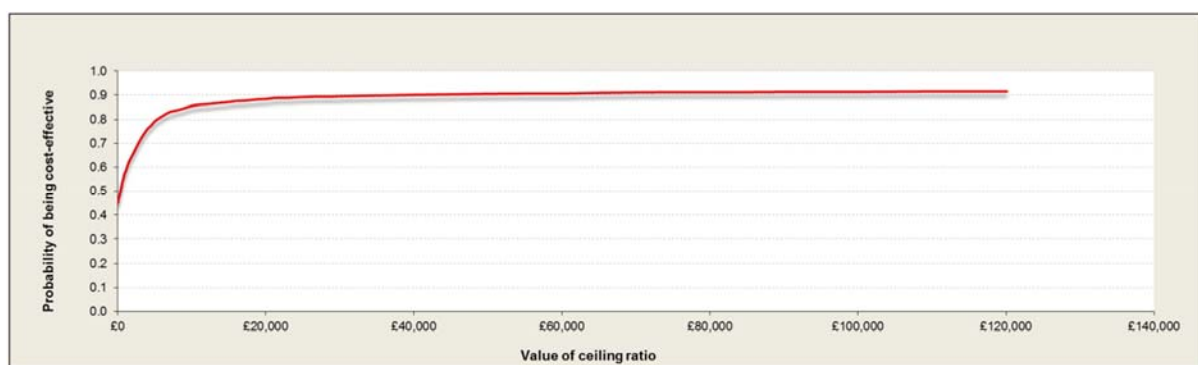


Figure B36. Scatter plot of PSA: vortioxetine vs. sertraline

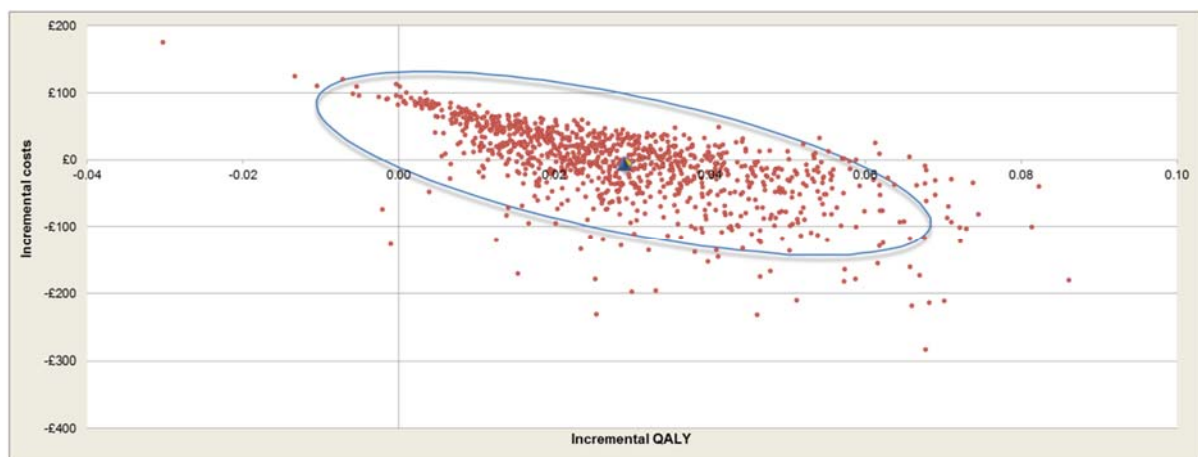


Figure B37. Cost-effectiveness acceptability curve: vortioxetine vs. sertraline

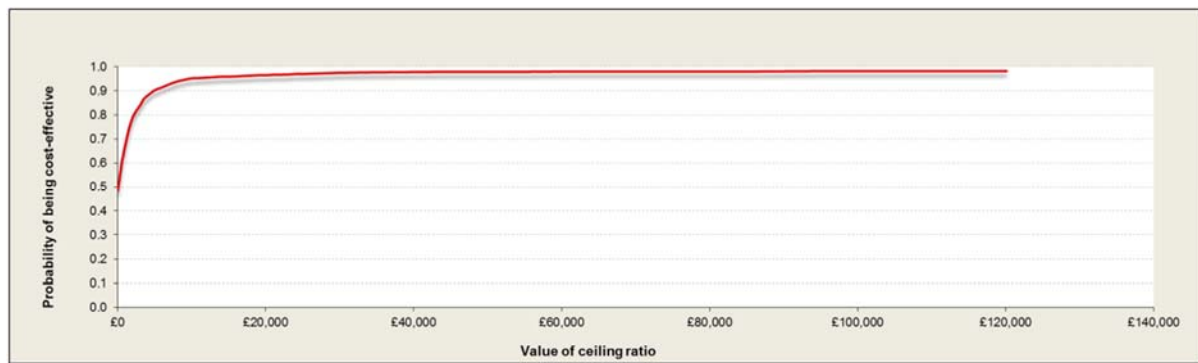


Figure B38. Scatter plot of PSA: vortioxetine vs. agomelatine

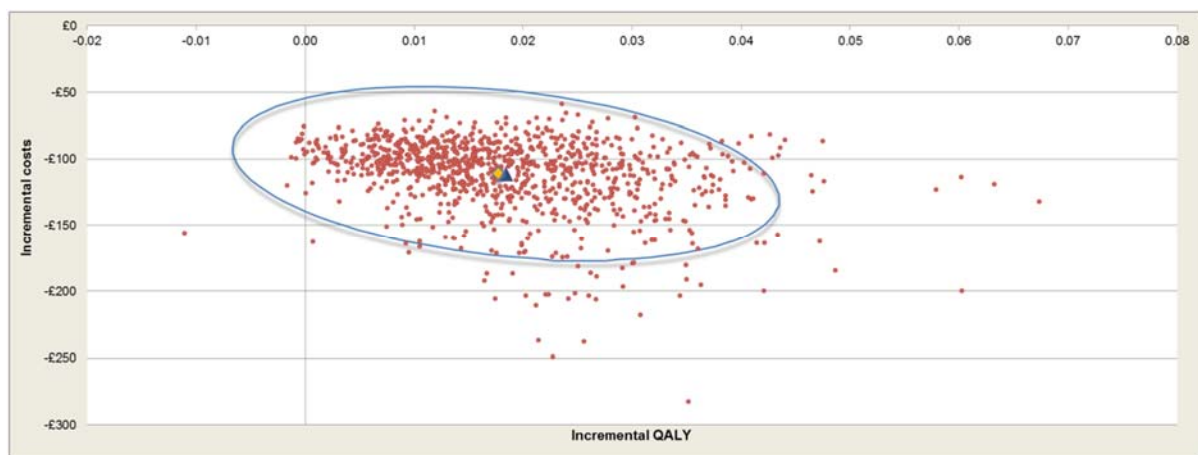


Figure B39. Cost-effectiveness acceptability curve: vortioxetine vs. agomelatine

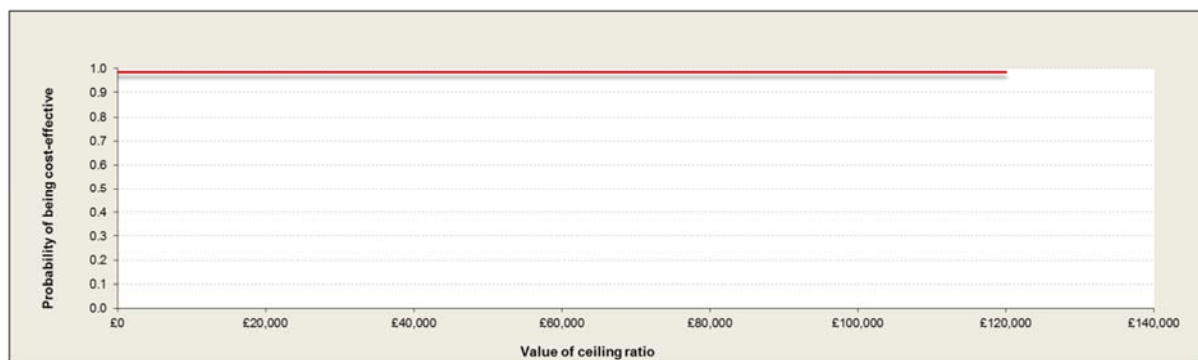


Figure B40. Multiple cost-effectiveness acceptability curves: all comparators

7.7.9 Scenario and structural sensitivity analyses

The scenario and structural sensitivity analyses were described in section 7.6.1 above (Table B66). Please refer to this table to view the assumptions as compared to the base case. The results of these analyses are shown in Table B83. For each input variable varied from the base case, a full incremental CUA is shown, in accordance with NICE guidance²⁰⁴.

Table B83. Scenario and structural sensitivity analyses: results vs. base case

Comparators	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Base case results (NHS PSS)					
Venlafaxine	£964	0.675	-	-	-
Vortioxetine	£971	0.694	£7	0.019	£378
Citalopram	£976	0.664	£5	-0.030	Dominated
Sertraline	£977	0.664	£0	0.001	Dominated
Agomelatine	£1,082	0.676	£105	0.012	Dominated ^d
Partial societal perspective					
Vortioxetine	£5,435	0.694	-	-	Dominant
Venlafaxine	£5,884	0.675	£449	-0.019	Dominated
Agomelatine	£6,150	0.676	£266	0.001	Dominated
Sertraline	£6,278	0.664	£128	-0.012	Dominated
Citalopram	£6,408	0.664	£129	-0.001	Dominated
Outcome scenarios					
Results from Bayesian MTC (base case: frequentist ITC results)					
Venlafaxine	£955	0.678	-	-	-
Citalopram	£966	0.667	£11	-0.011	Dominated
Vortioxetine	£971	0.694	£5	0.027	£952
Sertraline	£978	0.664	£7	-0.030	Dominated
Agomelatine	£1,082	0.676	£104	0.012	Dominated
Include additional 20% of patients into the “remitters” cohort ^a					
Citalopram	£867	0.700	-	-	-
Venlafaxine	£867	0.710	£0	0.010	£39
Sertraline	£869	0.700	£1	-0.010	Dominated
Vortioxetine	£892	0.730	£23	0.030	£1,223
Agomelatine	£1,040	0.710	£148	-0.020	Dominated
Increased relapse rates: CG90 model input 55% (base case 14.2%)					
Citalopram	£1,063	0.630	-	-	-
Venlafaxine	£1,064	0.640	£1	0.010	£124
Sertraline	£1,068	0.630	£3	-0.010	Dominated
Vortioxetine	£1,073	0.650	£6	0.020	£904
Agomelatine	£1,157	0.640	£83	-0.010	Dominated
Increased relapse rates: data from relapse prevention study 11985A 13.2% (base case 14.2%)					
Venlafaxine	£962	0.680	-	-	-
Vortioxetine	£969	0.690	£7	0.010	£680
Citalopram	£975	0.660	£6	-0.030	Dominated
Sertraline	£976	0.660	£0	0.000	Dominated
Agomelatine	£1,081	0.680	£105	0.020	Dominated
Weight gain rates from Uguz 2014 (base case: Serretti 2009)					
Venlafaxine	£965	0.670	-	-	-
Vortioxetine	£971	0.690	£6	0.020	£280
Citalopram	£977	0.660	£6	-0.030	Dominated
Sertraline	£977	0.660	£0	0.000	Dominated
Agomelatine ^c	£1,082	0.680	£105	0.020	Dominated

Comparators	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Utility and disutility scenarios					
Disutilities applied to all short-term AEs ^b					
Venlafaxine	£964	0.670	-	-	-
Vortioxetine	£971	0.690	£7	0.020	£357
Citalopram	£976	0.660	£5	-0.030	Dominated
Sertraline	£977	0.660	£0	0.000	Dominated
Agomelatine	£1,082	0.680	£105	0.020	Dominated
No disutilities applied to AEs					
Venlafaxine	£964	0.680	-	-	-
Vortioxetine	£971	0.700	£7	0.020	£357
Citalopram	£976	0.670	£5	-0.030	Dominated
Sertraline	£977	0.670	£0	0.000	Dominated
Agomelatine	£1,082	0.680	£105	0.010	Dominated
Disutilities duration for short-term AEs: 1 week (base case: 3 weeks)					
Venlafaxine	£964	0.680	-	-	-
Vortioxetine	£971	0.700	£7	0.020	£357
Citalopram	£976	0.670	£5	-0.030	Dominated
Sertraline	£977	0.670	£0	0.000	Dominated
Agomelatine	£1,082	0.680	£105	0.010	Dominated
Maintenance phase utilities from Mann 2009 (base case: Sapin 2004)					
Venlafaxine	£964	0.612	-	-	-
Vortioxetine	£971	0.630	£7	0.018	£389
Citalopram	£976	0.602	£5	-0.028	Dominated
Sertraline	£977	0.603	£1	0.001	Dominated
Agomelatine	£1,082	0.614	£105	0.011	Dominated
Structural assumptions					
100% stay on treatment / 0% switch (base case: 75% stay on treatment)					
Venlafaxine	£964	0.680	-	-	-
Vortioxetine	£971	0.690	£7	0.010	£692
Citalopram	£976	0.660	£6	-0.030	Dominated
Sertraline	£977	0.660	£0	0.000	Dominated
Agomelatine	£1,082	0.680	£105	0.020	Dominated
50% stay on treatment / 50% switch (base case: 75% stay on treatment)					
Venlafaxine	£964	0.680	-	-	-
Vortioxetine	£971	0.690	£7	0.010	£734
Citalopram	£976	0.660	£5	-0.030	Dominated
Sertraline	£977	0.660	£0	0.000	Dominated
Agomelatine	£1,082	0.680	£105	0.020	Dominated
Cost of subsequent treatment lines £10/day (base case: £0.06/day)					
Vortioxetine	£2,884	0.690	-	-	Dominant
Venlafaxine	£3,120	0.680	£236	-0.010	Dominated
Agomelatine	£3,286	0.680	£166	0.000	Dominated
Sertraline	£3,311	0.660	£25	-0.020	Dominated
Citalopram	£3,373	0.660	£62	0.000	Dominated
No patients consult GP for AEs (base case: 30% of patients)					

Comparators	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)
Venlafaxine	£939	0.675	-	-	-
Sertraline	£955	0.664	£16	-0.010	Dominated
Vortioxetine	£963	0.694	£8	0.029	£1,253
Citalopram	£966	0.664	£3	-0.030	Dominated
Agomelatine	£1,075	0.676	£109	0.012	Dominated
All patients consult GP for AEs (base case: 30% of patients)					
Vortioxetine	£989	0.694	-	-	Dominant
Citalopram	£1,001	0.664	£12	-0.030	Dominated
Venlafaxine	£1,021	0.675	£20	0.011	Dominated
Sertraline	£1,028	0.664	£7	-0.010	Dominated
Agomelatine	£1,099	0.676	£71	0.012	Dominated
Venlafaxine cost reduced to IR formulation (base case: XR)					
Venlafaxine (IR)	£971	0.694	-	-	-
Vortioxetine	£941	0.675	£29	0.019	£1,561
Citalopram	£976	0.664	£5	-0.030	Dominated
Sertraline	£977	0.664	£0	0.001	Dominated
Agomelatine	£1,082	0.676	£105	0.012	Dominated ^d

a: This scenario caters for the possibility that responders who have not achieved full remission at 8 weeks may stay on initial switch treatment.

b: In the base case, disutilities were applied to the following short-term AEs: sexual AEs, nausea, somnolence, headache, diarrhoea, insomnia. The disutility reported in Sullivan 2004 for "other" AEs was applied to dizziness, dry mouth, sweating.

c: Not applicable to agomelatine as the Uguz source was not applied.

d: Dominated by extended dominance.

IR: immediate release; XR: extended release (formulations of venlafaxine)

7.7.10 Sensitivity analysis findings

7.7.10.1 Deterministic sensitivity analyses

In the one-way DSAs, there were no differences of note in the pattern of results between the pairs of comparators. In all instances, the results were most sensitive to the difference in remission rate at 8 weeks between vortioxetine and each comparator. This variable was the main driver of both incremental costs and incremental QALYs. The next most influential factors on incremental costs were the costs of consultations with GPs and with psychotherapists in the event of no remission in the acute phase (weeks 0-8). The next most influential factors on incremental QALYs were the utility values associated with remission at 8 weeks and with the relapse health state in the maintenance phase (after week 8), followed by alternative assumptions for differential relapse rates.

In all but two sensitivity analysis in which parameter values were varied around the base case, vortioxetine remained dominant or had an ICER of below £15,670 per QALY gained. When the differences in 8-week remission rate were the sensitivity variable, vortioxetine was dominated by venlafaxine and by citalopram at the lower bound of the respective 95% confidence intervals around the difference.

Threshold analysis

Given that the remission rate at 8 weeks was the most influential driver of cost-effectiveness, a threshold analysis was conducted on this variable, in addition to the DSAs reported above.

Remission rates were held constant for the comparators to vortioxetine, while the remission rate for vortioxetine was reduced from the base-case value of 40.5% until the ICER reached thresholds of £20,000 and £30,000 per QALY gained in pairwise comparisons with each comparator. In the base case, vortioxetine and venlafaxine formed the cost-effectiveness frontier; the ICER for vortioxetine vs. venlafaxine was £378 per QALY gained. As Table B84 shows, if the absolute remission rate for vortioxetine is assumed to drop from 40.50% to 30.53%, i.e. a fall of approximately 10% in absolute terms and 25% in relative terms, the ICER for vortioxetine vs. venlafaxine reaches a threshold of approximately £20,000 per QALY gained. Although this assumed remission rate is slightly less than that of venlafaxine, vortioxetine achieves this ICER as a consequence of its superior profile on AEs and withdrawals due to AEs. The table shows the successively lower remission rates at which a similar ICER would result from comparisons with agomelatine, sertraline and citalopram. Corresponding values for a threshold ICER of £30,000 per QALY gained are shown alongside.

Table B84. Threshold analysis of remission rates of vortioxetine

Treatment	Remission rate at 8 weeks	£20,000/QALY threshold	Remission at 8 weeks	£30,000/QALY threshold
Vortioxetine (base case)	40.50%		40.50%	
Vortioxetine	30.53%		30.10%	
Venlafaxine	33.30%	£20,009	33.30%	£29,898
Vortioxetine	27.97%		28.54%	
Agomelatine	29.50%	£20,016*	29.50%	£29,973*
Vortioxetine	24.53%		24.00%	
Sertraline	26.10%	£20,075	26.10%	£30,062
Vortioxetine	24.10%		23.55%	
Citalopram	23.70%	£20,027	23.70%	£29,975

Figures in **bold** are base case remission rates.

* Threshold ICERs between vortioxetine and agomelatine are based on lower cost and fewer QALYs for vortioxetine, so the ICERs should be interpreted as willingness to accept QALYs lost, not willingness to pay for QALYs gained.

7.7.10.2 Probabilistic sensitivity analyses

The orientation of the 95% confidence ellipses in the scatter plots demonstrate a strong negative correlation between incremental costs and incremental QALYs for each comparison. This is an unsurprising finding as remission rates influence both the accrual of costs and QALYs, as demonstrated by the DSAs.

Given a ceiling ICER, i.e. willingness to pay (WTP), of £20,000-£30,000 per QALY gained, the probability that vortioxetine is cost-effective compared to each comparator varied in the ranges shown in Table B85, and was never less than 88%.

Table B85. Cost-effectiveness probabilities: vortioxetine vs. individual comparators

Vortioxetine vs.	Probability vortioxetine is cost-effective, given ceiling ICER of:	
	£20,000	£30,000
Venlafaxine	88%	90%
Citalopram	88%	90%
Sertraline	96%	97%
Agomelatine	98%	98%

When all five comparators were considered simultaneously in the PSA (Figure B40), vortioxetine was the most likely comparator to be cost-effective, except at WTP values below approximately £1,200, i.e. well below the conventionally acceptable range. At a WTP of £20,000 and £30,000, vortioxetine had probabilities of 78% and 81% of being the cost-effective option, respectively. The comparators trailed by a substantial margin. Venlafaxine was the next likeliest cost-effective option, albeit with probabilities of only 10% and 11% at a WTP of £20,000-£30,000, while the corresponding figures for agomelatine and citalopram were in single digits.

7.7.10.3 Structural and scenario analyses

When a partial societal perspective was taken instead of the reference case NHS/PSS perspective, vortioxetine became dominant in the comparison with venlafaxine and the margin of cost savings over the other three comparators increased. In this analysis, there was over a fivefold increase in costs for each comparator, while QALYs remained identical to the base case.

In all the remaining scenarios, vortioxetine was the most cost-effective treatment, being either dominant over the other four comparators or having an ICER of no greater than £1,561 per QALY gained. In the scenarios where vortioxetine was not dominant, venlafaxine was on the cost-effectiveness frontier.

The scenario analysis in which the cost of venlafaxine immediate-release (IR) was used in place of the cost of the extended-release (XR) formulation resulted in the greatest cost per QALY gained for vortioxetine (compared to venlafaxine) of all the scenario analyses. Expert opinion suggests that the efficacy and tolerability profile of the different formulations are similar and therefore this analysis provides an approximation of the cost-effectiveness of vortioxetine vs. venlafaxine IR.

In one of the efficacy scenarios, when an additional 20% of patients were added into the “remitters” cohort following 2nd line treatment (to represent responders who had not achieved remission but might continue treatment), the overall effect was to reduce costs and increase QALYs. This flat-rate assumption benefitted most the comparators with lowest base-case remission rates. As a result, the cost-effectiveness frontier included citalopram, venlafaxine and vortioxetine in ascending order of ICER. Vortioxetine remained cost-effective with an ICER of £1,223 per QALY gained.

7.7.11 Key drivers of the cost-effectiveness results

While the impact on results of a wide range of variables was tested in the sensitivity and scenario analyses, the single most influential factor was remission rates in the acute phase of treatment, and specifically the differences between rates for each comparator. The analyses have shown that vortioxetine is likely to be the most cost-effective option by a substantial margin, given the acute phase remission rate assumptions. The indirect

treatment comparison has limitations which have been acknowledged in section 6.7. It is therefore important to test how the cost-effectiveness of vortioxetine depends upon the accuracy of the remission rate estimates from the ITC. The threshold analysis described above suggests that, holding remission rates for comparators constant, the acute phase absolute remission rate for vortioxetine could be reduced by 10 percentage points (a relative reduction of 25%) while achieving an ICER of £20,000 versus venlafaxine, the only other comparator on the frontier. The other studied variables were far less influential on the results.

7.8 Validation

7.8.1 Methods used

The model has undergone internal and external validation.

As part of the internal validation, the model was quality assessed by the team having developed the UK economic model using a quality assessment checklist based on Phillips 2006²⁶⁷. During this process, the formulas and macros used in the model were reviewed and a set of sensitivity analyses including stress tests were carried out to ensure the coherence and validity of the results.

External validation was conducted through the process described in section 7.3.5. The model methodology was consistent with other models³⁴.

7.9 Subgroup analysis

7.9.1 Approach

No subgroup analyses were undertaken. The decision problem already specifies a population - switching patients - that can be considered a subgroup of the licensed population (see below).

7.9.2 Patient characteristics

Not applicable.

7.9.3 Statistical analysis

Not applicable.

7.9.4 Results

Not applicable.

7.9.5 Subgroups not considered

The switch population consists of patients with moderate-to-severe MDEs, corresponding to the recommendation in CG90 for use of antidepressants in patients with moderate-to-severe depression. It was not possible to analyse moderate and severe subgroups separately, as these data were not available for the comparators to vortioxetine in the available journal articles.

7.10 Interpretation of economic evidence

7.10.1 Consistency with literature

The results of the CEA carried out for this submission are consistent with those reported for a Finnish CEA using a local adaptation of the model. The Finnish report was published as a poster^{268,269} more recently than the date of the search for economic evaluations

7.10.2 Relevance to entire decision problem population

The population defined in the decision problem is as follows:

“Adult patients with moderate-to-severe MDD who are experiencing an MDE, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to alternative antidepressant”

The identification of trials for vortioxetine and comparators was directly in line with the decision problem. The majority of patients in the trials included within the network received an SSRI as their initial treatment, in line with UK guidelines¹⁰ and clinical practice.

There were some discrepancies in patient characteristics between the studies included in the ITC and the decision problem, as discussed earlier (see Table B33). All studies except STAR*D included patients who had failed to achieve an adequate response to treatment only in terms of efficacy, but not tolerability. STAR*D also included patients who could not tolerate initial therapy.

REVIVE included white patients predominately. However, subgroup analyses²⁷⁰ and pharmacokinetic studies² have not shown clinically meaningful differences in the effects of vortioxetine between patients of differing race or ethnicity. It is concluded that the results observed in the ITC are transferable to the decision problem population in England and Wales.

In summary, Lundbeck believes that the economic evaluation is relevant to the entire decision problem population.

7.10.3 Strengths and weaknesses of the evaluation

7.10.3.1 Strengths

The evaluation draws upon the precedents established by other recent economic evaluations, including the model developed alongside CG90, but adds a number of important features over some of these, providing a fuller representation of clinical practice. These features include the modelling of tolerability, treatment switching and use of remission as an outcome. Extensive use was made of expert opinion from clinicians (specialists and GPs), health economists and pharmacists in the development of the model, both in its specification and parameterisation.

The principal efficacy endpoints: i) remission after initial treatment and ii) recovery after maintenance treatment, were chosen because they are widely-used treatment success criteria, whereas initial response, as used in the CG90 model, is an intermediate endpoint. An important feature of the present model is that it addresses the impact of side-effects, the absence of which the authors of the CG90 model recognised was a shortcoming of that model. Our model considers individual, frequently-occurring side-effects, their timing (in the acute or/and maintenance phase) and duration, and their impact on resource use, patient

utility and withdrawal from current treatment. The model also allows for further switching in the event of lack of efficacy or intolerability.

The ITC permitted comparison of vortioxetine with the two most commonly used SSRIs and the most commonly used SNRI in the UK switch population. The ITC was used to populate pivotal model parameters. The analysis was conducted using frequentist and Bayesian approaches, but the CEA took a conservative approach by using the values from the frequentist analysis, which was less favourable to vortioxetine.

The potential sources to populate the model with utility values were consistent in their use of the EQ-5D UK tariff¹⁸⁵ and in the valuation of health states. Sensitivity analyses of accrued QALYs were robust to the use of alternative sources.

Resource use data has been taken from the observational PERFORM study and from Byford²³⁴, both of which studies were conducted in the UK. As switch patients draw upon more resources than the full MDD population²⁰, the resource use savings resulting from treatment success may have been underestimated and, in turn, the incremental cost-utility calculation may be biased against vortioxetine.

The cost-effectiveness findings were robust to a wide range of sensitivity and scenario analyses.

7.10.3.2 Weaknesses and other considerations

Structurally, the greatest weakness of the model is the infeasibility of extending the time horizon beyond the duration of a single episode without reaching an unacceptable level of uncertainty. This limitation was imposed by the available clinical data. The key parameters driving the modelled course of an MDE were derived from short-term studies of treatment and a single study of relapse rates, all within the timeframe of a single episode²²⁷. At present, data are not available to parameterise a longer-term model with sufficient confidence to be useful. Attempted and actual suicide are risks in patients with MDD, but evidence is not available to model treatment differences.

Other weaknesses of the evaluation mainly relate to uncertainty in the parameters. While the usual range of sensitivity analyses were performed, the 8-week remission rates were derived from an ITC built on a network of evidence that incorporates few studies. However, the included studies provide clinical data in the population directly relevant to the decision problem. While the included head-to-head trial comparisons are considered internally valid and robust, the indirect estimates of differential remission rates between comparators may be less so. Ideally, the ITC would have included a greater number of comparable studies in a closed network, limiting the effects of study heterogeneity and making the comparisons more reliable. Notwithstanding this weakness, the threshold analysis on remission rate shows that vortioxetine would remain cost-effective at a level of acceptability of £20,000 per QALY gained even if the assumed absolute remission rate was reduced by 10 percentage points (a 25% relative reduction). This margin represents a substantial buffer against the possibility of drawing an incorrect conclusion about the cost-effectiveness of vortioxetine.

Lack of comparable studies prevented the inclusion of fluoxetine and mirtazapine in the ITC and, hence, in the economic evaluation, but although these agents are commonly used in the UK their absence is not seen as a particular limitation. In practice, the profile of fluoxetine is similar to that of citalopram, and broadly similar results would be expected for these two SSRIs. According to expert opinion, the sedative effect of mirtazapine makes it more suitable for patients with sleep disturbance and those who do not require optimum alertness, so mirtazapine is only a direct comparator to vortioxetine for such patients.

Judgement and clinical expert opinion were required for certain parameter and structural assumptions, but all important assumptions were subjected to peer justification through advisory boards involving psychiatrists, GPs, mental health pharmacists and health economists as appropriate. To the extent possible, single sources of parameters were preferred to sources specific to individual comparators as a protection against bias.

Through contact with clinical experts it is clear that the treatment of MDEs needs to be highly individualised, as patients vary widely in their presentation and response to treatment. Modelling MDEs, however, is inevitably a simplification of clinical reality.

7.10.3.3 Conclusion

This section has described the principal strengths and weaknesses of the economic evaluation. The model is well-specified and was parameterised using the best-available evidence. For the pivotal efficacy parameter of remission at 8 weeks, data specific to switch populations were used, as efficacy rates are not interchangeable between the initial and switch settings for reasons discussed earlier. However, the availability of efficacy data in the switch setting is limited and the possible impact on the reliability of estimates used in the model has been acknowledged. On balance, the analysis leads to the conclusion that vortioxetine is cost-effective versus venlafaxine, citalopram, sertraline and agomelatine with a probability of 78-81%, given the conventional limits of £20,000-£30,000 per QALY gained. The conclusion that vortioxetine is cost-effective is robust to a wide range of sensitivity and scenario analyses.

7.10.4 Further potential analyses to enhance robustness and completeness

In the course of reviewing the model, further useful sensitivity analyses may be identified. The existing DSAs are one-way analyses. It may be possible to define pairs or groups of parameters that are likely to vary together. If so, these could be explored in two-way or multiple sensitivity analyses. The threshold analysis on the 8-week remission rate for vortioxetine could be extended to a probabilistic interpretation, to identify the threshold values that reduce the probability that vortioxetine is cost-effective to 75%, 50%, or other levels of interest to the decision maker.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 Patients eligible for treatment in England and Wales

The target population was estimated using the following information:

- Total adult population in England and Wales
- Diagnosed prevalence of depression
- Proportion of moderate and severe MDD patients
- Proportion of moderate and severe MDD patients receiving antidepressant treatment
- Proportion of switch patients

The total population was estimated in two steps. Given a mid-2013 UK adult population of 44,811,857⁷², the projected population from 2014 to 2019 was calculated using the ONS forecast annual growth rates, i.e. 0.68%, 0.67%, 0.70%, 0.68%, 0.68% and 0.67% for these years, respectively. The 2011 diagnosed prevalence of depression in England and Wales was estimated to be 10.7%²⁷¹; this value was based on a population weighting applied to the diagnosed prevalence rates in England (10.9%) and Wales (7.9%). According to a GP focus group conducted by Lundbeck in November 2014, the proportion of patients with moderate-to-severe MDD was estimated to be 54%²⁷². Of these patients, 90% were estimated to be prescribed pharmacological treatments. This value was calculated based on an average from two sources: a Lundbeck focus group which reported a value of 100%²⁷² and the NICE costing clinical guidelines, which stated 80%²⁷³.

Table C1. Number of patients eligible for treatment over five years

	2015	2016	2017	2018	2019
Total adult population (England and Wales)	45,418,797	45,735,758	46,047,714	46,362,172	4,667,2460
Number of diagnosed patients with depression	4,859,811	4,893,726	4,927,105	4,960,752	4,993,953
Number of moderate-to-severe MDD patients	2,616,821	2,635,083	2,653,057	2,671,174	2,689,052
Number of moderate-to-severe MDD patients prescribed pharmacological treatment	2,355,139	2,371,575	2,387,751	2,404,057	2,420,147

In addition, of the overall number of patients with moderate-to-severe depression treated with pharmacological treatments only a proportion of these will be switch patients. It is estimated that between 30-50% will fail to achieve an adequate response to an initial therapy and therefore will require a switch in treatment^{11,62}. Therefore, it is expected that approximately 700,000 and 1,175,000 patients will require a further pharmacological treatment and therefore would be eligible for treatment with vortioxetine per annum. This is in line with the decision problem population as described within the submission.

8.2 Assumption(s) about current treatment options and uptake of technologies

In Table C2 below, a breakdown is presented of the market shares for the current treatment options available in the UK. This analysis represents the scenario if vortioxetine were not available. The market shares over the next five years are based on forecasted assumptions.

The market share and hence budget impact calculations are presented for and conducted in the full MDD population rather than the switch population. However, it is assumed that vortioxetine is prescribed only in the switch population in line with the decision problem.

For currently available treatments, forecast assumptions are based on currently available patient data, although they are extrapolated for all years in the model. Based on extrapolation of recent prescribing patterns, the trend of decline in citalopram, fluoxetine and venlafaxine use, along with increasing market shares of escitalopram and sertraline, are expected to continue over the next five years.

As generic alternatives enter the market (i.e. duloxetine in 2014), it is assumed that within 3 months all prescribing will be of the generic product rather than the original brand.

The vortioxetine market forecast assumptions are based on previous uptake rates for new antidepressants in the UK, adjusted for differences in indications and eligible patient populations.

Table C2. Market share forecasts: scenario without vortioxetine

Drug	Brand or Generic	2015	2016	2017	2018	2019
Citalopram	Generic	20.0%	19.0%	18.2%	17.5%	16.4%
Escitalopram	Generic	1.5%	1.5%	1.9%	1.9%	2.3%
Duloxetine	Generic	2.5%	2.7%	2.9%	3.0%	3.2%
Sertraline	Generic	13.3%	14.4%	15.4%	16.4%	17.7%
Fluoxetine	Generic	12.7%	12.5%	12.4%	12.1%	12.1%
Agomelatine	Brand	0.1%	0.1%	0.1%	0.1%	0.1%
Mirtazapine	Generic	8.1%	8.4%	8.7%	8.8%	8.9%
Venlafaxine	Generic	5.2%	5.1%	5.0%	4.9%	4.7%
Paroxetine	Generic	2.3%	2.2%	2.0%	1.9%	1.7%
TCAs	Generic	31.9%	31.5%	31.1%	31.0%	30.6%
Others	Generic	2.5%	2.5%	2.4%	2.3%	2.2%

8.3 Market share assumptions

It is assumed vortioxetine will take a third of agomelatine's market share in 2015 and half of agomelatine's market share in each subsequent year; the remainder of the vortioxetine market share is taken equally from other all relevant comparators as defined in the submission (as per data shown in Section 2.7 of the submission): citalopram, sertraline, mirtazapine, fluoxetine and venlafaxine).

NICE final guidance on vortioxetine is not expected to be published until September 2015 at the earliest. As a result, the market shares for vortioxetine were only estimated to be 0.034% in 2015.

Table C3. Market share forecasts: scenario with vortioxetine

Drug	Brand or Generic	2015	2016	2017	2018	2019
Vortioxetine	Brand	0.0%	0.5%	0.9%	1.4%	2.1%
Citalopram	Generic	20.0%	19%	18.0%	17.2%	16.0%
Escitalopram	Generic	1.5%	1.5%	1.9%	1.9%	2.3%
Duloxetine	Generic	2.5%	2.7%	2.9%	3.0%	3.2%
Sertraline	Generic	13.3%	14.3%	15.2%	16.2%	17.3%
Fluoxetine	Generic	12.7%	12.4%	12.2%	11.7%	11.7%
Agomelatine	Brand	0.0%*	0.0%*	0.0%*	0.0%*	0.0%*
Mirtazapine	Generic	8.1%	8.3%	8.5%	8.5%	8.5%
Venlafaxine	Generic	5.2%	5.1%	4.8%	4.6%	4.3%
Paroxetine	Generic	2.3%	2.2%	2.0%	1.9%	1.7%
TCAs	Generic	31.9%	31.5%	31.1%	31.0%	30.6%
Others		2.5%	2.5%	2.4%	2.3%	2.2%

*Greater than zero but not shown due to rounding.

8.4 Other significant costs associated with treatment

Acquisition cost is considered to be the only significant cost associated with the use of vortioxetine.

8.5 Measurement of unit costs

In Table C4 below, the unit costs of pharmacological treatment are presented. The introduction of generic duloxetine has also been considered with 95% erosion in price. This is an assumption but has been based on historical precedence. The WHO DDD for each antidepressant has been used to calculate the cost.

It is assumed that treatment length is 8 months (1 month is assumed to equate to 28 days). This is based on a 2-month acute phase and 6-month maintenance phase¹⁰.

Table C4. Drug unit costs

Drug	Brand or Generic	Pack price	Number of tablets	DDD mg	Price per DDD	Reference
Vortioxetine	Brand	£27.72	28	10	£0.99	MIMS December 2014
Citalopram	Generic	£1.10	28	20	£0.04	MIMS December 2014
Escitalopram	Generic	£1.98	28	10	£0.07	MIMS December 2014
Duloxetine	Generic	£1.39	28	60	£0.05	MIMS December 2014 including 95% price erosion due to generic introduction
Sertraline	Generic	£1.75	28	50	£0.06	MIMS December 2014
Fluoxetine	Generic	£1.09	28	20	£0.04	MIMS December 2014
Agomelatine	Brand	£30.00	28	25	£1.07	MIMS December 2014
Mirtazapine	Generic	£1.67	28	30	£0.06	MIMS December 2014
Venlafaxine	Generic	£12.20	28	100	£0.44	MIMS December 2014
Paroxetine	Generic	£1.89	28	20	£0.07	MIMS December 2014
TCAs	Generic	£2.11	28	75	£0.08	MIMS December 2014 /Amitriptyline cost (as an assumed common cost for TCAs as the majority of prescribing is amitriptyline in this group).
Others	Generic		0	0	£0.34	Assumption average of all other AD costs

8.6 Estimates of resource savings

Not applicable.

8.7 Annual budget impact for the NHS in England and Wales

The budget impact of vortioxetine has been estimated over a 5 year time horizon. The calculation has been undertaken calculating the difference in cost between two scenarios: the estimated total spend associated with pharmacological treatment where vortioxetine is and is not available.

Assuming vortioxetine achieves the market shares outlined above **the budget impact ranges from £37,018 in 2015 to £9,708,981 in 2019**. The increase in budget is explained by an increasing number of patients being treated with vortioxetine rather than other switch treatment options. **The total number of patients receiving vortioxetine is estimated to be 119,842 over the next five years.**

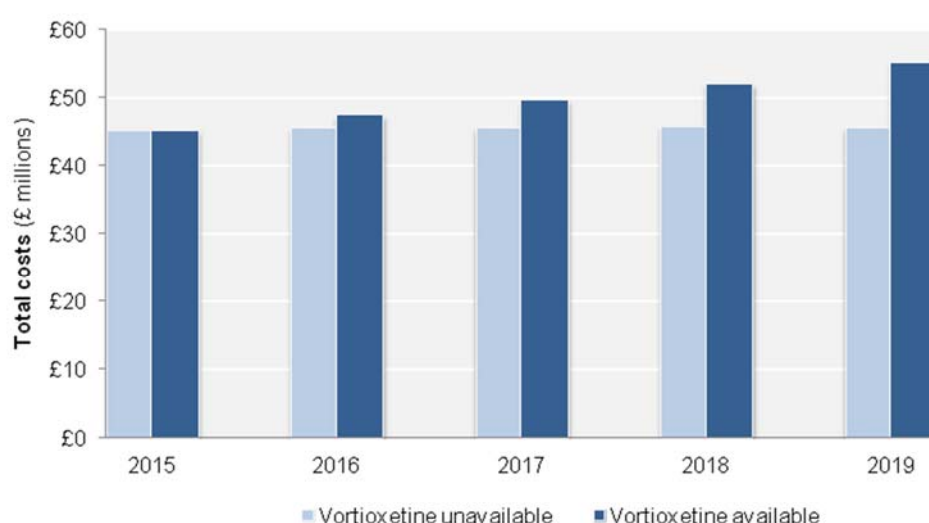
It should be noted that as the defined daily dose (DDD) is used to calculate the cost of medicine, the inherent assumption within the model is that this reflects the average dose of antidepressants prescribed and taken by patients in the UK. Expert opinion suggests that in fact the DDD does not reflect clinical practice and prescribing; mean doses in reality are greater than the DDD. As the price of vortioxetine tablets is equivalent regardless of dose, which is not so for comparators, it is likely that the budget impact of vortioxetine is overestimated.

Table C5. Estimated budget impact to the NHS over the next five years

	2015	2016	2017	2018	2019	Total
Patients prescribed vortioxetine*	801	10,909	22,445	34,138	51,549	119,842
Acquisition cost of vortioxetine	£177,574	£2,419,243	£4,977,372	£7,570,356	£11,431,533	£26,576,069
Scenario without vortioxetine	£45,228,020	£45,548,608	£45,582,011	£45,764,072	£45,577,750	£227,700,461
Scenario with vortioxetine	£45,265,037	£47,454,053	£49,697,127	£52,116,654	£55,286,731	£249,819,603
Budget impact: absolute growth	£37,018	£1,905,445	£4,115,116	£6,352,582	£9,708,981	£22,119,142
Budget impact: percentage growth	0.08%	4.18%	9.03%	13.88%	21.30%	9.71%

*Vortioxetine usage assumed to occur in the switch population only

Figures rounded to nearest whole number

Figure C1. Estimated budget impact to the NHS over the next five years

8.8 Other opportunities for resource savings

Within this submission, versus agomelatine, sertraline, citalopram and venlafaxine, vortioxetine has demonstrated that a higher proportion of switch patients reach remission and recovery. In addition it has also been shown that vortioxetine is associated with short- and long-term tolerability benefits relative these products. Both of these clinical benefits associated with vortioxetine result in fewer patients needing to switch treatment compared to other antidepressants as compared to within this submission. This benefit has not been captured within the budget impact analysis. Furthermore, within this budget impact calculation the wider societal cost savings associated with reduced absenteeism have not been included.

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Single Technology Appraisal (STA)

Vortioxetine for the treatment of major depressive disorder [ID583]

Dear [REDACTED],

The Evidence Review Group, the Centre for Reviews & Dissemination and Centre for Health Economics at the University of York, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 6 February 2015 by Lundbeck. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data. Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 11 March 2015. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed. Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Martyn Burke, Technical Lead (martyn.burke@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Nicola Hay
Technical Adviser

On behalf of Dr Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Literature searches

- A1. Section D, Appendix Table D13: Please provide a rationale for lines 64 to 79 of the search strategy.
- A2. Section D, Appendix Tables D33 and D34: Please provide an explanation for the term “2501” in line 13 of these strategies.
- A3. Section D, Appendix Table D14: The typographical error in line 44 will have resulted in some records not been identified. Please check whether correcting the typographical error may have led to relevant records being missed.

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REVIVE trial

- A4. Patients were enrolled into the REVIVE trial if they received treatment with citalopram, escitalopram, paroxetine, sertraline, duloxetine or venlafaxine monotherapy. Please clarify why patients who received prior treatment with other serotonin reuptake inhibitors [SRIs], such as fluoxetine, were not included.
- A5. Please clarify whether patients were allowed to receive additional support (such as GP care or counselling) during the course of the study.
- A6. The REVIVE trial is described as being blinded, yet the dose of agomelatine was fixed at 25 mg per day for the first 2 weeks of treatment, whereas the dose of vortioxetine could be changed at week 1. Please clarify further how blinding was retained given this difference in the dose-modification pattern across treatment arms.
- A7. Patients were eligible to be enrolled into the REVIVE trial if they were either an inpatient in a psychiatric hospital or an outpatient at a psychiatric setting at the time of the study entry. Please provide the proportion of patients who were inpatients and the proportion who were outpatients at the time they were recruited to the trial.
- A8. The REVIVE trial included patients who had depressive symptoms considered as non or partially responsive to no more than one adequate course of SRI monotherapy, and who were candidates for a switch in the investigator's opinion and wished to change antidepressant treatment. Please clarify whether there were any specific criteria used to define patients as non-responsive or partially responsive.

TAK318 trial

- A9. Please provide details of the recruitment setting for the TAK318 trial (that is, primary care, secondary care).
- A10. Patients in the TAK318 trial received treatment with citalopram, paroxetine or sertraline. Please clarify why patients who received prior treatment with other selective serotonin reuptake inhibitors [SSRIs], such as fluoxetine, were not included.
- A11. Figure B14 (page of 98 of the company's submission) presents a plot of changes in MADRS and CGI-I scores in the TAK318 trial. Please provide tabulated data on changes in scores used to produce these figures, with mean differences between arms, standard errors and 95% confidence intervals. Please provide similar data for all depression rating scales measured in the TAK318 trial.

Outcomes

- A12. **Priority question:** The final scope issued by NICE lists several outcomes that are not presented in the results section (section 6.5 of the company's submission). Where possible, please provide summary tables and/or figures of results for the following outcomes, or clarify where data were not collected:
- a. relapse (including relapse rate and time from remission to relapse)
 - b. sleep quality (in addition to sleep related adverse events)
 - c. cognitive dysfunction
 - d. time to response
 - e. adverse effects of treatment discontinuation
- A13. For each depression rating scale used (for example, Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Depression Rating Scale [HAM-D], Clinical Global Impression - Severity Scale [CGI-S]) please explain what is considered a clinically meaningful change or difference in these scales.

Switching and initial-use trials

- A14. **Priority question:** In section 6.1 of the company's submission, it is stated that the relative efficacy of anti-depressants cannot be assumed to be constant between initial and switch usage. Please provide any further supporting evidence for this statement beyond the quoted meta-analysis (Papakostas et al 2008). In particular, please provide any evidence that the relative efficacy of non-selective serotonin reuptake inhibitors (non-SSRIs) will differ between initial and switch usage.

- A15. **Priority question:** Please provide results from meta-analyses or other forms of evidence syntheses based on all randomised controlled trials comparing vortioxetine with an active comparator and/or placebo in initial-use or mixed initial and switching use. Please provide results on the following outcomes, if available:
- a. Differences in mean change from baseline in depression rating scales (MADRS, HAM-D, CGI-S etc.) between treatments
 - b. Relative risks or risk differences in response, remission and withdrawal rates
 - c. Adverse events (AEs):
 - i. Number of discontinuation as a result of AEs
 - ii. Number and types of severe adverse events

Indirect treatment comparisons

- A16. For the indirect treatment comparison (ITC) analysis, the company assumed that the different definitions of remission across trials (using different depression rating scales) were equivalent and could be pooled in the analysis. Please provide justification for this assumption.
- A17. **Priority question:** In the company's submission, the results of its ITC analysis were presented in terms of risk differences. Please present results from the ITC analysis in terms of relative risks.
- A18. **Priority question:** Results for the company's ITC are provided for remission and withdrawal rates because of adverse events only.
- a. Please state which efficacy and safety outcomes were excluded from the ITC, and why.
 - b. Please also provide results from similar analyses using response rate as the outcome.
 - c. Please also provide results from similar analyses using change in depression rating scales from baseline as the outcome (for example, by performing a standardised mean difference analysis). If possible, please provide results for both frequentist and Bayesian models.
- A19. Please explain why the TAK318 trial was excluded from the ITC analysis.
- A20. Table B39, last line (page 124 of the company's submission): please clarify how the adjusted indirect comparison estimated rate of withdrawals because of AEs was 18.0% for citalopram, compared with 5.3% in the original publication (Lenox-Smith et al. 2008).
- A21. Please provide details of the recruitment setting for trials included in the ITC (that is, primary care, secondary care).

Adverse events

- A22. Table B44 (page 133 of the company's submission), please provide the number and percentage of patients with a severe adverse event, and the number of discontinuations because of an adverse event per dosage (2.5-10.0 mg; 15-20 mg).
- A23. **Priority question:** The scope of the literature search for adverse event studies was expanded to include 'non-switch populations' (see Section 6.9.1.2 of the company's submission). Given this, please clarify why most vortioxetine trials listed in Table B4, (page 64 of the company's submission), were not included in this review. If available, please provide summary adverse event data, including severe adverse events and discontinuation because of an adverse event, for all trials of vortioxetine and for all comparator treatment arms (including placebo). For example, by providing relative risks or risk differences between treatments, and results from meta-analyses, if these have been performed.

Section B: Clarification on cost-effectiveness data

Model time horizon

- B1. It is noted that the recovery period in the company's economic model denotes a period of 4 months where the patient is not at-risk. Please carry out exploratory analyses around the time horizon, and present the cost-effectiveness results for time horizons of 2 and 8 months.
- B2. According to NICE's guidance on [depression in adults](#) (see NICE Clinical Guideline 90), patients at risk of relapse should be treated with anti-depressants for at least 2 years. Please incorporate an additional scenario in the economic model where this is included and present the revised cost-effectiveness results for vortioxetine compared with each of the comparators.

EQ-5D data

- B3. **Priority question:** Using results from the REVIVE trial, please provide average baseline and week 8 EQ-5D scores (and associated standard errors) for 'remitters' and 'non-remitters' separately. Please do this separately for those treated with vortioxetine and for those treated with agomelatine, as well as, a combined analysis. Please present the results according to the observed cases [OC], last observation carried forward [LOCF] and mixed model for repeated measures [MMRM] methods (that is, an expanded version of Table B15, page 91 of the company's submission).

- B4. **Priority question:** Using results from the REVIVE trial, please provide average change in EQ-5D scores from baseline at week 8 (and associated standard errors) for remitters and non-remitters separately. Please do this separately for those treated with vortioxetine and for those treated with agomelatine, as well as, a combined analysis. Please present the results according to the OC, LOCF and MMRM methods.

Costs data

- B5. It is noted that there is a 'switch cost' associated with changing therapy in the company's economic model. Please justify why this is additional to GP/specialist care visits, and whether switching would take place in primary or secondary care.

Probabilistic analysis

- B6. **Priority question:** Please clarify how distributions have been assigned to the model parameter inputs in tables B59 and B60, pages 168 and 171 of the company's submission. Please present the data that underpins them, for example, standard deviation, standard error, number of observations etc.

Vortioxetine for the treatment of major depressive disorder [ID583]

NICE Single Technology Appraisal

Responses to request for clarification of manufacturer submission

Submitted: 11 March 2015

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Table of Contents

A1. Section D, Appendix Table D13: Please provide a rationale for lines 64 to 79 of the search strategy.	7
A2. Section D, Appendix Tables D33 and D34: Please provide an explanation for the term “2501” in line 13 of these strategies.	7
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Global Impression - Severity Scale [CGI-S]) please explain what is considered a clinically meaningful change or difference in these scales.....	18
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Table of Tables and Figures

Table 1. Analysis of change from baseline in MADRS total score by study visit (MMRM) Repeated measures analysis. Full Analysis Set.....	10
Table 2. Analysis of change from baseline in CGI-I score by study visit (MMRM) Repeated measures analysis. Full Analysis Set.	11
Table 3. Analysis of change from baseline in CGI-S score by study visit (MMRM) Repeated measures analysis. Full Analysis Set.	12
Figure 1 	15
Figure 2 	16
Figure 3: Study 14178A (REVIVE): Kaplan-Meier plot of time to first 50% response.....	17
Table 4. Clinical relevance of changes in symptom scores on depression rating scales.....	19
Table 5: Publications of interest identified in the searches	21
Table 6. Overview of meta-analyses Included in the clinical efficacy data package.....	25
Figure 4. Change from baseline in MADRS total score at week 6/8 (FAS, MMRM) – short-term, placebo-controlled pool	26
Figure 5. MADRS 50% response at week 6/8 (FAS, LOCF): short-term, placebo-controlled pool	27
Figure 6. Remission (MADRS ≤10) week 6/8 (FAS, LOCF): short-term, placebo-controlled pool	27
Figure 7: Response rates at Week 6/8 - short-term placebo-controlled pool.....	28
Figure 8: Remission rates at Week 6/8 - short-term placebo-controlled pool	29
Figure 5. CGI-I Score at week 6/8 (FAS/MMRM): short-term, placebo-controlled pool	30
Table 7. Overview of MDD pools for the evaluation of the safety and tolerability of vortioxetine	31
Table 8. Patient disposition and withdrawals by primary reason by dose (APTS) - MDD Short-term Pool.....	32
Table 9. TEAEs Leading to Withdrawal by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool	33
Table 10. Severe TEAEs by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool	40
Table 11. TEAEs with an Incidence of 5% or More by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool.....	46
Table 12. Insomnia-related TEAEs by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool	47
Table 13. TESD, Core Treatment Period, by Dose (APTS, Mantel-Haenszel) - Studies 11984A, 304, 13267A, 315, 316, 317 and 308	48
Table 14. TEAEs with an incidence of 2% or more by preferred term, core treatment period (APTS) - MDD Short-term placebo-controlled pool	48
Figure 9. Forest plot of relative risk of TEAEs with an incidence of 2% or more by preferred term, core treatment period (APTS) - MDD Short-term placebo-controlled pool: vortioxetine 5-20mg vs. placebo	49
Table 15. TEAEs leading to withdrawal by preferred term, core treatment period, (APTS) - MDD Open-label Long-term Pool	50
Table 16. Severe TEAEs by Preferred Term, Core Treatment Period (APTS) - MDD Open-label Long-term Pool.....	54

Table 17. ITC of remission rates: raw data parameter inputs	61
Table 18. ITC of remission rates: estimates by adjusted indirect comparison using relative risks	62
Table 19. ITC of withdrawal rates: raw data parameter inputs	63
Table 20. ITC of withdrawal rates due to AEs: estimates by adjusted indirect comparison using relative risks	64
Table 21. ITC of response rates: raw data parameter inputs.....	66
Table 22. ITC of response rates: estimates by adjusted indirect comparison using risk differences, relative risks and odds ratios.....	67
Table 23. Comparison of endpoint measurements in studies included in ITC.....	68
Table 24. Effect size estimation: REVIVE, using MADRS change from baseline.....	69
Table 25. Effect size estimation: Kasper 2013, using HAM-D ₁₇ change from baseline	70
Table 26. Effect size estimation: Rush 2006 (STAR*D), using QIDS-SR ₁₆ change from baseline	71
Table 27. Effect size estimation: Lenox-Smith 2008 (STAR*D), using HAM-D ₂₁ change from baseline	72
Table 28. Standardised mean difference of change from baseline on efficacy assessment scales: inputs	73
Table 29. Adjusted indirect comparison with SMD of change from baseline	74
Table 30. Bayesian indirect comparison with SMD of change from baseline (fixed effect) ..	74
Table 31. Calculation of risk differences for withdrawal due to AEs by Bucher method	75
Table 32. Recruitment and treatment settings for the studies included in the ITC	76
Table 33. Base case scenario: 12-month horizon (NHS/PSS perspective)	79
Table 34. Scenario: 2-month time horizon (NHS/PSS perspective)	79
Table 35. Scenario: 8-month time horizon (NHS/PSS perspective)	80
Table 36. Scenario: 2-year time horizon (NHS/PSS perspective)	80
Table 37. EQ-5D summary index (FAS, MMRM): MADRS non-remitters and remitters.....	82
Table 38. EQ-5D summary index (FAS, OC): MADRS non-remitters.....	83
Table 39. EQ-5D summary index (FAS, OC): MADRS remitters.....	83
Table 40. EQ-5D Summary Index (FAS, LOCF): MADRS non-remitters.....	83
Table 41. EQ-5D summary index (FAS, LOCF): MADRS remitters.....	84
Table 42. Changes from baseline in EQ-5D summary index (FAS, MMRM): MADRS non-remitters and remitters.....	85
Table 43. Change from baseline in EQ-5D summary index (FAS, OC): MADRS non-remitters	85
Table 44. Changes from baseline in EQ-5D summary index (FAS, OC): MADRS remitters ..	85
Table 45. Changes from baseline in EQ-5D summary index (FAS, LOCF): MADRS non-remitters	85
Table 46. Changes from baseline in EQ-5D summary index (FAS, LOCF): MADRS remitters	86
Table 47. Results when GP visit for switch set to zero (NHS/PSS perspective).....	87
Table 48. Model parameter inputs: utility values.....	88
Table 49. Model parameter inputs: healthcare resource utilisation	89

Section A: Clarification on effectiveness data

Literature searches

A1. Section D, Appendix Table D13: Please provide a rationale for lines 64 to 79 of the search strategy.

The systematic literature review in switch was an adaptation of a review previously undertaken by the 'Agency for Healthcare Research and Quality' (AHRQ), published in April 2012, assessing 'Treatment for Depression After Unsatisfactory Response to SSRIs^{1,2}'. The only change from AHRQ search was additional search string for monotherapy and deletion of search terms corresponding to adjunctive/combotherapy considering the objective of the Lundbeck review was to focus on antidepressant monotherapies only.

In terms of the rationale for lines 65 to 79 were introduced to remove editorial, notes, and general review from overall search hits (#64), while including meta-analysis, pooled studies, or systematic reviews, along with clinical data.

A2. Section D, Appendix Tables D33 and D34: Please provide an explanation for the term "2501" in line 13 of these strategies.

This is an error in the write-up of the search string. The original search strings have been revisited and the search term was as follows "CEA.mp." rather than "2501" as recorded in Tables D33 and D34 within Section D of the submission.

A3. Section D, Appendix Table D14: The typographical error in line 44 will have resulted in some records not been identified. Please check whether correcting the typographical error may have led to relevant records being missed.

44 "light thearpy" ;ti,ab,kw 0

Correcting the typographical error "light thearpy":ti,ab,kw" to "light therapy":ti,ab,kw" led to the addition of one record. This additional record evaluated combination therapy and hence does not meet the eligibility criteria of the review (monotherapies only). Hence, no relevant records have been missed as a consequence of the typographical error.

REVIVE trial

A4. Patients were enrolled into the REVIVE trial if they received treatment with citalopram, escitalopram, paroxetine, sertraline, duloxetine or venlafaxine monotherapy. Please clarify why patients who received prior treatment with other serotonin reuptake inhibitors [SRIs], such as fluoxetine, were not included.

The REVIVE study design included a screening period of 4–10 days, from which eligible patients were directly switched from their previous treatment to vortioxetine or agomelatine. Fluoxetine, the only other SSRI widely used in the UK (see Figure A10 of the main submission), was not permitted as a previous treatment due to its long half-life, in order to minimise potential carry-over effect, which could have interfered with the study results.

A5. Please clarify whether patients were allowed to receive additional support (such as GP care or counselling) during the course of the study.

Additional support was not allowed in order to avoid interference with the evaluation of the study drugs. Patients were excluded from the study if they were receiving formal cognitive or behavioral therapy or systematic, psychotherapy, or plans to start such therapy during the study (exclusion criterion n°17).

A6. The REVIVE trial is described as being blinded, yet the dose of agomelatine was fixed at 25 mg per day for the first 2 weeks of treatment, whereas the dose of vortioxetine could be changed at week 1. Please clarify further how blinding was retained given this difference in the dose-modification pattern across treatment arms.

All patients in REVIVE were started on the lower dose of either vortioxetine or agomelatine (10mg and 25mg respectively). In REVIVE, at week 1 the investigator had the opportunity to adjust (increase) the dose if initial response was unsatisfactory. As the allocated treatment was blinded, the investigator did not know whether the dose of vortioxetine or agomelatine was actually modified if the dose was adjusted at week 1. The study medication was packed in a way that the investigator chose between high or low dose. At week 1, both high and low dose in the agomelatine arm contained 25mg agomelatine.

A7. Patients were eligible to be enrolled into the REVIVE trial if they were either an inpatient in a psychiatric hospital or an outpatient at a psychiatric setting at the time of the study entry. Please provide the proportion of patients who were inpatients and the proportion who were outpatients at the time they were recruited to the trial.

The overwhelming majority (97.2%) patients recruited to REVIVE were outpatients; only the remaining 2.8% were inpatients at the time of recruitment.

A8. The REVIVE trial included patients who had depressive symptoms considered as non or partially responsive to no more than one adequate course of SRI monotherapy, and who were candidates for a switch in the investigator's opinion and wished to change antidepressant treatment. Please clarify whether there were any specific criteria used to define patients as non-responsive or partially responsive.

In REVIVE, both non-responders and partial-responders to previous SRI treatment were included, because both patient categories are eligible for a switch therapy. Together, these patients are termed "inadequate responders".

The patient population of inadequate responders was ensured by including patients who were considered by the investigators still symptomatic to a clinically significant extent following previous adequate antidepressant treatment and who were candidates for a switch in antidepressant treatment. The patients also had to be willing to change their current treatment due to inadequate response. Both the clinicians' and patients' perspectives of the limited effect of the previous antidepressant were considered, reflecting clinical practice. Inadequate responders were defined as non or partial responders to an adequate course (licensed dose for at least 6 weeks) of an SSRI/SNRI monotherapy, that is patients that fail to achieve an adequate improvement of depressive symptoms (even after a dose increase) were selected for enrolment based on the clinical criteria (investigator's judgment), which also included a cut-off of the MADRS total score ≥ 22 points and an item 1 score ≥ 3 points (apparent sadness) to ensure that patients still had a substantial level of depressive symptoms.

In summary, the evaluation of inadequate response to the prior antidepressant followed a process that reflects routine outcome monitoring in real-life practice, taking into account the investigators' assessments of clinically meaningful response and review of treatment compliance.

Lundbeck notes that a possible interpretation of question A8 is whether non- and partial responders were defined as distinct subgroups for analysis; these data were not collected and therefore no such subgroups could be identified.

TAK318 trial

A9. Please provide details of the recruitment setting for the TAK318 trial (that is, primary care, secondary care).

TAK318 was conducted in psychiatry outpatient settings only. All study sites were selected based on their prior experience conducting clinical trials in patients with major depressive disorder (MDD).

A10. Patients in the TAK318 trial received treatment with citalopram, paroxetine or sertraline. Please clarify why patients who received prior treatment with other selective serotonin reuptake inhibitors [SSRIs], such as fluoxetine, were not included.

Patients with a diagnosis of a Major Depressive Episode (MDE) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) receiving SSRI monotherapy (citalopram, paroxetine, or sertraline), for at least 8 weeks prior to the Screening Visit, and who were experiencing sexual dysfunction, were eligible. The study was conducted in US and Canada. An immediate switch from the previous antidepressant causing sexual dysfunction was chosen as it more clearly reflects clinical practice.

Due to this immediate switch and in order to minimise potential interactions, fluoxetine was excluded for the same reasons as described in answer to question A4.

A11. Figure B14 (page of 98 of the company's submission) presents a plot of changes in MADRS and CGI-I scores in the TAK318 trial. Please provide tabulated data on changes in scores used to produce these figures, with mean differences between arms, standard errors and 95% confidence intervals. Please provide similar data for all depression rating scales measured in the TAK318 trial.

Tables 1-3 below provide the tabulated data of change from baseline by study visit for the following symptom scores:

- MADRS total score
- CGI-I
- CGI-S

Table 1. Analysis of change from baseline in MADRS total score by study visit (MMRM) Repeated measures analysis. Full Analysis Set.

Study visit	Escitalopram (n=207)	Vortioxetine (n=217)
Baseline value		
N	203	211
LS mean (SE)	8.5 (0.38)	8.2 (0.37)
P-value, vortioxetine vs. escitalopram		0.574
Change from baseline visit at Week 2		
N	203	211

Change from baseline visit at Week 4		
N	188	187
Change from baseline visit at Week 6		
N	176	175
Change from baseline visit at Week 8		
N	174	165
LS mean (SE)	-1.7 (0.46)	-1.2 (0.47)
P-value, vortioxetine vs. escitalopram		0.520
LS mean differences (SE) from escitalopram		0.4 (0.65)
95% CI for differences		(-0.86, -1.71)

Notes: Baseline value is defined as the last observation prior to the first dose of double-blind medication. Baseline LS means and P-values were from an ANOVA model with terms for treatment and pooled center. Post-baseline LS means and P-values were from an MMRM model with baseline*week, pooled center, week, treatment and week*treatment as factors in the analysis.

Table 2. Analysis of change from baseline in CGI-I score by study visit (MMRM) Repeated measures analysis. Full Analysis Set.

Study visit	Escitalopram (n=207)	Vortioxetine (n=217)
Baseline CGI-S value		
N	207	217
LS mean (SE)	2.1 (0.05)	2.1 (0.05)
P-value, vortioxetine vs. escitalopram		0.938
CGI-I Week 1 Score		
N	206	212
CGI-I Week 2 Score		
N	200	202
CGI-I Week 4 Score		

N	188	187
██████████	██████████	██████████
████████████████████		██████████
████████████████████████████		██████████
██████████████████		████████████████
CGI-I Week 6 Score		
N	176	175
██████████	██████████	██████████
████████████████████		██████████
████████████████████████████		██████████
██████████████████		████████████████
CGI-I Week 8 Score		
N	174	165
LS mean (SE)	3.4 (0.08)	3.2 (0.08)
P-value, vortioxetine vs. escitalopram		0.342
LS mean differences (SE) from escitalopram		-0.1 (0.11)
95% CI for differences		(-0.33, -0.11)

Notes: Baseline value is defined as the last observation prior to the first dose of double-blind medication. Baseline LS means and P-values were from an ANOVA model with terms for treatment and pooled center. Post-baseline LS means and P-values were from an MMRM model with baseline*week, pooled center, week, treatment and week*treatment as factors in the analysis.

Table 3. Analysis of change from baseline in CGI-S score by study visit (MMRM) Repeated measures analysis. Full Analysis Set.

Study visit	Escitalopram (n=207)	Vortioxetine (n=217)
Baseline CGI-S value		
N	207	217
LS mean (SE)	2.1 (0.05)	2.1 (0.05)
P-value, vortioxetine vs. escitalopram		0.938
Change from baseline at Week 1		
N	206	212
██████████	██████████	██████████
████████████████████		██████████
████████████████████████████		██████████
██████████████████		████████████████
Change from baseline at Week 2		
N	200	202
██████████	██████████	██████████
████████████████████		██████████
████████████████████████████		██████████
██████████████████		████████████████
Change from baseline at Week 4		
N	188	187

Change from baseline at Week 6

N	176	175

Change from baseline at Week 8

N	174	165
LS mean (SE)	-0.2 (0.06)	-0.2 (0.06)
P-value, vortioxetine vs. escitalopram		0.400
LS mean differences (SE) from escitalopram		-0.1 (0.08)
95% CI for differences		(-0.23, -0.09)

Notes: Baseline value is defined as the last observation prior to the first dose of double-blind medication. Baseline LS means and P-values were from an ANOVA model with terms for treatment and pooled center. Post-baseline LS means and P-values were from an MMRM model with baseline*week, pooled center, week, treatment and week*treatment as factors in the analysis.

Outcomes

A12. Priority question: *The final scope issued by NICE lists several outcomes that are not presented in the results section (section 6.5 of the company's submission). Where possible, please provide summary tables and/or figures of results for the following outcomes, or clarify where data were not collected:*

As the population of interest given the decision problem was switch patients data only data which is relevant and applicable to this population has been reported. This either consists of direct evidence collected in the switch population or, based on clinical advice and opinion, from the full MDD population if deemed transferable.

a. relapse (including relapse rate and time from remission to relapse)

There is one relapse prevention study (NCT00596817), as reported in Table B4 of the main submission, which was excluded based on the population (i.e. it did not include a switch population). Therefore no long-term relapse data are available in the population of interest.

As a post hoc analysis in response to NICE's question A12a, relapse data are provided for Study TAK318, the study of treatment-emergent sexual dysfunction in otherwise well-controlled patients. MADRS score was a secondary endpoint in this study, which enabled calculation of relapse rates according to the criterion of a MADRS total score of ≥ 22 . [REDACTED]

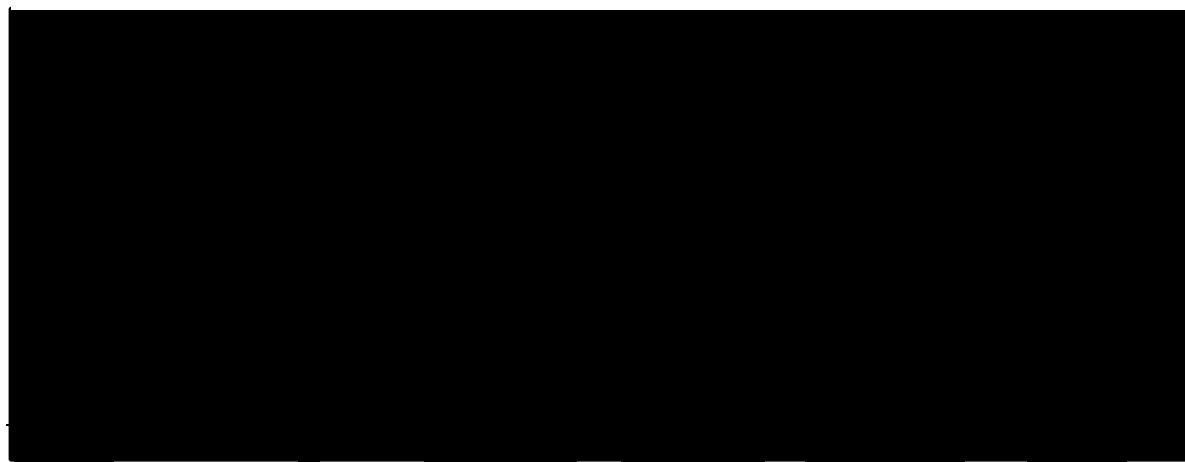
[REDACTED]

[REDACTED]

[REDACTED]

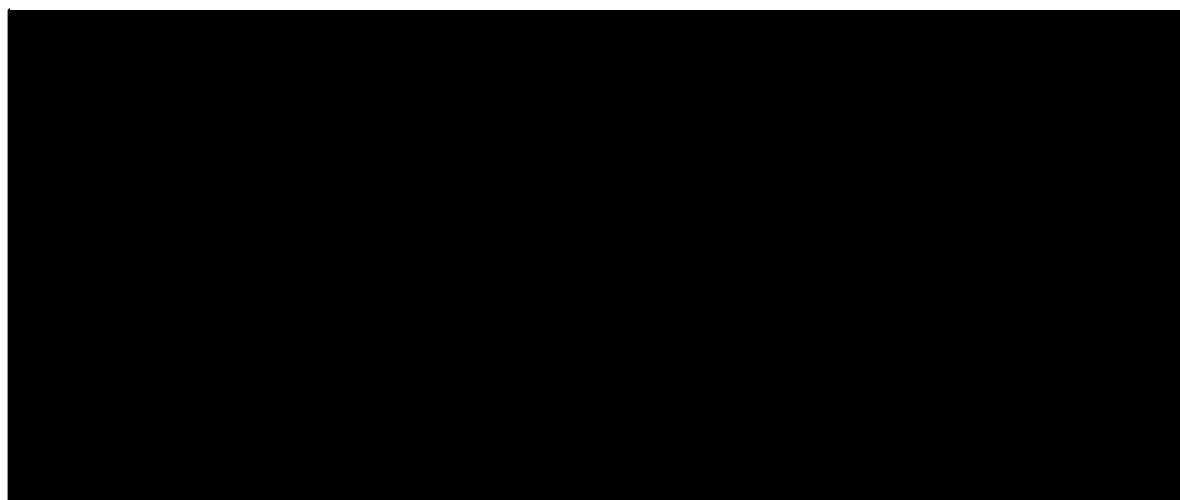
[REDACTED]

Figure 1 [REDACTED]



[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Figure 2



b. sleep quality (in addition to sleep related adverse events)

Sleep quality data (other than those associated with sleep-related AEs e.g. insomnia) were not collected in any of the vortioxetine clinical trials in adults with MDD and hence are not available. Sleep related AE data are reported in the main submission for REVIVE and 318 and also for the short- and long-term MDD pools in response to QA15.

c. cognitive dysfunction

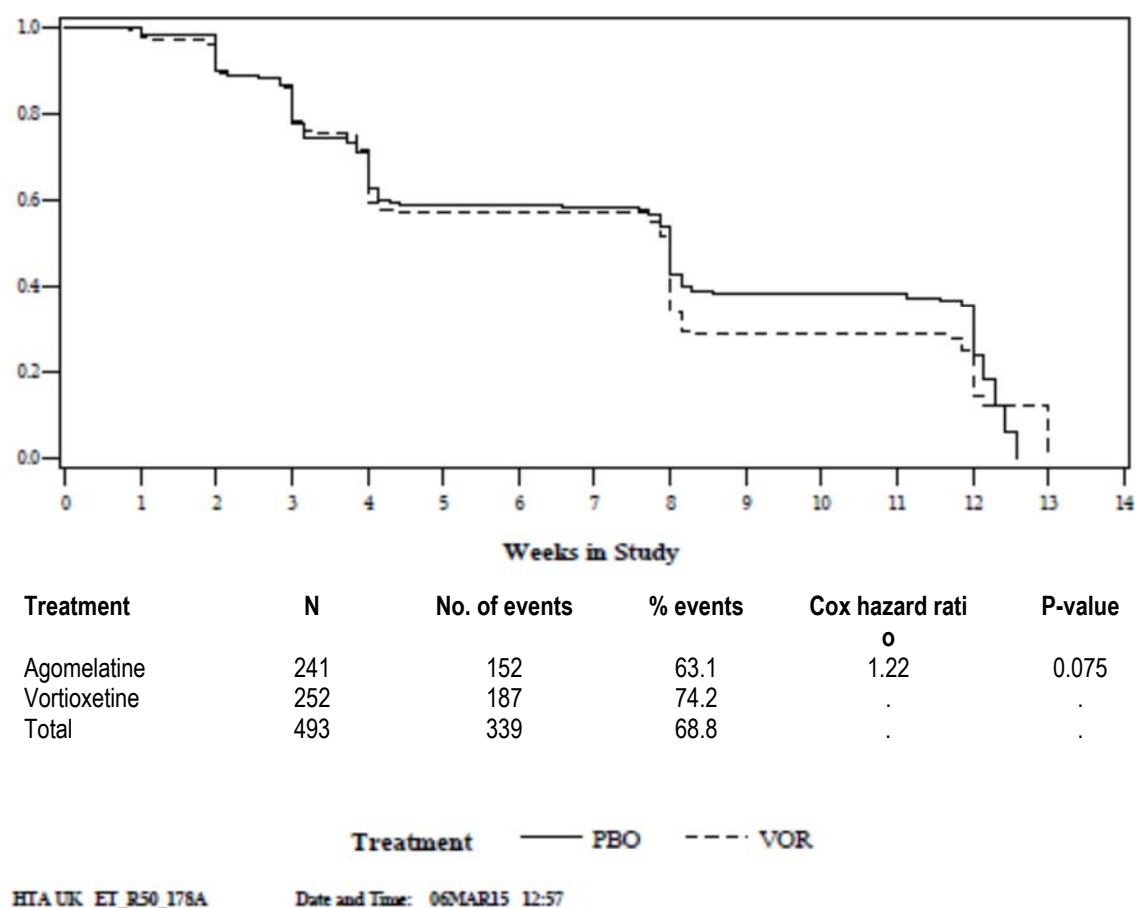
No data are currently available in the population of interest given the decision problem and therefore results have not been presented. As stated in Section 4.1.2 of the submission there is a growing body of evidence supporting the effects of vortioxetine on cognitive dysfunction. As part of this development programme Lundbeck are conducting a study specifically in the switch population (NCT02272517). This study is currently at the participant recruitment stage.

d. time to response

Below is a time-to-event analysis of first response in Study 14178A (REVIVE), in which response is defined as a $\geq 50\%$ reduction in MADRS score. This is a post hoc analysis conducted only for the purpose of responding to the above specific question: it was not pre-planned or pre-specified in the study protocol or the statistical analysis plan. Rather, response rates were reported at each clinical assessment. By visual inspection of the Kaplan-Meier plot in Figure 3 separation between groups in favour of vortioxetine is apparent from 8 weeks. This finding is in line with the separation in response rates assessed at each

visit. That being said, the values differ slightly from the response rates obtained at each clinical assessment in the protocol-defined OC/LOCF analysis, since there are a few patients who respond at early assessments but do not maintain response until the end of the study. Hence, this time-to-event analysis reports time to *first* response, regardless of whether it is sustained to the end of study.

Figure 3: Study 14178A (REVIVE): Kaplan-Meier plot of time to first 50% response



e. adverse effects of treatment discontinuation

Adverse event data specifically associated with treatment discontinuation data are not available in the trials in switch populations (REVIVE, TAK318). However, the question of AEs following treatment discontinuation can be answered by reference to studies in general MDD populations.

On review of the evidence base available, the European Medicines Agency accepted that there was no evidence of clinically relevant discontinuation symptoms that warranted a dose tapering of vortioxetine. Due to the long plasma elimination half-life of 66 hours and the gradual elimination from the central 5-HT transporter, there is a relatively long natural down-taper. At this time, discontinuation symptoms are referred to in the SmPC as not relevant for vortioxetine and subsequently, there seems to be no need for gradual dose reduction of the substance.

In contrast, as stated in Section 4.1.3. of the main submission through a review of all antidepressants, Haddad and Anderson³ concluded that discontinuation symptoms are associated with 25 of the available antidepressants including those most widely used in the UK (citalopram, sertraline, fluoxetine, mirtazapine, venlafaxine), with common symptoms including dizziness, headache, nausea and lethargy.

A13. For each depression rating scale used (for example, Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Depression Rating Scale [HAM-D], Clinical Global Impression - Severity Scale [CGI-S]) please explain what is considered a clinically meaningful change or difference in these scales.

Table 4 details what is considered a clinically meaningful change in symptom scores for the relevant scales. These clinically relevant differences are however in the context of assessing pharmacological compounds versus placebo. As discussed by Montgomery (2011)⁴, this clinically relevant difference versus placebo is not to be generalised for comparisons between two active drugs, and one rule that can be applied for the translation from placebo-control to active-control comparison is 50% of the difference judged as clinically relevant in placebo-controlled studies:

“The criteria used to establish a clinically relevant difference have almost all been focused on a comparison of drug and placebo. Comparing differences between two active treatments applying the same criterion used to define a clinically relevant difference on the pivotal scale between active drug and placebo is very stringent, since this means that the difference to placebo of the superior treatment must be at least twice that of the comparator antidepressant. However, 50% of the difference between active drug and placebo has also been used as a criterion to indicate probable clinical relevance when comparing two established treatments.”

The London New Drugs Group (LNDG) has accepted this criterion when assessing evidence to inform local decision-making⁵. This is demonstrated in their discussion of agomelatine and what should be considered a clinically relevant change in HAM-D17 score:

“The agomelatine/placebo difference in HAMD score was not always greater than 3 points (ref 8 and the active control studies), the difference considered to be clinically significant by NICE. The agomelatine/sertraline HAMD score difference was greater than 1.5 points, which is considered clinically significant.”

Table 4. Clinical relevance of changes in symptom scores on depression rating scales

Scale	Clinically relevant difference in change in symptom score: active treatment versus placebo control		References
		Half of the score considered clinically relevant in placebo controlled studies based on Montgomery 2011 ⁴	
MADRS	2 points	1 point	Batterham 2009 ⁶ Melander 2008 ⁷ Bruce 1994 ⁸
	1.6 to 1.9 points	0.8 to 0.95 points	Duru 2008 ⁹
HAM-D ₂₄	2 points	1 point	Duru 2008 ⁹ Montgomery 2009 ¹⁰
HAM-D ₁₇	3 point	1.5 points	Denby ⁵
CGI-S/CGI-I	No clear consensus		Bandelow 2006 ¹¹

Switching and initial-use trials

A14. Priority question: *In section 6.1 of the company's submission, it is stated that the relative efficacy of anti-depressants cannot be assumed to be constant between initial and switch usage. Please provide any further supporting evidence for this statement beyond the quoted meta-analysis (Papakostas et al 2008). In particular, please provide any evidence that the relative efficacy of non-selective serotonin reuptake inhibitors (non-SSRIs) will differ between initial and switch usage.*

To respond to this question, Lundbeck has conducted a basic structured literature review to identify publications which may provide additional information to the evidence identified by UK clinical experts in the submission regarding the difference in relative treatment effects at different treatment lines.

Results

The articles which were identified as relevant to this question are reported in Table 5.

Table 5: Publications of interest identified in the searches

Author (year)	Citation	Summary and evidence																														
Bauer 2009	The effect of venlafaxine compared with other antidepressants and placebo in the treatment of major depression: A meta-analysis. <i>European Archives of Psychiatry and Clinical Neuroscience</i> 259:172–185	Meta-analysis comparing venlafaxine (non-SSRI) with other antidepressants. Data is reported in before switch populations and after switch (TRD) populations. Odds ratios (OR) are a measure of relative efficacy. These data suggest that the relative efficacy of venlafaxine (a non-SSRI) compared with other antidepressants is greater in switch usage than in before switch usage. The differences may not be significant. <table> <tr> <th>Outcome</th><th colspan="2">Odds ratio [95% CI]</th></tr> <tr> <th>Venlafaxine versus</th><th>Trials of Initial treatment</th><th>Trials of switch treatment</th></tr> <tr> <td>Response</td><td></td><td></td></tr> <tr> <td>SSRIs</td><td>1.15 [1.02–1.29]</td><td>-</td></tr> <tr> <td>TCAs</td><td>1.22 [0.96–1.54]</td><td>-</td></tr> <tr> <td>Any AD</td><td>-</td><td>1.38 [0.67–3.38]</td></tr> <tr> <td>Remission</td><td></td><td></td></tr> <tr> <td>SSRIs</td><td>1.19 [1.06–1.34]</td><td>-</td></tr> <tr> <td>TCAs</td><td>1.06 [0.74–1.63]</td><td>-</td></tr> <tr> <td>Any AD</td><td>-</td><td>1.36 [0.99–2.10]</td></tr> </table>	Outcome	Odds ratio [95% CI]		Venlafaxine versus	Trials of Initial treatment	Trials of switch treatment	Response			SSRIs	1.15 [1.02–1.29]	-	TCAs	1.22 [0.96–1.54]	-	Any AD	-	1.38 [0.67–3.38]	Remission			SSRIs	1.19 [1.06–1.34]	-	TCAs	1.06 [0.74–1.63]	-	Any AD	-	1.36 [0.99–2.10]
Outcome	Odds ratio [95% CI]																															
Venlafaxine versus	Trials of Initial treatment	Trials of switch treatment																														
Response																																
SSRIs	1.15 [1.02–1.29]	-																														
TCAs	1.22 [0.96–1.54]	-																														
Any AD	-	1.38 [0.67–3.38]																														
Remission																																
SSRIs	1.19 [1.06–1.34]	-																														
TCAs	1.06 [0.74–1.63]	-																														
Any AD	-	1.36 [0.99–2.10]																														
Souery 2011	Citalopram versus desipramine in treatment resistant depression: Effect of continuation or switching strategies. A randomized open study. <i>The World Journal of Biological Psychiatry</i> . 12: 364–375	Crossover study of citalopram (SSRI) and desipramine* (non-SSRI). No direct analysis of relative efficacy of the interventions before and after crossover is reported, but data in Table III may be able to be used to calculate a demonstrable difference: Response rate differences (calculated) (%): Before switch: Citalopram (cit) 54.12% vs desipramine (des) 55.22% = 1.1% After switch: Cit→des 50.00% vs. des→cit 37.50% = 12.5% Remission rate difference (calculated) (%): Before switch: Citalopram 18.82% vs desipramine 31.34% = 12.52% After switch: Cit→des 40.00% vs des→cit 37.5% = 2.5% The differences may not be significant. The publication focuses on whether, after inadequate response to 4 weeks of treatment, a treatment switch is an effective option. This treatment duration is unlikely to affect conclusions that relative treatment effects may differ but the magnitude of this difference in relative effect may change if an adequate treatment length of roughly 8 weeks is given (in line with NICE guidance). *not licensed in the UK																														
Keller 1998 and Thase 2002	The treatment of chronic depression, Part 2: A double blind, randomized trial of sertraline and imipramine. <i>Journal of Clinical Psychiatry</i> 59:11 598-607. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. <i>Archives of General Psychiatry</i> . 59: 233-239	Initial and subsequent crossover trial of sertraline (SSRI) and imipramine (non-SSRI). Calculation of the differences in change from baseline for each intervention (taken from Table 4 of Keller 1998 and Table 3 of Thase 2002) may indicate a small difference in relative efficacy of the two therapy classes in the before switch (Keller 1998) and post-switch (Thase 2002) populations. The differences may not be significant. Difference in mean change from baseline between sertraline and imipramine (calculated): HAM-D Before switch (Keller 1998): 0.1; After switch (Thase 2002): 2.8 MADRS Before switch (Keller 1998): 0.4; After switch (Thase 2002): 2.9																														

Abbreviations: OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; TRD, treatment resistant depression

Discussion

No studies were identified that aimed to specifically answer the question in the objective of this search. However, three studies were identified that do provide evidence in support of differences in relative treatment effects at different treatment lines.

The Bauer 2009 study¹² was a large meta-analysis, including over ten thousand patients. It compared venlafaxine with other antidepressants in initial vs. switch usage. The particular benefit of this meta-analysis, in addition to being large and comprehensive, is that it compares venlafaxine with four other groups of antidepressants or populations, allowing further comparisons to be made. Odds ratios for remission and treatment response are calculated, allowing comparison of the relative efficacy of venlafaxine (a non-SSRI) in the initial usage populations and the switch usage. The difference between the remission odds ratios for venlafaxine versus other antidepressants before switch (1.06 and 1.19) and after switch (1.36) is quite large, which suggests that the relative efficacy does differ between initial and switch usage, although it is not known whether it is statistically significant. Similar results are seen for the treatment response odds ratios.

Importantly, no studies were identified explicitly showing that the relative efficacy of SSRIs and non-SSRIs does not differ between initial and switch populations. A study by Wohlreich (2005)¹³ identified through the search showed that the absolute rate of efficacy of duloxetine did not differ between initial usage and following switch from a SSRI. However, this is not clear evidence of the difference in relative efficacy between SSRIs and non-SSRIs between initial and switch usage as there is no comparison of duloxetine to an SSRI in the first line setting.

In addition, internally the study GSK AK1102365^{14;15} was highlighted as providing supportive of this difference in relative treatment effects at different treatment lines. The study results indicate that, when used in switch patients, bupropion is only as effective as placebo. Although not licensed in the UK for the treatment of MDD, this result is not in line with the placebo-controlled data which would have been presented to regulatory agencies internationally to gain approval in countries in which it is now marketed for the treatment of MDD.

The results of the search demonstrate that there is a paucity of data specifically examining the relative efficacy of treatments before and after switching antidepressants. This is unsurprising given the limited totality of evidence currently available for antidepressants in the switch setting as supported by the systematic review in switch, presented in the main dossier; the NICE switch review and the AHRQ review.

However, on reflection of the data reported here, Lundbeck's contention that the relative efficacy of anti-depressants cannot be assumed to be constant between initial and switch usage is supported by the findings of all studies identified, including two large meta-analyses concerning two major antidepressant classes (Papakostas and Bauer). This is a difficult question to research as the few available studies are heterogeneous and potentially confounding factors cannot be eliminated in meta-analysing them. Nevertheless, Lundbeck contends that on the basis of the available evidence it would be inappropriate to assume that the efficacy of vortioxetine relative to comparators in initial use is transferable to the switch setting and this is supported by UK clinical expert opinion.

A15. Priority question: Please provide results from meta-analyses or other forms of evidence syntheses based on all randomised controlled trials comparing vortioxetine with an active comparator and/or placebo in initial-use or mixed initial and switching use. Please provide results on the following outcomes, if available:

- a. Differences in mean change from baseline in depression rating scales (MADRS, HAM-D, CGI-S etc.) between treatments
- b. Relative risks or risk differences in response, remission and withdrawal rates
- c. Adverse events (AEs):
 - i. Number of discontinuation as a result of AEs
 - ii. Number and types of severe adverse events

Meta-analyses and evidence syntheses in switch

The population of interest given the decision problem is switch patients. At present the only evidence synthesis undertaken in the switch population is the indirect treatment comparison presented in the submission (Section 6.7). As stated in Section 6.1 of the submission “*the relative efficacy of antidepressants cannot be assumed to be constant between initial and switch usage*” whereas clinical opinion suggests that tolerability is likely to be. Therefore it is appropriate to use only relative efficacy rates from said switch ITC, but relative tolerability can be inferred from the full data packages available for antidepressants.

In spite of this, all evidence syntheses known to Lundbeck regardless of treatment line are presented below. These are as follows:

1. Meta-analyses (Lundbeck)
 - a. Efficacy: vortioxetine short-term placebo-controlled pool
2. Pooled analyses (Lundbeck)
 - a. Vortioxetine short-term safety and tolerability
 - b. Vortioxetine long-term safety
3. Meta-analyses (external) including discussion on methodological inaccuracies
 - a. Pae (2014)¹⁶
 - b. Berhan and Barker (2014)¹⁷
 - c. Citrome (2014)¹⁸
4. Indirect treatment comparisons/meta-regressions
 - a. Llorca (2015)¹⁹
5. Analyses included in reimbursement submissions to authorities

Meta-analyses and pooled analyses of vortioxetine

Vortioxetine vs. placebo: Lundbeck meta-analysis

Data supporting comparisons of vortioxetine vs placebo are available from 14 placebo-controlled studies, of which data from 11 can be pooled for reasons detailed below. The 14 short-term studies (including the dedicated study in the elderly) were all designed in accordance with the guidelines in depression^{20;21}. Seven of the 14 short-term, placebo-controlled studies (including the dedicated study in the elderly) included an active reference for evaluation of the internal validity of the studies²⁰.

Comparative efficacy between vortioxetine and 3 other marketed antidepressants are available from 3 active-comparator studies. Due to the differences in comparators and populations the studies cannot be pooled.

- Study 14178A (REVIVE): comparative evidence of vortioxetine *versus* agomelatine in patients with inadequate response after treatment with an SSRI or SNRI.
- Study 13926A (SOLUTION): comparative evidence of vortioxetine *versus* venlafaxine for the treatment of MDD in Asian patients.
- Study TAK318: comparative evidence of vortioxetine *versus* escitalopram on sexual functioning in patients with well-treated MDD who were experiencing SSRI-induced sexual dysfunction

These active comparator studies should not be confused with studies that include an active reference. Active references cannot be used to provide valid, unbiased comparisons with the study drug; the purpose of their inclusion in studies is to confirm assay sensitivity only. Active references were included in 7 of the 14 placebo-controlled studies: duloxetine was the active reference in 6 studies and venlafaxine in one study. All patients assigned to these active references were known responders. As stated in Section 1.4.1 of the submission, the EPAR noted: *“although no formal comparison was conducted, numerically larger effect sizes were observed for the active reference than for vortioxetine, except in studies 11492A and 11984A. The exclusion of non-responders and the inclusion of previous responders in the active reference arm could have introduced a bias in favour of the efficacy of the active reference, so differences in the efficacy of vortioxetine versus the active reference cannot be inferred on the basis of these studies.”* For these reasons, results for the active references in trials (used only for internal control) have not been reported here on an individual study basis, but are available on request. A fuller rationale for the use of active references in trials of antidepressants can be found in Section 2.8.2 of the submission.

Meta-analyses for the evaluation of efficacy of vortioxetine from the short-term placebo-controlled pool

For comparisons across studies, a meta-analysis rather than a pooled analysis was considered the statistical methodology that would provide the most reliable estimates of treatment effect. Since not all doses of vortioxetine were included in all the studies, the comparison to an overall placebo group in a pooled analysis could be misleading. The meta-analyses were stratified geographically by all studies and all non-US studies for reasons explained in the Appendix.

Table 6. Overview of meta-analyses Included in the clinical efficacy data package

Meta-analysis	No. of studies included	Study IDs
All short-term placebo-controlled studies in adults	11	11492A , 11984A, 305, 13267A, 315, 316, 14122A, CCT-002, 303, 304, and 317
Non-US short-term placebo-controlled studies in adults	6	11492A , 11984A, 305, 13267A, 14122A, and CCT-002
Rationale for studies excluded from the meta-analysis: Study 12541A: dedicated study in the elderly, and was therefore not included in the meta-analysis of short-term placebo-controlled studies in adult patients. Study 202: the only short-term placebo-controlled study with flexible dosing (10 to 20mg/day) Study CCT-003: exclusively conducted in Japanese patients		

Placebo-controlled studies do not provide a proxy subgroup for switch population

With respect to prior treatment of patients recruited into the short-term, placebo-controlled trials, information was collected on the treatment of the current episode on the concomitant medication form. Medication used up to 3 months prior to screening was recorded, including the name of drug, dose, start and stop date, but no information on whether the patient responded or tolerated the drug. The trials mandated a washout period of at least 14 days prior to screening, which eliminated the possibility of a direct switch as required in the dedicated switch studies.

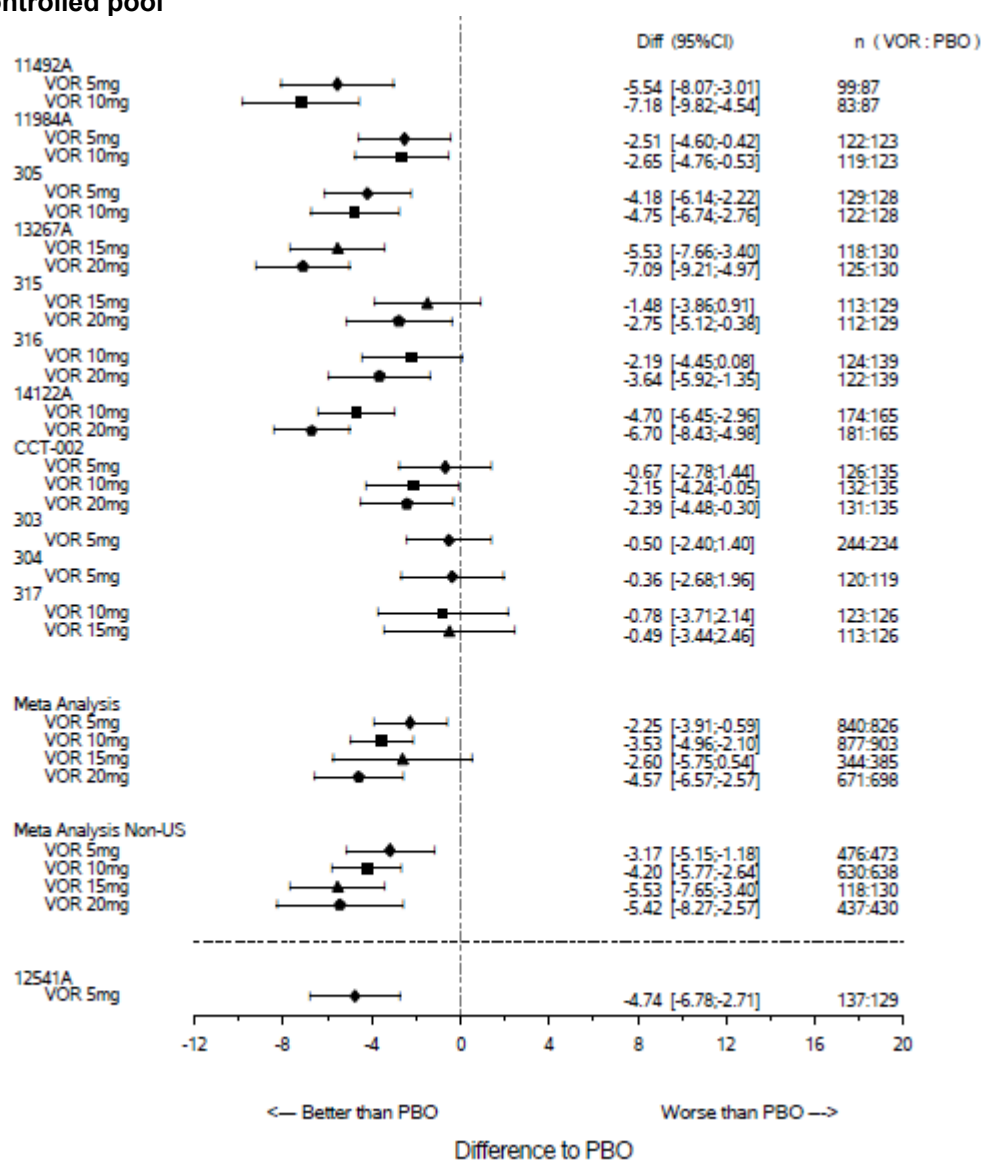
While it is possible, therefore, to identify patients who had received a previous antidepressant, such patients do not comprise a valid proxy subgroup for a switch population as defined in the decision problem.

Endpoints: MADRS score change from baseline

The magnitude of the drug-placebo difference (effect size) in the mean change from baseline to endpoint on the pivotal efficacy assessment tool has been used to make a judgement of the clinical relevance of the efficacy. In the short-term, placebo-controlled studies in adults with vortioxetine, the effect sizes on the MADRS increase with increasing dose of vortioxetine (Figure 4).

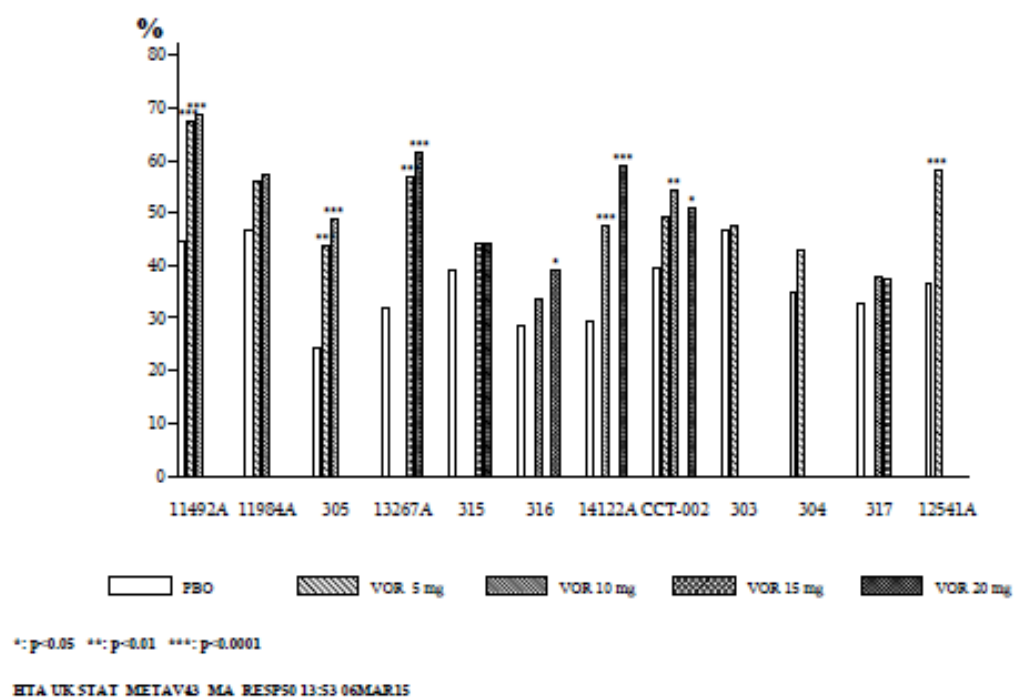
The meta-analysis of all the short-term, placebo-controlled studies in adults supported the results of the individual studies, with a statistically significant effect size across studies of -2.3 points ($p < 0.007$), -3.6 points ($p < 0.001$), and -4.6 points ($P < 0.001$) at Week 6/8 for the 5mg, 10mg, and 20mg/day doses, respectively. The 15mg/day dose was not statistically significantly different from placebo in the meta-analysis, but the effect size was -2.6 points. Thus, the effect size for each of the therapeutic doses of vortioxetine was greater than the usual 2-point difference from placebo at endpoint that is frequently used in short-term, placebo-controlled studies to establish the clinical relevance of antidepressant efficacy^{6,8}.

In the meta-analysis of all the short-term, placebo-controlled, non-US studies in adults, the effect sizes and the increased effect with increasing dose were more pronounced. The effect sizes were -3.2, -4.2, -5.5, and -5.4 points at Week 6/8 for the 5mg, 10mg, 15mg, and 20mg/day doses, respectively.

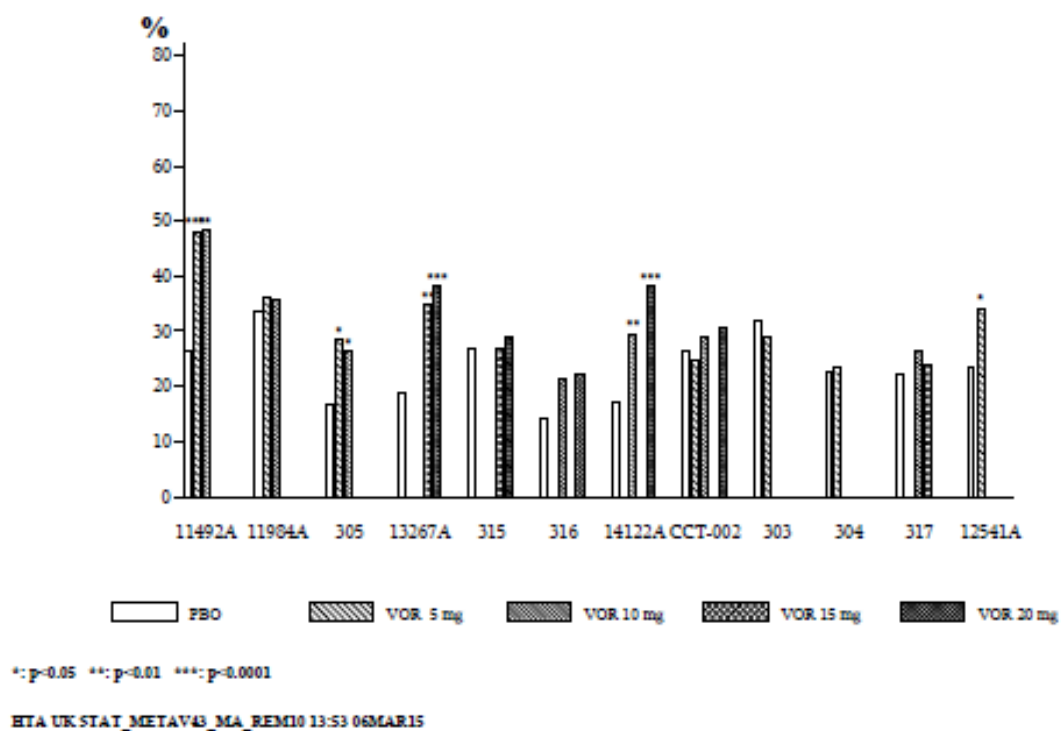
Figure 4. Change from baseline in MADRS total score at week 6/8 (FAS, MMRM) – short-term, placebo-controlled pool**Endpoints: Response, remission and CGI-I score**

The clinical relevance of the effect of vortioxetine in MDD was corroborated in the analyses of responders and remitters and in the analysis of the CGI-I score.

In the responder analysis (Figure 5) vortioxetine separated from placebo ($P < 0.05$) at Week 6/8 in 6 of the 11 short-term, placebo-controlled studies in adults. In 4 of these studies (all non-US), the difference was >16 percentage points, which is regarded as sufficient to establish the clinical relevance of investigational treatments in studies submitted for licensing approval^{2;7;10}.

Figure 5. MADRS 50% response at week 6/8 (FAS, LOCF): short-term, placebo-controlled pool

Vortioxetine also separated from placebo ($P < 0.05$) at Week 6/8 in the remitter analysis in 4 of the 11 short-term, placebo-controlled studies in adults (all non-US studies) (Figure 6).

Figure 6. Remission (MADRS ≤ 10) week 6/8 (FAS, LOCF): short-term, placebo-controlled pool

The meta-analysed results for response and remission rates vs. placebo are shown in Figure 7 and Figure 8, respectively.

Figure 7: Response rates at Week 6/8 - short-term placebo-controlled pool

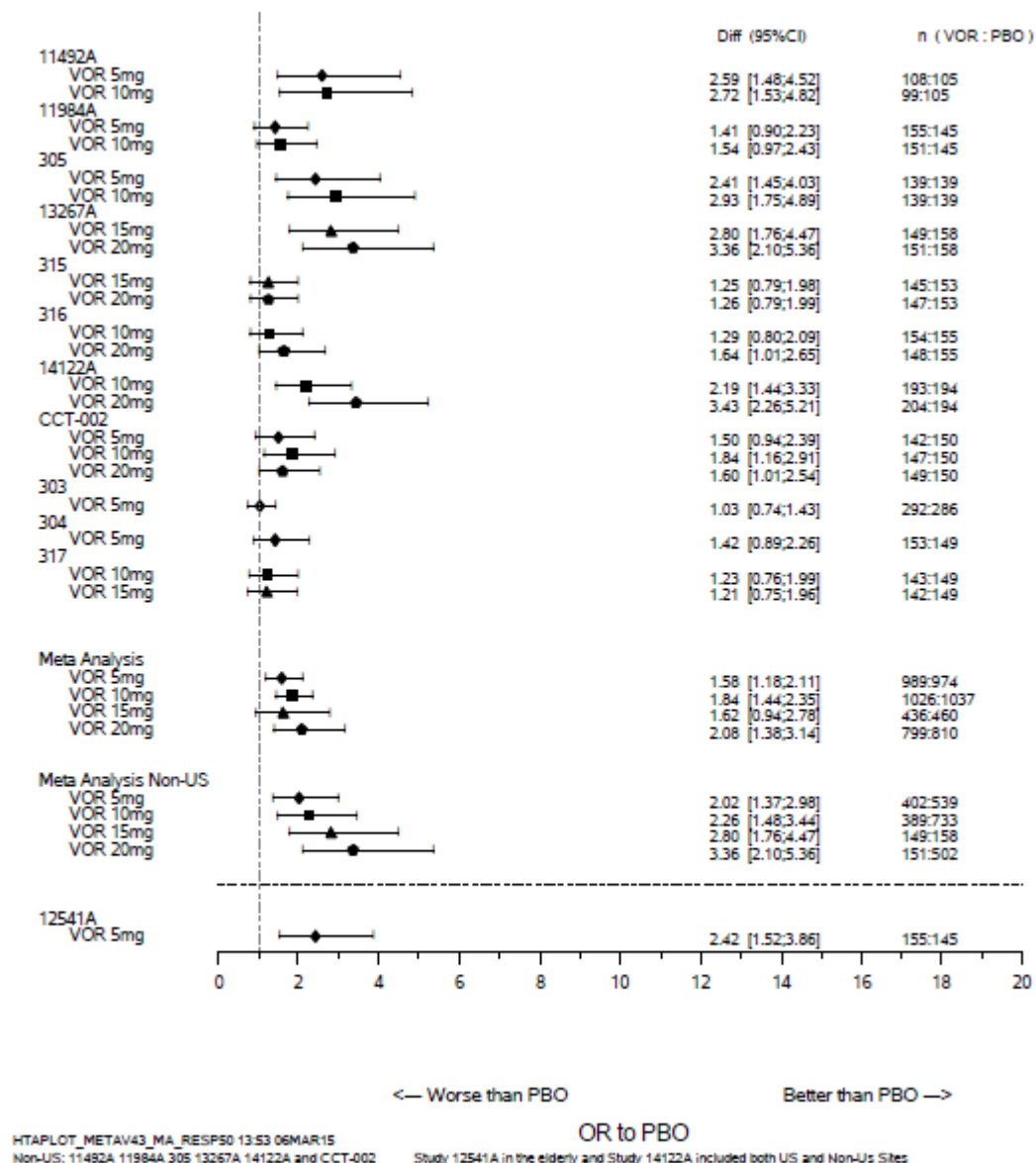
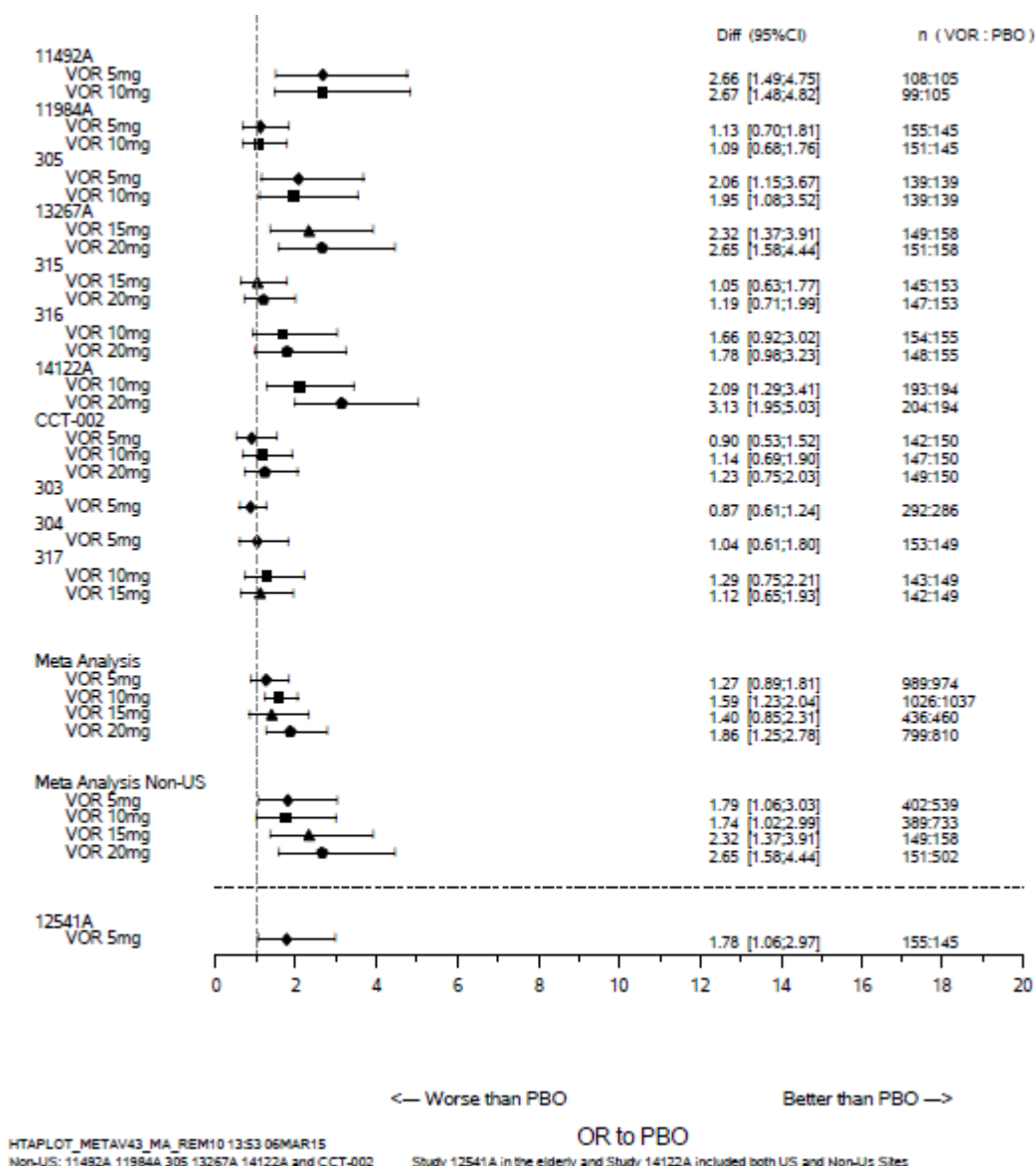
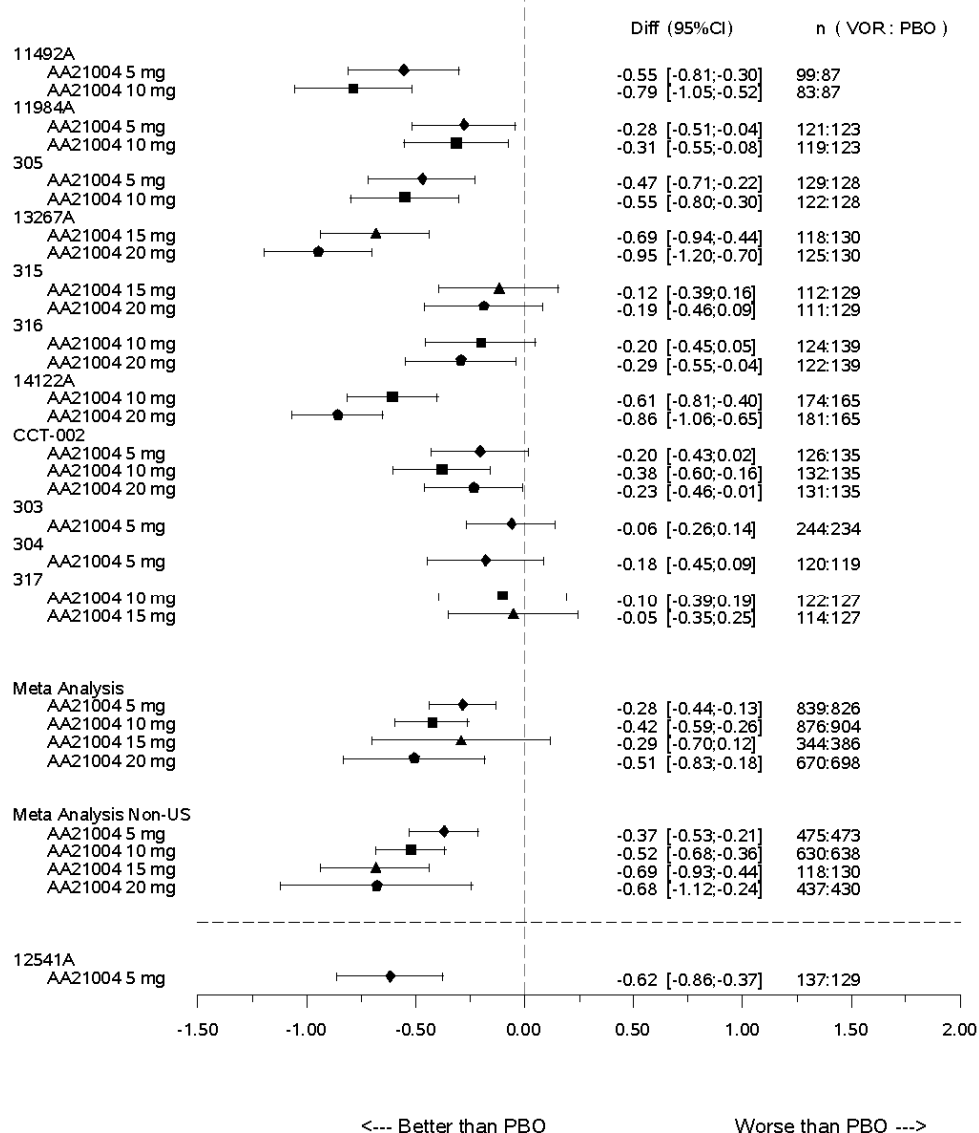


Figure 8: Remission rates at Week 6/8 - short-term placebo-controlled pool

The improvement in the CGI-I score at week 6/8 was greater ($P < 0.05$) in the vortioxetine group than in the placebo group in 7 (in all 6 non-US studies and in one US study) of the 11 short-term, placebo-controlled studies in adults. The meta-analysis of all the short-term, placebo-controlled studies in adults supported the results of the individual studies, and showed an increased effect with increasing dose of vortioxetine (Figure 5).

In the dedicated study in the elderly, the clinical relevance of the effect on the MADRS was shown by the 16 percentage-point greater ($P < 0.05$) proportion of responders, the greater ($P < 0.05$) proportion of remitters, and the greater ($P < 0.05$) improvement in the CGI-I score at week 8 in the vortioxetine group than in the placebo group.

Figure 5. CGI-I Score at week 6/8 (FAS/MMRM): short-term, placebo-controlled pool

MAA Approval PLOT_METAV43_CGII_21 13:34 30AUG13

Non-US: 11492A 11984A 305 13267A 14122A CCT-002

Study 12541A in the elderly and Study 14122A included both US and Non-US Sites

Pooled analyses for the evaluation of the safety and tolerability of vortioxetine

In order to evaluate the safety and tolerability of vortioxetine, two pools were used, the MDD Short-term Pool, and the MDD Open-label Long-term Pool (Table 7As). The short-term safety data are based on the MDD Short-term Pool, which included 12 short-term placebo-controlled studies, including one study (12541A) in patients aged over 65 years. Studies 202 and CCT-003 were not included in the pool as the former was a flexible-dose study and the later was undertaken wholly in Japanese patients. The safety data for these studies are available upon request.

Table 7. Overview of MDD pools for the evaluation of the safety and tolerability of vortioxetine

Pool	Number of studies included	Study ID
MDD Short-term Pool ^a	12	11492A , 11984A, 305, 13267A, 315, 316, 14122A, CCT-002, 303, 304, and 317, and 12541A
MDD Open-label Long-term Pool ^b	5	11492C, 11984B, 301, 13267B, and 314

Safety and tolerability in the studies in MDD in adults and the elderly

Short-term, placebo-controlled studies

Withdrawals and withdrawals due to adverse events

The safety data cut-off date was 31 July 2013 (consistent with the European regulatory assessment of vortioxetine) for this updated MDD Short-term Pool (as defined in Table 7). The pool included 3,904 patients treated with vortioxetine.

Withdrawals

As shown in Table 8, the withdrawal rate in the vortioxetine total group and the placebo group was similar (17% and 16%, respectively). Also, in the therapeutic vortioxetine dose groups (5, 10, and 20 mg/day), the withdrawal rate was similar to that in the placebo group (15%, 15%, and 17%, respectively), except in the 15mg group, in which the withdrawal rate was slightly higher (22%).

Withdrawals due to adverse events

The most common reason for withdrawal in all the therapeutic vortioxetine dose groups was adverse events. Slightly greater proportions of patients in the therapeutic vortioxetine dose groups than in the placebo group withdrew due to adverse events (vortioxetine: 4.8% [5mg], 5.8% [10mg], 8.0% [15mg], and 7.0% [20mg]; placebo: 4.0% Rates of withdrawals due to specific AEs are presented in Table 9.

Table 8. Patient disposition and withdrawals by primary reason by dose (APTS) - MDD Short-term Pool

	Placebo		Vortioxetine 5mg		Vortioxetine 10mg		Vortioxetine 15mg*		Vortioxetine 20mg		Total vortioxetine	
	n	%	N	%	n	%	n	%	n	%	n	%
All Patients Treated Set (APTS)	1,968		1,157		1,042		449		812		3,460	
Completed	1,653	(84.0)	978	(84.5)	881	(84.5)	351	(78.2)	670	(82.5)	2,880	83.2
Withdrawn	315	(16.0)	179	(15.5)	161	(15.5)	98	(21.8)	142	(17.5)	580	16.8
Adverse event(s)	78	(4.0)	56	(4.8)	60	(5.8)	36	(8.0)	57	(7.0)	209	6.0
Lack of efficacy	64	(3.3)	28	(2.4)	19	(1.8)	8	(1.8)	9	(1.1)	64	1.8
Non-compliance	10	(0.5)	5	(0.4)	5	(0.5)	5	(1.1)	4	(0.5)	19	0.5
Protocol violation	33	(1.7)	15	(1.3)	10	(1.0)	8	(1.8)	17	(2.1)	50	1.4
Withdrawal of consent	58	(2.9)	37	(3.2)	39	(3.7)	21	(4.7)	18	(2.2)	115	3.3
Lost to follow-up	56	(2.8)	30	(2.6)	21	(2.8)	12	(2.7)	27	(3.3)	90	2.6
Administrative or other reasons	16	(0.8)	8	(0.7)	7	(0.7)	8	(1.8)	10	(1.2)	33	1.0
*Vortioxetine 15mg will not be made available in the UK.												

Table 9. TEAEs Leading to Withdrawal by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool

Preferred Term	Placebo		Vortioxetine 5mg		Vortioxetine 10 mg		Vortioxetine 15 mg*		Vortioxetine 20 mg		Total vortioxetine	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of Patients	1968		1157		1042		449		812		3460	
Patient years exposure	262.7		149.3		143.4		60.7		112.5		466.0	
Patients with Adverse Events	70	(3.6)	48	(4.1)	51	(4.9)	35	(7.8)	55	(6.8)	189	(5.5)
Nausea	6	(0.3)	13	(1.1)	15	(1.4)	17	(3.8)	27	(3.3)	72	(2.1)
Headache	4	(0.2)	1	(<0.1)	5	(0.5)	4	(0.9)	6	(0.7)	16	(0.5)
Dizziness	6	(0.3)	1	(<0.1)	2	(0.2)	2	(0.4)	4	(0.5)	9	(0.3)
Constipation	0		1	(<0.1)	1	(<0.1)	0		3	(0.4)	5	(0.1)
Vomiting	2	(0.1)	1	(<0.1)	5	(0.5)	2	(0.4)	3	(0.4)	11	(0.3)
Erection increased (SS)	0		0		0		0		1	(0.4)	1	(<0.1)
Abdominal pain	1	(<0.1)	0		0		0		2	(0.2)	2	(<0.1)
Abdominal pain upper	3	(0.2)	0		2	(0.2)	1	(0.2)	2	(0.2)	5	(0.1)
Hypertension	0		0		1	(<0.1)	0		2	(0.2)	3	(<0.1)
Irritability	2	(0.1)	0		1	(<0.1)	1	(0.2)	2	(0.2)	4	(0.1)
Sedation	0		0		1	(<0.1)	0		2	(0.2)	3	(<0.1)
Alcoholic liver disease	0		0		0		0		1	(0.1)	1	(<0.1)
Anorgasmia	0		0		0		0		1	(0.1)	1	(<0.1)
Anxiety	4	(0.2)	2	(0.2)	2	(0.2)	2	(0.4)	1	(0.1)	7	(0.2)
Asthenia	0		1	(<0.1)	0		0		1	(0.1)	2	(<0.1)
Bronchopneumonia	0		0		0		0		1	(0.1)	1	(<0.1)
Chest discomfort	0		1	(<0.1)	0		1	(0.2)	1	(0.1)	3	(<0.1)
Diarrhoea	2	(0.1)	2	(0.2)	3	(0.3)	3	(0.7)	1	(0.1)	9	(0.3)

Vortioxetine for the treatment of MDD [ID583]

Dry mouth	0	2	(0.2)	0	0	1	(0.1)	3	(<0.1)	
Feeling cold	0	0		0	0	1	(0.1)	1	(<0.1)	
Flatulence	0	0		1	(<0.1)	0	1	(0.1)	2	(<0.1)
Hot flush	0	0		0	0	1	(0.1)	1	(<0.1)	
Hypersensitivity	0	0		0	0	1	(0.1)	1	(<0.1)	
Influenza like illness	0	0		0	0	1	(0.1)	1	(<0.1)	
Irritable bowel syndrome	0	0		0	0	1	(0.1)	1	(<0.1)	
Myalgia	0	0		0	0	1	(0.1)	1	(<0.1)	
Palpitations	1	(<0.1)	0	0	0	1	(0.1)	1	(<0.1)	
Renal pain	0	0		0	0	1	(0.1)	1	(<0.1)	
Sleep disorder	1	(<0.1)	0	0	0	1	(0.1)	1	(<0.1)	
Suicidal ideation	3	(0.2)	0	1	(<0.1)	0	1	(0.1)	2	(<0.1)
Suicide attempt	0	1	(<0.1)	1	(<0.1)	0	1	(0.1)	3	(<0.1)
Tension	0	0		1	(<0.1)	0	1	(0.1)	2	(<0.1)
Urinary retention	0	0		0	0	1	(0.1)	1	(<0.1)	
Urticaria	0	0		0	1	(0.2)	1	(0.1)	2	(<0.1)
Vertigo	0	1	(<0.1)	0	0	1	(0.1)	2	(<0.1)	
Abdominal discomfort	1	(<0.1)	1	(<0.1)	1	(<0.1)	0	0	2	(<0.1)
Agitation	2	(0.1)	1	(<0.1)	0	0	0	1	(<0.1)	
Akathisia	1	(<0.1)	0	0	0	0	0	0		
Alanine aminotransferase increased	2	(0.1)	0	0	0	0	0	0		
Anaemia	0	0		0	1	(0.2)	0	1	(<0.1)	
Anal fissure	0	1	(<0.1)	0	0	0	0	1	(<0.1)	
Anger	1	(<0.1)	0	0	0	0	0	0		
Angina pectoris	1	(<0.1)	0	0	0	0	0	0		

Vortioxetine for the treatment of MDD [ID583]

Arthralgia	0	0	0	1 (0.2)	0	1 (<0.1)
Aspartate aminotransferase increased	1 (<0.1)	0	0	0	0	0
Atrial fibrillation	0	1 (<0.1)	0	0	0	1 (<0.1)
Atrioventricular block first degree	0	0	1 (<0.1)	0	0	1 (<0.1)
Balance disorder	1 (<0.1)	0	0	0	0	0
Blood alkaline phosphatase increased	0	1 (<0.1)	0	0	0	1 (<0.1)
Blood creatine phosphokinase increased	0	2 (0.2)	1 (<0.1)	0	0	3 (<0.1)
Blood pressure increased	0	0	1 (<0.1)	0	0	1 (<0.1)
Chest pain	0	0	1 (<0.1)	0	0	1 (<0.1)
Chills	0	1 (<0.1)	1 (<0.1)	0	0	2 (<0.1)
Chronic obstructive pulmonary disease	0	0	1 (<0.1)	0	0	1 (<0.1)
Confusional state	1 (<0.1)	0	0	0	0	0
Convulsion	0	1 (<0.1)	0	0	0	1 (<0.1)
Crying	2 (0.1)	0	0	0	0	0
Decreased appetite	0	1 (<0.1)	0	0	0	1 (<0.1)
Depressed mood	1 (<0.1)	0	0	0	0	0
Depression	9 (0.5)	0	5 (0.5)	0	0	5 (0.1)
Depressive symptom	0	0	0	2 (0.4)	0	2 (<0.1)
Dermatitis allergic	0	0	0	1 (0.2)	0	1 (<0.1)
Dermatitis bullous	1 (<0.1)	0	0	0	0	0
Diabetes mellitus	0	0	1 (<0.1)	0	0	1 (<0.1)
Distractibility	1 (<0.1)	0	0	0	0	0

Vortioxetine for the treatment of MDD [ID583]

Disturbance in attention	2	(0.1)	0	0	0	0	0
Dizziness postural	0		0	1	(<0.1)	0	1 (<0.1)
Dry eye	0		0	0	1	(0.2)	1 (<0.1)
Dry skin	1	(<0.1)	0	0	0	0	0
Dysgeusia	1	(<0.1)	0	0	0	0	0
Dyspepsia	2	(0.1)	0	0	0	0	0
Dyspnoea	2	(0.1)	0	0	0	0	0
Echocardiogram abnormal	1	(<0.1)	0	0	0	0	0
Eczema	0		0	1	(<0.1)	0	1 (<0.1)
Enteritis infectious	1	(<0.1)	0	0	0	0	0
Epigastric discomfort	0		0	0	1	(0.2)	1 (<0.1)
Face oedema	0		0	0	1	(0.2)	1 (<0.1)
Fatigue	1	(<0.1)	1 (<0.1)	2	(0.2)	0	3 (<0.1)
Feeling jittery	1	(<0.1)	0	0	0	0	0
Gamma-glutamyltransferase increased	0		1 (<0.1)	0	0	0	1 (<0.1)
Glossodynia	1	(<0.1)	0	0	0	0	0
Head injury	0		1 (<0.1)	0	0	0	1 (<0.1)
Hepatic function abnormal	0		0	1	(<0.1)	0	1 (<0.1)
Herpes zoster	0		1 (<0.1)	0	0	0	1 (<0.1)
Hiatus hernia	1	(<0.1)	0	0	0	0	0
Hyperhidrosis	1	(<0.1)	1 (<0.1)	1	(<0.1)	0	2 (<0.1)
Hypoaesthesia	1	(<0.1)	0	0	0	0	0
Hypomania	0		0	1	(<0.1)	0	1 (<0.1)
Increased appetite	1	(<0.1)	0	0	1	(0.2)	1 (<0.1)

Vortioxetine for the treatment of MDD [ID583]

Injury	0	1	(<0.1)	0	0	0	1	(<0.1)
Insomnia	1	(<0.1)	5	(0.4)	1	(<0.1)	1	(0.2)
Intentional overdose	0	1	(<0.1)	0	0	0	1	(<0.1)
Kidney infection	0	0		1	(<0.1)	0	1	(<0.1)
Laceration	0	0		0	1	(0.2)	1	(<0.1)
Laryngeal cancer	1	(<0.1)	0	0	0	0	0	
Loss of libido	0	1	(<0.1)	0	0	0	1	(<0.1)
Lumbar radiculopathy	1	(<0.1)	0	0	0	0	0	
Major depression	0	1	(<0.1)	0	1	(0.2)	2	(<0.1)
Malaise	0	0		1	(<0.1)	0	1	(<0.1)
Memory impairment	1	(<0.1)	0	0	0	0	0	
Menorrhagia (SS)	0	0		0	1	(0.3)	1	(<0.1)
Mood swings	1	(<0.1)	0	0	0	0	0	
Mouth ulceration	1	(<0.1)	0	0	0	0	0	
Mucosal dryness	0	0		1	(<0.1)	0	1	(<0.1)
Muscle fatigue	0	0		1	(<0.1)	0	1	(<0.1)
Oedema peripheral	1	(<0.1)	0	0	0	0	0	
Overdose	1	(<0.1)	0	0	0	0	0	
Pain in extremity	0	0		1	(<0.1)	0	1	(<0.1)
Pancreatitis	0	0		1	(<0.1)	0	1	(<0.1)
Panic attack	0	1	(<0.1)	0	0	0	1	(<0.1)
Parosmia	1	(<0.1)	0	0	0	0	0	
Pelvic fracture	0	0		1	(<0.1)	0	1	(<0.1)
Peptic ulcer	1	(<0.1)	0	0	0	0	0	
Pregnancy (SS)	1	(<0.1)	0	0	0	0	0	

Vortioxetine for the treatment of MDD [ID583]

Pruritus	1	(<0.1)	0	1	(<0.1)	0	0	1	(<0.1)		
Pruritus generalised	0		1	(<0.1)	3	(0.3)	1	(0.2)	5	(0.1)	
Rash erythematous	0		0		0		1	(0.2)	0	1	(<0.1)
Rash macular	1	(<0.1)	0		0		1	(0.2)	0	1	(<0.1)
Rash maculo-papular	0		0		2	(0.2)	0		0	2	(<0.1)
Rash pruritic	0		0		0		1	(0.2)	0	1	(<0.1)
Rash pustular	1	(<0.1)	0		0		0		0	0	
Restlessness	1	(<0.1)	1	(<0.1)	0		0		0	1	(<0.1)
Serotonin syndrome	1	(<0.1)	0		0		0		0	0	
Sexual dysfunction	0		0		0		1	(0.2)	0	1	(<0.1)
Skin burning sensation	0		0		1	(<0.1)	0		0	1	(<0.1)
Sleep apnoea syndrome	0		0		0		1	(0.2)	0	1	(<0.1)
Somnolence	2	(0.1)	1	(<0.1)	1	(<0.1)	0		0	2	(<0.1)
Stress fracture	0		0		0		1	(0.2)	0	1	(<0.1)
Tachycardia	1	(<0.1)	0		0		0		0	0	
Tension headache	1	(<0.1)	0		1	(<0.1)	0		0	1	(<0.1)
Tinnitus	0		1	(<0.1)	0		1	(0.2)	0	2	(<0.1)
Tremor	1	(<0.1)	2	(0.2)	0		1	(0.2)	0	3	(<0.1)
Upper limb fracture	0		1	(<0.1)	0		0		0	1	(<0.1)
Urinary tract infection bacterial	0		0		1	(<0.1)	0		0	1	(<0.1)
Vision blurred	2	(0.1)	1	(<0.1)	0		1	(0.2)	0	2	(<0.1)
Weight increased	1	(<0.1)	1	(<0.1)	0		0		0	1	(<0.1)
White blood cell count decreased	1	(<0.1)	0		0		0		0	0	

(SS) Sex Specific Dictionary: MedDRA 14.1. * Vortioxetine 15 mg will not be made available in the UK.

Treatment-emergent adverse events

The Treatment-emergent adverse event (TEAE) with the highest incidence in all the active treatment groups was nausea. The incidence of nausea was 8% in the placebo group and 31% in the vortioxetine 15mg group, which was the treatment group with the highest incidence.

Headache, which was the TEAE with the highest incidence in the placebo group, had similar incidences in all the treatment groups (approximately 13%).

For the majority of the remaining TEAEs, the incidences in the therapeutic vortioxetine dose groups were either slightly higher than those in the placebo group or at placebo level. The incidences were generally higher in the 15mg and 20mg groups than in the 5mg and 10mg groups.

For the majority of the patients with TEAEs, the TEAEs were mild or moderate. The incidence of severe TEAEs was similar in the placebo group and in the vortioxetine total group (4.4% and 5.6%, respectively).

In the therapeutic vortioxetine dose groups, the incidence of severe TEAEs ranged from 4.1% in the 20mg group to 7.0% in the 5mg group.

Data on the occurrence of severe TEAEs by preferred term are provided in Table 10. The severe TEAEs with an incidence $\geq 1\%$ in any of the therapeutic vortioxetine dose groups were nausea and headache. The incidence of severe nausea was 0.1% (2 patients) in the placebo group and 1.6% (7 patients) in the vortioxetine 15 mg group, which was the therapeutic vortioxetine dose group with the highest incidence. The incidence of severe headache was 0.6% (12 patients) in the placebo group and 1.4% (16 patients) in the vortioxetine 5mg group, which was the therapeutic vortioxetine dose group with the highest incidence.

Table 10 provides a summary of the TEAEs reported by $\geq 5\%$ subjects in the MDD placebo-controlled short-term pool studies in MDD.

Table 10. Severe TEAEs by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool

Preferred Term	Placebo		Vortioxetine 5 mg		Vortioxetine 10 mg		Vortioxetine 15 mg*		Vortioxetine 20 mg		Total vortioxetine	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of Patients	1968		1157		1042		449		812		3460	
Patient years exposure	262.7		149.3		143.4		60.7		112.5		466.0	
Patients with Adverse Events	87	(4.4)	81	(7.0)	56	(5.4)	22	(4.9)	33	(4.1)	192	(5.5)
Headache	12	(0.6)	16	(1.4)	10	(1.0)	1	(0.2)	7	(0.9)	34	(1.0)
Nausea	2	(0.1)	5	(0.4)	10	(1.0)	7	(1.6)	7	(0.9)	29	(0.8)
Vomiting	0		3	(0.3)	3	(0.3)	2	(0.4)	3	(0.4)	11	(0.3)
Sedation	1	(<0.1)	0		0		0		2	(0.2)	2	(<0.1)
Abdominal distension	0		0		0		0		1	(0.1)	1	(<0.1)
Abdominal pain	1	(<0.1)	0		0		0		1	(0.1)	1	(<0.1)
Anxiety	4	(0.2)	1	(<0.1)	0		1	(0.2)	1	(0.1)	3	(<0.1)
Back pain	3	(0.2)	2	(0.2)	0		1	(0.2)	1	(0.1)	4	(0.1)
Constipation	1	(<0.1)	1	(<0.1)	2	(0.2)	0		1	(0.1)	4	(0.1)
Dizziness	6	(0.3)	0		1	(<0.1)	2	(0.4)	1	(0.1)	4	(0.1)
Dysgeusia	0		0		0		0		1	(0.1)	1	(<0.1)
Dyspepsia	1	(<0.1)	1	(<0.1)	1	(<0.1)	0		1	(0.1)	3	(<0.1)
Fatigue	3	(0.2)	4	(0.3)	1	(<0.1)	0		1	(0.1)	6	(0.2)
Flatulence	1	(<0.1)	0		0		0		1	(0.1)	1	(<0.1)
Gastroenteritis	1	(<0.1)	0		1	(<0.1)	1	(0.2)	1	(0.1)	3	(<0.1)
Influenza	0		1	(<0.1)	0		0		1	(0.1)	2	(<0.1)
Influenza like illness	0		0		0		0		1	(0.1)	1	(<0.1)
Insomnia	9	(0.5)	6	(0.5)	2	(0.2)	2	(0.4)	1	(0.1)	11	(0.3)

Vortioxetine for the treatment of MDD [ID583]

Irritability	3	(0.2)	0	0	0	1	(0.1)	1	(<0.1)		
Middle insomnia	0		0	0	0	1	(0.1)	1	(<0.1)		
Myoclonus	0		0	0	0	1	(0.1)	1	(<0.1)		
Orgasm abnormal	0		0	0	0	1	(0.1)	1	(<0.1)		
Overdose	0		1	(<0.1)	0	0	1	(0.1)	2	(<0.1)	
Renal pain	0		0	0	0	1	(0.1)	1	(<0.1)		
Salivary gland pain	0		0	0	0	1	(0.1)	1	(<0.1)		
Salivary hypersecretion	0		0	0	0	1	(0.1)	1	(<0.1)		
Tension	0		0	0	0	1	(0.1)	1	(<0.1)		
Urinary retention	0		0	0	0	1	(0.1)	1	(<0.1)		
Urticaria	0		0	0	0	1	(0.1)	1	(<0.1)		
Abdominal discomfort	1	(<0.1)	0	0	0	0		0			
Abdominal pain upper	1	(<0.1)	1	(<0.1)	1	(<0.1)	1	(0.2)	0	3	(<0.1)
Abnormal dreams	0		1	(<0.1)	0	0	0		0	1	(<0.1)
Accidental overdose	2	(0.1)	3	(0.3)	1	(<0.1)	1	(0.2)	0	5	(0.1)
Agitation	2	(0.1)	1	(<0.1)	0	0	0		0	1	(<0.1)
Alcoholism	0		0	0	0	1	(0.2)	0		1	(<0.1)
Anorgasmia	0		0	1	(<0.1)	0	0		0	1	(<0.1)
Anxiety disorder	1	(<0.1)	0	0	0	0	0		0	0	
Arthralgia	0		0	1	(<0.1)	0	0		0	1	(<0.1)
Asthenia	0		1	(<0.1)	0	0	0		0	1	(<0.1)
Asthma	1	(<0.1)	0	0	0	0	0		0	0	
Atrial fibrillation	0		1	(<0.1)	0	0	0		0	1	(<0.1)
Blood creatine phosphokinase increased	1	(<0.1)	1	(<0.1)	0	0	0		0	1	(<0.1)

Vortioxetine for the treatment of MDD [ID583]

Blood creatinine increased	1	(<0.1)	0	0	0	0	0
Blood uric acid increased	1	(<0.1)	0	0	0	0	0
Bronchitis	0		1 (<0.1)	0	0	0	1 (<0.1)
Cholelithiasis	1	(<0.1)	0	0	0	0	0
Contusion	1	(<0.1)	0	0	0	0	0
Convulsion	0		1 (<0.1)	0	0	0	1 (<0.1)
Cystitis	0		1 (<0.1)	0	0	0	1 (<0.1)
Deep vein thrombosis	0		0	0	1 (0.2)	0	1 (<0.1)
Depression	3	(0.2)	0	4 (0.4)	0	0	4 (0.1)
Diarrhoea	0		0	2 (0.2)	1 (0.2)	0	3 (<0.1)
Disturbance in sexual arousal	0		1 (<0.1)	0	0	0	1 (<0.1)
Dizziness postural	0		0	1 (<0.1)	0	0	1 (<0.1)
Dry mouth	5	(0.3)	1 (<0.1)	2 (0.2)	0	0	3 (<0.1)
Dysmenorrhoea (SS)	1	(<0.1)	2 (0.3)	0	0	0	2 (<0.1)
Ear infection	0		1 (<0.1)	0	0	0	1 (<0.1)
Ejaculation delayed (SS)	0		0	1 (0.3)	0	0	1 (<0.1)
Electrocardiogram qt prolonged	0		0	1 (<0.1)	0	0	1 (<0.1)
Erectile dysfunction (SS)	0		1 (0.3)	0	0	0	1 (<0.1)
Euphoric mood	0		0	1 (<0.1)	0	0	1 (<0.1)
Facial pain	0		0	1 (<0.1)	0	0	1 (<0.1)
Fall	1	(<0.1)	0	0	0	0	0
Feeling hot	1	(<0.1)	0	0	0	0	0
Flushing	0		1 (<0.1)	0	0	0	1 (<0.1)
Foreign body in eye	0		0	0	1 (0.2)	0	1 (<0.1)
Furuncle	0		1 (<0.1)	0	0	0	1 (<0.1)

Vortioxetine for the treatment of MDD [ID583]

Gastritis	0	1	(<0.1)	0	0	0	1	(<0.1)
Gastroenteritis viral	1	(<0.1)	0	2	(0.2)	0	2	(<0.1)
Gastrooesophageal reflux disease	1	(<0.1)	0	0	0	0	0	
Glossitis	0	1	(<0.1)	0	0	0	1	(<0.1)
Head injury	0	1	(<0.1)	0	0	0	1	(<0.1)
Herpes zoster	0	1	(<0.1)	0	0	0	1	(<0.1)
Hot flush	1	(<0.1)	0	0	0	0	0	
Hyperhidrosis	1	(<0.1)	0	1	(<0.1)	0	1	(<0.1)
Hypertension	1	(<0.1)	0	1	(<0.1)	0	1	(<0.1)
Hypoaesthesia	1	(<0.1)	0	0	0	0	0	
Increased appetite	0	1	(<0.1)	0	1	(0.2)	2	(<0.1)
Initial insomnia	1	(<0.1)	0	0	0	0	0	
Injury	0	1	(<0.1)	0	0	0	1	(<0.1)
Intentional overdose	0	1	(<0.1)	0	0	0	1	(<0.1)
Intertrigo	0	0		1	(<0.1)	0	1	(<0.1)
Joint swelling	0	0		1	(<0.1)	0	1	(<0.1)
Kidney infection	0	0		1	(<0.1)	0	1	(<0.1)
Laceration	1	(<0.1)	0	0	0	0	0	
Laryngeal cancer	1	(<0.1)	0	0	0	0	0	
Libido decreased	0	1	(<0.1)	1	(<0.1)	0	2	(<0.1)
Liver function test abnormal	0	1	(<0.1)	0	0	0	1	(<0.1)
Loss of libido	0	1	(<0.1)	0	0	0	1	(<0.1)
Lumbar radiculopathy	1	(<0.1)	0	0	0	0	0	
Major depression	0	1	(<0.1)	0	1	(0.2)	2	(<0.1)

Vortioxetine for the treatment of MDD [ID583]

Memory impairment	0	0	1	(<0.1)	0	0	1	(<0.1)
Micturition frequency decreased	1	(<0.1)	0	0	0	0	0	
Migraine	1	(<0.1)	2	(0.2)	2	(0.2)	4	(0.1)
Mucosal dryness	0	0	1	(<0.1)	0	0	1	(<0.1)
Muscle spasms	0	1	(<0.1)	0	0	0	1	(<0.1)
Musculoskeletal discomfort	1	(<0.1)	0	0	0	0	0	
Neck pain	0	1	(<0.1)	0	0	0	1	(<0.1)
Neuralgia	0	1	(<0.1)	0	0	0	1	(<0.1)
Oropharyngeal pain	1	(<0.1)	0	0	0	0	0	
Pain in extremity	1	(<0.1)	0	1	(<0.1)	0	1	(<0.1)
Palpitations	0	1	(<0.1)	0	0	0	1	(<0.1)
Pancreatitis	1	(<0.1)	0	0	0	0	0	
Panic attack	0	1	(<0.1)	0	0	0	1	(<0.1)
Pelvic fracture	0	0	1	(<0.1)	0	0	1	(<0.1)
Pelvic pain	0	1	(<0.1)	0	0	0	1	(<0.1)
Peptic ulcer	1	(<0.1)	0	0	0	0	0	
Plantar fasciitis	0	0	1	(<0.1)	0	0	1	(<0.1)
Pneumonia	1	(<0.1)	0	2	(0.2)	0	2	(<0.1)
Pneumonia mycoplasmal	0	1	(<0.1)	0	0	0	1	(<0.1)
Polyarthritis	1	(<0.1)	0	0	0	0	0	
Polyuria	0	0	1	(<0.1)	0	0	1	(<0.1)
Procedural pain	0	1	(<0.1)	0	1	(0.2)	2	(<0.1)
Pruritus	0	1	(<0.1)	0	0	0	1	(<0.1)
Pruritus generalised	1	(<0.1)	0	0	0	0	0	
Pulpitis dental	0	1	(<0.1)	0	0	0	1	(<0.1)

Vortioxetine for the treatment of MDD [ID583]

Renal colic	0	1	(<0.1)	0	0	0	1	(<0.1)
Restlessness	0	1	(<0.1)	0	0	0	1	(<0.1)
Road traffic accident	0	0		1	(<0.1)	0	1	(<0.1)
Sinusitis	1	(<0.1)	0	0	0	0	0	
Sinusitis bacterial	1	(<0.1)	0	0	0	0	0	
Skin burning sensation	0	0		1	(<0.1)	0	1	(<0.1)
Sleep disorder	0	1	(<0.1)	0	0	0	1	(<0.1)
Somnolence	3	(0.2)	1	(<0.1)	2	(0.2)	3	(<0.1)
Sternal fracture	0	1	(<0.1)	0	0	0	1	(<0.1)
Stress fracture	0	0		0	1	(0.2)	1	(<0.1)
Suicide attempt	0	1	(<0.1)	0	0	0	1	(<0.1)
Tachycardia	0	1	(<0.1)	0	0	0	1	(<0.1)
Tension headache	0	0		2	(0.2)	0	2	(<0.1)
Thoracic vertebral fracture	0	1	(<0.1)	0	0	0	1	(<0.1)
Tooth abscess	1	(<0.1)	0	0	0	0	0	
Tooth fracture	0	0		1	(<0.1)	0	1	(<0.1)
Tooth infection	0	1	(<0.1)	0	0	0	1	(<0.1)
Toothache	1	(<0.1)	1	(<0.1)	2	(0.2)	3	(<0.1)
Traumatic lung injury	0	1	(<0.1)	0	0	0	1	(<0.1)
Upper limb fracture	0	1	(<0.1)	0	0	0	1	(<0.1)
Urinary tract infection	0	1	(<0.1)	1	(<0.1)	0	2	(<0.1)
Uterine leiomyoma (SS)	1	(<0.1)	0	0	0	0	0	
Vertigo	1	(<0.1)	0	0	0	0	0	

(SS) Sex Specific Dictionary: MedDRA 14.1. * Vortioxetine 15 mg will not be made available in the UK.

Table 11. TEAEs with an Incidence of 5% or More by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool

Preferred Term	Placebo		Vortioxetine 5 mg		Vortioxetine 10 mg		Vortioxetine 15 mg		Vortioxetine 20 mg		Total vortioxetine	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of Patients	1968		1157		1042		449		812		3460	
Patient years exposure	262.7		149.3		143.4		60.7		112.5		466.0	
Patients with Adverse Events	1140	(57.9)	749	(64.7)	636	(61.0)	309	(68.8)	529	(65.1)	2223	(64.2)
Nausea	159	(8.1)	237	(20.5)	235	(22.6)	140	(31.2)	221	(27.2)	833	(24.1)
Headache	254	(12.9)	159	(13.7)	132	(12.7)	66	(14.7)	101	(12.4)	458	(13.2)
Dry mouth	111	(5.6)	74	(6.4)	57	(5.5)	27	(6.0)	53	(6.5)	211	(6.1)
Dizziness	104	(5.3)	64	(5.5)	54	(5.2)	32	(7.1)	51	(6.3)	201	(5.8)
Diarrhoea	108	(5.5)	76	(6.6)	56	(5.4)	42	(9.4)	45	(5.5)	219	(6.3)
Nasopharyngitis	77	(3.9)	61	(5.3)	42	(4.0)	16	(3.6)	40	(4.9)	159	(4.6)
Constipation	57	(2.9)	39	(3.4)	38	(3.6)	25	(5.6)	36	(4.4)	138	(4.0)
Vomiting	21	(1.1)	31	(2.7)	38	(3.6)	29	(6.5)	36	(4.4)	134	(3.9)

(SS) Sex Specific Dictionary: MedDRA 14.1. * Vortioxetine 15 mg will not be made available in the UK.

Insomnia and Somnolence

The incidence of insomnia-related TEAEs in the vortioxetine total group was low and similar to that in the placebo group (3.9% and 3.7%, respectively) in the short-term pool (see Table 12).

Table 12. Insomnia-related TEAEs by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool

Preferred Term	Proportion of subjects (%)	
	Placebo (n=1,968)	Vortioxetine total (n=3,460)
Patients with insomnia-related TEAEs	3.7	3.8
Insomnia	2.5	2.7
Initial insomnia	0.3	0.5
Middle insomnia	0.3	0.3
Sleep disorder	0.4	0.2
Poor quality sleep	0.3	<0.1
Terminal insomnia	0	<0.1
Dyssomnia	0.1	<0.1
Hyposomnia	0	<0.1

Dictionary: MedDRA 14.1

The incidence of somnolence during treatment with vortioxetine was 3.0%, which was similar to that in the placebo group (2.3%). There was no indication of a dose-response relationship in the incidence of somnolence.

Sexual Dysfunction

Sexual Dysfunction based on TEAEs

The overall incidence of sexual dysfunction TEAEs in the vortioxetine total group was low and similar to that in the placebo group (1.6% and 0.9%, respectively).

Sexual Dysfunction based on the Arizona Sexual Experience Scale (ASEX)

Sexual dysfunction was defined as at least one of the following: an ASEX total score ≥ 19 , a score ≥ 5 on any ASEX item, or a score ≥ 4 on ≥ 3 items at the same visit.

The incidence of TESD during treatment was 38% in the vortioxetine total group, which was slightly higher than that in the placebo group (32%) and driven by the highest vortioxetine dose group. The treatment difference to placebo in TESD incidence was 6.3% for the vortioxetine total group.

Table 13. TESD, Core Treatment Period, by Dose (APTS, Mantel-Haenszel) - Studies 11984A, 304, 13267A, 315, 316, 317 and 308

Treatment	N	n	Incidence Difference	
			Estimate (%)	95% CI
Vortioxetine 5mg	136	35	-4.6	[-15.1 ; 6.0]
Placebo	138	41		
Vortioxetine 10mg	190	67	6.1	[-3.4 ; 15.5]
Placebo	182	52		
Vortioxetine 15mg*	126	54	5.2	[-7.1 ; 17.5]
Placebo	121	44		
Vortioxetine 20mg	128	59	9.9	[-1.9 ; 21.7]
Placebo	135	47		
Vortioxetine total	580	215	4.2	[-2.4 ; 10.7]
Placebo	309	99		

N: Number of patients without sexual dysfunction at baseline
n: Number of patients with TESD
* Vortioxetine 15 mg will not be made available in the UK.

Relative risk of short-term adverse events

Table 14 and Figure 9 show the estimated relative risk of adverse events (with 95% confidence intervals) for vortioxetine compared to placebo using the Cochran Mantel-Haenszel approach stratified by study. A relative risk of 1.0 means no difference to placebo and a relative risk of 2.0 means that the risk of adverse events is double for the active treatment compared with placebo.

The analysis includes data for vortioxetine 5 to 20mg/day from all studies in the MDD Short-term Pool. The analysis includes adverse events with an incidence $\geq 2\%$ for either vortioxetine 5 to 20mg/day or placebo.

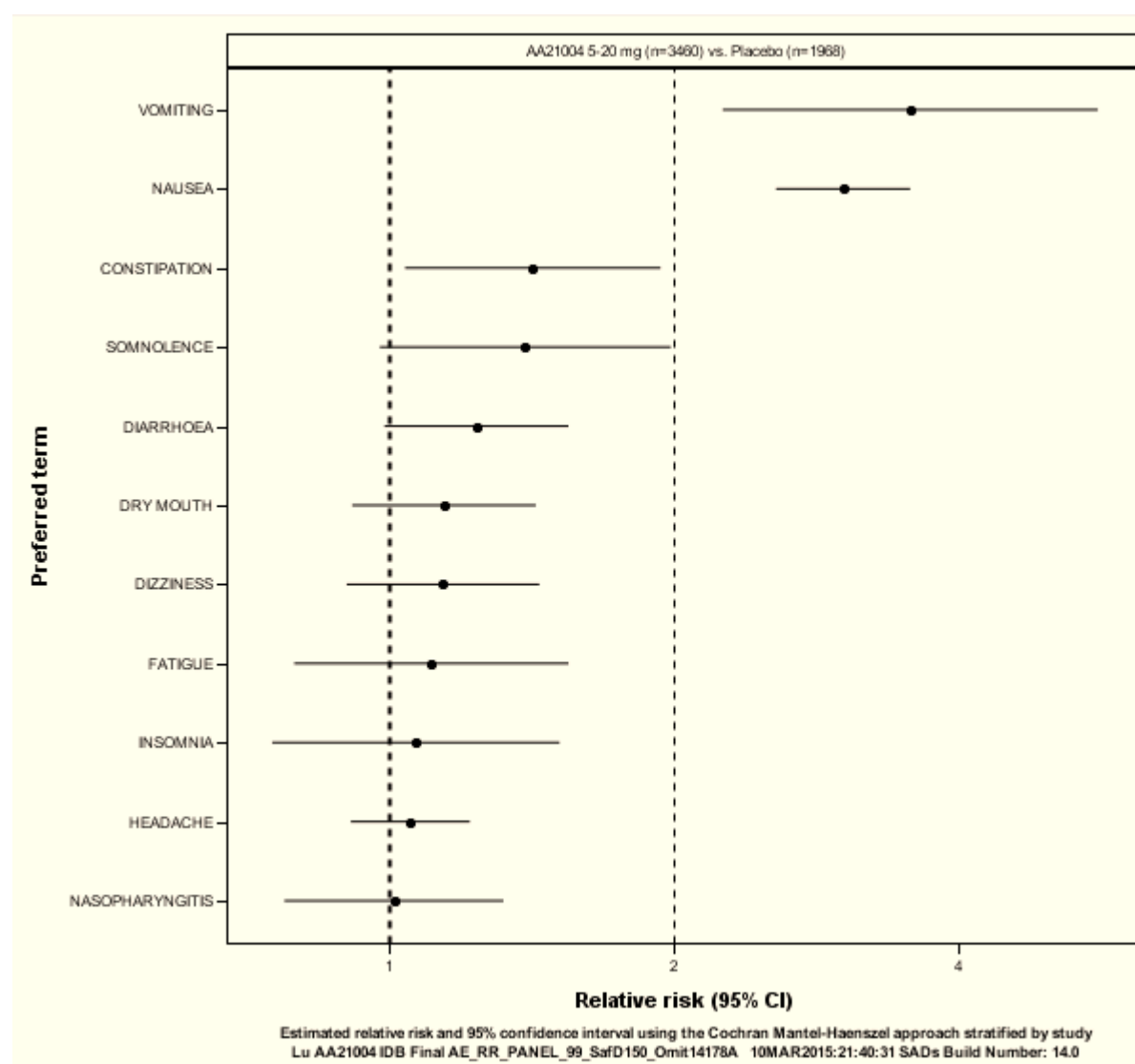
Table 14. TEAEs with an incidence of 2% or more by preferred term, core treatment period (APTS) - MDD Short-term placebo-controlled pool

Preferred term	Vortioxetine 5-20 mg		Placebo		Relative risk (95% CI)
	N	(%)	N	(%)	
Number of patients	3460		1968		
Nausea	833	(24.1)	159	(8.1)	3.02 [2.57 ; 3.55]
Headache	458	(13.2)	254	(12.9)	1.06 [0.91 ; 1.22]
Diarrhoea	219	(6.3)	108	(5.5)	1.24 [0.99 ; 1.55]
Dry mouth	211	(6.1)	111	(5.6)	1.15 [0.92 ; 1.43]
Dizziness	201	(5.8)	104	(5.3)	1.14 [0.90 ; 1.44]
Nasopharyngitis	159	(4.6)	77	(3.9)	1.01 [0.78 ; 1.32]
Constipation	138	(4.0)	57	(2.9)	1.42 [1.04 ; 1.94]

Vomiting	134	(3.9)	21	(1.1)	3.55 [2.25 ; 5.60]
Somnolence	107	(3.1)	45	(2.3)	1.40 [0.98 ; 1.99]
Fatigue	102	(2.9)	53	(2.7)	1.11 [0.80 ; 1.55]
Insomnia	93	(2.7)	50	(2.5)	1.07 [0.76 ; 1.52]

Preferred terms with incidence of 2% or more in overall vortioxetine 5-20 mg or placebo treatment arm
Only studies where both treatments are included. Relative risks stratified by study

Figure 9. Forest plot of relative risk of TEAEs with an incidence of 2% or more by preferred term, core treatment period (APTS) - MDD Short-term placebo-controlled pool: vortioxetine 5-20mg vs. placebo



The analysis shows that, except for an increased risk of vomiting and nausea for patients taking vortioxetine, the risk of adverse events for vortioxetine 5 to 20mg/day is not different from placebo.

Open-label Long-term Pool

The following data has been provided to supplement data reported in *Table B44 "Incidence of TEAEs of ≥5% in the open-label, long-term pool"* in the main submission. Table 15

presents the withdrawal rates due to specific AEs. Table B44 in the submission summarises the TEAEs in the core treatment period with an incidence $\geq 5\%$ in either group. In addition, Table 16 presents the rates of severe TEAEs from the Open-label Long-term Pool.

Details of the studies included in this pool can be found in Section 6.9.2.1 (page 133) of the submission.

Table 15. TEAEs leading to withdrawal by preferred term, core treatment period, (APTS) - MDD Open-label Long-term Pool

Preferred term	Vortioxetine 2.5-10mg		Vortioxetine 15-20mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Number of patients	1,443		1,144		2,587	
Patient-years exposure	1,097		775.4		1,873	
Patients with adverse events	89	(6.2)	120	(10.5)	209	(8.1)
Nausea	14	(1.0)	31	(2.7)	45	(1.7)
Depression	10	(0.7)	5	(0.4)	15	(0.6)
Vomiting	3	(0.2)	11	(1.0)	14	(0.5)
Headache	2	(0.1)	8	(0.7)	10	(0.4)
Weight increased	2	(0.1)	6	(0.5)	8	(0.3)
Insomnia	2	(0.1)	5	(0.4)	7	(0.3)
Anxiety	5	(0.3)	1	(<0.1)	6	(0.2)
Fatigue	1	(<0.1)	5	(0.4)	6	(0.2)
Somnolence	5	(0.3)	1	(<0.1)	6	(0.2)
Agitation	2	(0.1)	2	(0.2)	4	(0.2)
Dizziness	3	(0.2)	1	(<0.1)	4	(0.2)
Aspartate aminotransferase increased	1	(<0.1)	2	(0.2)	3	(0.1)
Constipation	0		3	(0.3)	3	(0.1)
Diarrhoea	2	(0.1)	1	(<0.1)	3	(0.1)
Disturbance in attention	2	(0.1)	1	(<0.1)	3	(0.1)
Dry mouth	2	(0.1)	1	(<0.1)	3	(0.1)
Dyspepsia	1	(<0.1)	2	(0.2)	3	(0.1)
Flatulence	1	(<0.1)	2	(0.2)	3	(0.1)
Gamma-glutamyltransferase increased	3	(0.2)	0		3	(0.1)
Hepatic enzyme	0		3	(0.3)	3	(0.1)

Preferred term	Vortioxetine 2.5-10mg		Vortioxetine 15-20mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
increased						
Intentional overdose	2	(0.1)	1	(<0.1)	3	(0.1)
Pruritus generalised	1	(<0.1)	2	(0.2)	3	(0.1)
Suicidal ideation	3	(0.2)	0		3	(0.1)
Breast cancer female (SS)	0		2	(0.2)	2	(0.1)
Alanine aminotransferase increased	1	(<0.1)	1	(<0.1)	2	(<0.1)
Arthralgia	0		2	(0.2)	2	(<0.1)
Atrial fibrillation	1	(<0.1)	1	(<0.1)	2	(<0.1)
Blood creatine phosphokinase increased	1	(<0.1)	1	(<0.1)	2	(<0.1)
Blood triglycerides increased	1	(<0.1)	1	(<0.1)	2	(<0.1)
Depressive symptom	2	(0.1)	0		2	(<0.1)
Electrocardiogram qt prolonged	2	(0.1)	0		2	(<0.1)
Fall	2	(0.1)	0		2	(<0.1)
Irritability	2	(0.1)	0		2	(<0.1)
Liver function test abnormal	1	(<0.1)	1	(<0.1)	2	(<0.1)
Major depression	2	(0.1)	0		2	(<0.1)
Memory impairment	1	(<0.1)	1	(<0.1)	2	(<0.1)
Suicide attempt	1	(<0.1)	1	(<0.1)	2	(<0.1)
White blood cell count decreased	2	(0.1)	0		2	(<0.1)
Abortion induced (SS)	1	(0.1)	0		1	(<0.1)
Metrorrhagia (SS)	0		1	(0.1)	1	(<0.1)
Pregnancy (SS)	0		1	(0.1)	1	(<0.1)
Pregnancy test positive (SS)	1	(0.1)	0		1	(<0.1)
Abdominal discomfort	0		1	(<0.1)	1	(<0.1)
Abdominal pain upper	1	(<0.1)	0		1	(<0.1)
Abnormal behaviour	1	(<0.1)	0		1	(<0.1)
Accidental overdose	0		1	(<0.1)	1	(<0.1)
Alcohol abuse	1	(<0.1)	0		1	(<0.1)

Preferred term	Vortioxetine 2.5-10mg		Vortioxetine 15-20mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Blood alkaline phosphatase increased	1	(<0.1)	0		1	(<0.1)
Blood creatinine increased	0		1	(<0.1)	1	(<0.1)
Blood pressure increased	1	(<0.1)	0		1	(<0.1)
Breast cancer stage i	0		1	(<0.1)	1	(<0.1)
Chest pain	1	(<0.1)	0		1	(<0.1)
Cholecystitis acute	0		1	(<0.1)	1	(<0.1)
Cholecystitis chronic	1	(<0.1)	0		1	(<0.1)
Cholelithiasis	0		1	(<0.1)	1	(<0.1)
Confusional state	1	(<0.1)	0		1	(<0.1)
Conjunctivitis	1	(<0.1)	0		1	(<0.1)
Crying	1	(<0.1)	0		1	(<0.1)
Depressed mood	1	(<0.1)	0		1	(<0.1)
Derealisation	0		1	(<0.1)	1	(<0.1)
Dermatitis bullous	0		1	(<0.1)	1	(<0.1)
Dermatitis herpetiformis	1	(<0.1)	0		1	(<0.1)
Diverticulitis	1	(<0.1)	0		1	(<0.1)
Emphysema	0		1	(<0.1)	1	(<0.1)
Feeling jittery	1	(<0.1)	0		1	(<0.1)
Femoral neck fracture	1	(<0.1)	0		1	(<0.1)
Fibromyalgia	0		1	(<0.1)	1	(<0.1)
Flat affect	0		1	(<0.1)	1	(<0.1)
Food craving	0		1	(<0.1)	1	(<0.1)
Gastric ulcer	1	(<0.1)	0		1	(<0.1)
Gastroenteritis	1	(<0.1)	0		1	(<0.1)
Hallucination, auditory	1	(<0.1)	0		1	(<0.1)
Hot flush	0		1	(<0.1)	1	(<0.1)
Hyperhidrosis	0		1	(<0.1)	1	(<0.1)
Hypertension	1	(<0.1)	0		1	(<0.1)
Hypervigilance	1	(<0.1)	0		1	(<0.1)
Increased appetite	0		1	(<0.1)	1	(<0.1)
Influenza	1	(<0.1)	0		1	(<0.1)
Influenza like illness	0		1	(<0.1)	1	(<0.1)

Preferred term	Vortioxetine 2.5-10mg		Vortioxetine 15-20mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Ingrowing nail	0		1	(<0.1)	1	(<0.1)
Lip swelling	0		1	(<0.1)	1	(<0.1)
Malignant melanoma	0		1	(<0.1)	1	(<0.1)
Mania	0		1	(<0.1)	1	(<0.1)
Mastitis	1	(<0.1)	0		1	(<0.1)
Meniscus lesion	1	(<0.1)	0		1	(<0.1)
Monocyte count increased	1	(<0.1)	0		1	(<0.1)
Muscle strain	0		1	(<0.1)	1	(<0.1)
Musculoskeletal chest pain	0		1	(<0.1)	1	(<0.1)
Musculoskeletal pain	0		1	(<0.1)	1	(<0.1)
Neutrophil count decreased	1	(<0.1)	0		1	(<0.1)
Nightmare	1	(<0.1)	0		1	(<0.1)
Palpitations	1	(<0.1)	0		1	(<0.1)
Phlebitis superficial	0		1	(<0.1)	1	(<0.1)
Pneumonia	0		1	(<0.1)	1	(<0.1)
Poor quality sleep	0		1	(<0.1)	1	(<0.1)
Pruritus	0		1	(<0.1)	1	(<0.1)
Psoriasis	1	(<0.1)	0		1	(<0.1)
Rash erythematous	0		1	(<0.1)	1	(<0.1)
Rhinorrhoea	0		1	(<0.1)	1	(<0.1)
Road traffic accident	1	(<0.1)	0		1	(<0.1)
Sedation	0		1	(<0.1)	1	(<0.1)
Sensation of foreign body	0		1	(<0.1)	1	(<0.1)
Sleep apnoea syndrome	0		1	(<0.1)	1	(<0.1)
Sports injury	0		1	(<0.1)	1	(<0.1)
Swelling face	0		1	(<0.1)	1	(<0.1)
Syncope	1	(<0.1)	0		1	(<0.1)
Tearfulness	1	(<0.1)	0		1	(<0.1)
Tension	1	(<0.1)	0		1	(<0.1)
Throat tightness	1	(<0.1)	0		1	(<0.1)
Tinnitus	1	(<0.1)	0		1	(<0.1)

Preferred term	Vortioxetine 2.5-10mg		Vortioxetine 15-20mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Transient ischaemic attack	0		1	(<0.1)	1	(<0.1)
Tremor	1	(<0.1)	0		1	(<0.1)
Urinary retention	1	(<0.1)	0		1	(<0.1)
Urticaria	0		1	(<0.1)	1	(<0.1)
Vertigo	0		1	(<0.1)	1	(<0.1)
Visual impairment	1	(<0.1)	0		1	(<0.1)
Weight decreased	1	(<0.1)	0		1	(<0.1)
Wolff-Parkinson-White syndrome	1	(<0.1)	0		1	(<0.1)

(SS) Sex Specific Dictionary: MedDRA 14.1

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Table 16. Severe TEAEs by Preferred Term, Core Treatment Period (APTS) - MDD Open-label Long-term Pool

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Number of patients	1443		1144		2587	
Patient-years exposure	1097		775.4		1873	
Patients with adverse events	135	(9.4)	95	(8.3)	230	(8.9)
Nausea	16	(1.1)	11	(1.0)	27	(1.0)
Headache	9	(0.6)	5	(0.4)	14	(0.5)
Insomnia	7	(0.5)	6	(0.5)	13	(0.5)
Vomiting	6	(0.4)	4	(0.3)	10	(0.4)
Accidental overdose	8	(0.6)	1	(<0.1)	9	(0.3)
Diarrhoea	6	(0.4)	1	(<0.1)	7	(0.3)
Dizziness	5	(0.3)	2	(0.2)	7	(0.3)
Migraine	4	(0.3)	3	(0.3)	7	(0.3)
Bronchitis	2	(0.1)	4	(0.3)	6	(0.2)
Depression	4	(0.3)	2	(0.2)	6	(0.2)
Fatigue	2	(0.1)	4	(0.3)	6	(0.2)
Influenza	4	(0.3)	2	(0.2)	6	(0.2)

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Back pain	3	(0.2)	2	(0.2)	5	(0.2)
Blood creatine phosphokinase increased	3	(0.2)	2	(0.2)	5	(0.2)
Somnolence	4	(0.3)	1	(<0.1)	5	(0.2)
Suicidal ideation	3	(0.2)	2	(0.2)	5	(0.2)
Fall	4	(0.3)	0		4	(0.2)
Male sexual dysfunction (SS)	0		1	(0.3)	1	(0.1)
Anxiety	1	(<0.1)	2	(0.2)	3	(0.1)
Constipation	1	(<0.1)	2	(0.2)	3	(0.1)
Pneumonia	0		3	(0.3)	3	(0.1)
Suicide attempt	2	(0.1)	1	(<0.1)	3	(0.1)
Upper respiratory tract infection	2	(0.1)	1	(<0.1)	3	(0.1)
Abdominal pain	1	(<0.1)	1	(<0.1)	2	(<0.1)
Abdominal pain upper	2	(0.1)	0		2	(<0.1)
Ankle fracture	1	(<0.1)	1	(<0.1)	2	(<0.1)
Appendicitis	2	(0.1)	0		2	(<0.1)
Asthma	0		2	(0.2)	2	(<0.1)
Dry mouth	0		2	(0.2)	2	(<0.1)
Dyspepsia	2	(0.1)	0		2	(<0.1)
Gastroenteritis	1	(<0.1)	1	(<0.1)	2	(<0.1)
Haemorrhoids	0		2	(0.2)	2	(<0.1)
Hot flush	1	(<0.1)	1	(<0.1)	2	(<0.1)
Increased appetite	1	(<0.1)	1	(<0.1)	2	(<0.1)
Irritability	1	(<0.1)	1	(<0.1)	2	(<0.1)
Nasopharyngitis	2	(0.1)	0		2	(<0.1)
Nephrolithiasis	1	(<0.1)	1	(<0.1)	2	(<0.1)
Night sweats	0		2	(0.2)	2	(<0.1)
Pain in extremity	2	(0.1)	0		2	(<0.1)
Panic attack	2	(0.1)	0		2	(<0.1)
Pharyngitis streptococcal	0		2	(0.2)	2	(<0.1)
Plantar fasciitis	0		2	(0.2)	2	(<0.1)
Sedation	0		2	(0.2)	2	(<0.1)
Toothache	1	(<0.1)	1	(<0.1)	2	(<0.1)
Abortion spontaneous (SS)	0		1	(0.1)	1	(<0.1)

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Amenorrhoea (SS)	1	(0.1)	0		1	(<0.1)
Breast cancer female (SS)	0		1	(0.1)	1	(<0.1)
Haemorrhagic ovarian cyst (SS)	0		1	(0.1)	1	(<0.1)
Menorrhagia (SS)	0		1	(0.1)	1	(<0.1)
Uterine leiomyoma (SS)	0		1	(0.1)	1	(<0.1)
Vulval abscess (SS)	0		1	(0.1)	1	(<0.1)
Abdominal discomfort	0		1	(<0.1)	1	(<0.1)
Abscess limb	1	(<0.1)	0		1	(<0.1)
Acne cystic	0		1	(<0.1)	1	(<0.1)
Agitation	0		1	(<0.1)	1	(<0.1)
Alcohol abuse	1	(<0.1)	0		1	(<0.1)
Anaemia	0		1	(<0.1)	1	(<0.1)
Antibiotic resistant staphylococcus test positive	1	(<0.1)	0		1	(<0.1)
Arthralgia	0		1	(<0.1)	1	(<0.1)
Arthritis	1	(<0.1)	0		1	(<0.1)
Aspartate aminotransferase increased	0		1	(<0.1)	1	(<0.1)
Asthenia	1	(<0.1)	0		1	(<0.1)
Atrial fibrillation	1	(<0.1)	0		1	(<0.1)
Blood albumin increased	1	(<0.1)	0		1	(<0.1)
Blood triglycerides increased	0		1	(<0.1)	1	(<0.1)
Bradykinesia	0		1	(<0.1)	1	(<0.1)
Breast cancer in situ	1	(<0.1)	0		1	(<0.1)
Breast cancer stage i	0		1	(<0.1)	1	(<0.1)
Bronchitis viral	0		1	(<0.1)	1	(<0.1)
Bruxism	1	(<0.1)	0		1	(<0.1)
Cat scratch disease	1	(<0.1)	0		1	(<0.1)
Cellulitis	1	(<0.1)	0		1	(<0.1)
Cholecystitis	0		1	(<0.1)	1	(<0.1)
Cholecystitis acute	0		1	(<0.1)	1	(<0.1)
Complicated migraine	0		1	(<0.1)	1	(<0.1)
Dental caries	1	(<0.1)	0		1	(<0.1)
Depressive symptom	1	(<0.1)	0		1	(<0.1)

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Disturbance in attention	1	(<0.1)	0		1	(<0.1)
Diverticulitis	1	(<0.1)	0		1	(<0.1)
Dupuytren`s contracture	1	(<0.1)	0		1	(<0.1)
Ear injury	1	(<0.1)	0		1	(<0.1)
Electrocardiogram qt prolonged	1	(<0.1)	0		1	(<0.1)
Femur fracture	1	(<0.1)	0		1	(<0.1)
Fibromyalgia	1	(<0.1)	0		1	(<0.1)
Fibula fracture	1	(<0.1)	0		1	(<0.1)
Flatulence	1	(<0.1)	0		1	(<0.1)
Foot fracture	0		1	(<0.1)	1	(<0.1)
Gastric ulcer	1	(<0.1)	0		1	(<0.1)
Gastritis	1	(<0.1)	0		1	(<0.1)
Gastroenteritis viral	1	(<0.1)	0		1	(<0.1)
Gastrointestinal infection	1	(<0.1)	0		1	(<0.1)
H1N1 influenza	1	(<0.1)	0		1	(<0.1)
Haematoma	1	(<0.1)	0		1	(<0.1)
Hip fracture	1	(<0.1)	0		1	(<0.1)
Hyperglycaemia	0		1	(<0.1)	1	(<0.1)
Hyperhidrosis	0		1	(<0.1)	1	(<0.1)
Ingrowing nail	1	(<0.1)	0		1	(<0.1)
Intentional overdose	0		1	(<0.1)	1	(<0.1)
Laryngitis	1	(<0.1)	0		1	(<0.1)
Latent syphilis	0		1	(<0.1)	1	(<0.1)
Libido increased	1	(<0.1)	0		1	(<0.1)
Ligament sprain	1	(<0.1)	0		1	(<0.1)
Major depression	1	(<0.1)	0		1	(<0.1)
Malignant melanoma	0		1	(<0.1)	1	(<0.1)
Melanosis coli	0		1	(<0.1)	1	(<0.1)
Meniscus lesion	1	(<0.1)	0		1	(<0.1)
Muscle spasms	1	(<0.1)	0		1	(<0.1)
Musculoskeletal pain	0		1	(<0.1)	1	(<0.1)
Onychoclasia	1	(<0.1)	0		1	(<0.1)
Onychomadesis	1	(<0.1)	0		1	(<0.1)

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Osteoarthritis	1	(<0.1)	0		1	(<0.1)
Pancreatitis acute	0		1	(<0.1)	1	(<0.1)
Papilloedema	1	(<0.1)	0		1	(<0.1)
Periarthritis	0		1	(<0.1)	1	(<0.1)
Pharyngitis	1	(<0.1)	0		1	(<0.1)
Post-traumatic neck syndrome	1	(<0.1)	0		1	(<0.1)
Pregnancy of partner	1	(<0.1)	0		1	(<0.1)
Procedural pain	0		1	(<0.1)	1	(<0.1)
Pyrexia	1	(<0.1)	0		1	(<0.1)
Retinopathy hypertensive	1	(<0.1)	0		1	(<0.1)
Road traffic accident	1	(<0.1)	0		1	(<0.1)
Sciatica	1	(<0.1)	0		1	(<0.1)
Seasonal allergy	0		1	(<0.1)	1	(<0.1)
Sinusitis	0		1	(<0.1)	1	(<0.1)
Slow speech	0		1	(<0.1)	1	(<0.1)
Sports injury	0		1	(<0.1)	1	(<0.1)
Stress urinary incontinence	0		1	(<0.1)	1	(<0.1)
Supraventricular tachycardia	1	(<0.1)	0		1	(<0.1)
Syncope	1	(<0.1)	0		1	(<0.1)
Tachycardia paroxysmal	1	(<0.1)	0		1	(<0.1)
Tension headache	1	(<0.1)	0		1	(<0.1)
Thyroiditis	1	(<0.1)	0		1	(<0.1)
Tibia fracture	1	(<0.1)	0		1	(<0.1)
Tonsillitis	0		1	(<0.1)	1	(<0.1)
Tooth abscess	1	(<0.1)	0		1	(<0.1)
Tooth extraction	1	(<0.1)	0		1	(<0.1)
Transient ischaemic attack	0		1	(<0.1)	1	(<0.1)
Umbilical hernia, obstructive	1	(<0.1)	0		1	(<0.1)
Upper gastrointestinal haemorrhage	1	(<0.1)	0		1	(<0.1)
Upper respiratory tract inflammation	1	(<0.1)	0		1	(<0.1)
Urinary retention	1	(<0.1)	0		1	(<0.1)
Urinary tract infection	0		1	(<0.1)	1	(<0.1)
Vertigo	0		1	(<0.1)	1	(<0.1)

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Vertigo positional	0		1	(<0.1)	1	(<0.1)
Viral infection	0		1	(<0.1)	1	(<0.1)
Viral upper respiratory tract infection	0		1	(<0.1)	1	(<0.1)
Vision blurred	1	(<0.1)	0		1	(<0.1)
Weight increased	0		1	(<0.1)	1	(<0.1)
Wolff-parkinson-white syndrome	1	(<0.1)	0		1	(<0.1)
Wrist fracture	0		1	(<0.1)	1	(<0.1)

(SS) Sex Specific Dictionary: MedDRA 14.1

Lu AA21004 IDB Final ST_AE_SEV_PT_C_OL 07FEB2014:15:07:16 SADs Build Number: 14.0

Meta-analyses (external)

Lundbeck is also aware of three externally-produced meta-analyses (Pae 2014¹⁶, Berhan 2014¹⁷ and Citrome 2014¹⁸).

The company believes the analysis undertaken by Pae is fundamentally flawed as it includes active reference arms as if they were active comparators. For reasons already explained in this document and in the main submission section 1.4.1 (*“Active reference arms do not allow valid head-to-head comparison”*) section 2.8.2 (*“The use of active references”*) of the main submission, the comparison of efficacy between active reference and vortioxetine is invalid and the results cannot be considered reliable.

Meta-regression

In addition to the three active comparator trials that have been undertaken to date as part of the vortioxetine development programme, Lundbeck has published an indirect comparison in the full MDD population a meta-regression of placebo-controlled short-term trials (Llorca 2015)¹⁹.

The conclusions of the Llorca analysis, concentrating on comparators widely use in the UK, are as follows:

- There are no statistically significant differences in efficacy (either remission or response) between vortioxetine and escitalopram, venlafaxine, sertraline and duloxetine
- With respect to withdrawals due to adverse events, there are no statistically significant differences between vortioxetine and duloxetine and escitalopram, but vortioxetine is superior to sertraline and venlafaxine.

Analyses included in reimbursement submissions to authorities

Further comparative analyses have been undertaken where necessary to meet the evidence base requirements of local HTA agencies as below:

- The Pharmaceutical Benefits Advisory Committee (PBAC), Australia; details of these are included in the public summary document²².
- The Canadian Agency for Drugs and Technologies in Health (CADTH); additional information is available on request²³.

Summary

All meta-analyses and evidence synthesis known to Lundbeck are detailed above. To reiterate, these analyses were undertaken using data available in the full MDD population. As stated already in this document and in Section 6.1 of the main submission, efficacy is not transferable between treatment lines whereas tolerability is likely to be. Therefore these analyses only provide relative tolerability to inform the comparison between vortioxetine and other compounds in the switch population.

Indirect treatment comparisons

A16. *For the indirect treatment comparison (ITC) analysis, the company assumed that the different definitions of remission across trials (using different depression rating scales) were equivalent and could be pooled in the analysis. Please provide justification for this assumption.*

In the studies in which remission rates were reported, remission is defined as the proportion of patients who achieved a depressive symptom score below a threshold value on the rating scale used. The studies that reported remission used either HAM-D or MADRS, and remission was defined as a HAM-D score ≤ 7 or a MADRS ≤ 10 , which are commonly used definitions^{24,25}.

A17. *Priority question: In the company's submission, the results of its ITC analysis were presented in terms of risk differences. Please present results from the ITC analysis in terms of relative risks.*

ITC parameter inputs: remission rates

Table 17 shows the relative risks of remission calculated from raw remission rates reported in the studies included in the ITC.

Table 17. ITC of remission rates: raw data parameter inputs

Study ID	Parameter	Vortioxetine	Agomel- atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
REVIVE	Remission rate	40.5% (N=252)	29.5% (N=241)	-	-	-	-
	RR vs. vortioxetine	-	0.73	-	-	-	-
	95% CI	-	[0.57; 0.93]	-	-	-	-
Kasper 2013	Remission rate	-	27.9% (N=80)	24.5% (N=96)	-	-	-
	RR vs. agomelatine	-	-	0.91	-	-	-
	95% CI	-	-	[0.55; 1.49]	-	-	-
Rush 2006 (STAR*D)	Remission rate	-	-	17.6% (N=238)	24.8% (N=250)	21.3% (N=239)	-
	RR vs. sertraline	-	-	-	1.41	1.21	-
	95% CI	-	-	-	[0.99; 1.99]	[0.84; 1.75]	-
Lenox- Smith 2008	Remission rate	-	-	-	36.8% (N=57)	-	27.3% (N=55)
	RR vs. venlafaxine	-	-	-	-	-	0.74
	95% CI	-	-	-	-	-	[0.43; 1.28]

RR: relative risk; CI: confidence interval; N: number of patients; XR: extended release; SR: sustained release

ITC parameter estimates: remission rates

Table 18 shows the remission rates estimated by adjusted indirect comparison using relative risks.

Table 18. ITC of remission rates: estimates by adjusted indirect comparison using relative risks

	Vortioxetine	Agomel- atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
Direct comparison of agomelatine vs. vortioxetine through REVIVE						
Remission rate	40.5%	29.5%	-	-	-	-
RR vs. vortioxetine	-	0.73	-	-	-	-
95% CI	-	[0.57; 0.93]	-	-	-	-
Adjusted indirect comparison of sertraline vs. vortioxetine through REVIVE and Kasper 2013						
Remission rate	40.5%	-	26.8%	-	-	-
RR vs. vortioxetine	-	-	0.66	-	-	-
95% CI	-	-	[0.38; 1.15]	-	-	-
Adjusted indirect comparison of venlafaxine XR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Remission rate	40.5%	-	-	37.6%	-	-
RR vs. vortioxetine	-	-	-	0.93	-	-
95% CI	-	-	-	[0.48; 1.79]	-	-
Adjusted indirect comparison of bupropion SR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Remission rate	40.5%	-	-	-	32.4%	-
RR vs. vortioxetine	-	-	-	-	0.80	-
95% CI	-	-	-	-	[0.41; 1.56]	-
Adjusted indirect comparison of citalopram vs. vortioxetine through REVIVE, Kasper 2013, STAR*D and Lenox-Smith 2008						
Remission rate	40.5%	-	-	-	-	27.8%
RR vs. vortioxetine	-	-	-	-	-	0.69
95% CI	-	-	-	-	-	[-0.29; 1.62]

RR: relative risk; CI: confidence interval; XR : extended release; SR: sustained release.

As reported in Table 18, the remission rate associated with vortioxetine was numerically greater than that for sertraline, venlafaxine, bupropion and citalopram, but not statistically significantly so. Using relative risks instead of risk differences slightly reduced the differences in estimated remission rates between vortioxetine and the comparators.

ITC parameter inputs: withdrawal rates due to adverse events

Table 19 shows the relative risks of withdrawal due to AEs calculated from raw withdrawal rates reported in the studies included in the ITC.

Table 19. ITC of withdrawal rates: raw data parameter inputs

Study ID	Parameter	Vortioxetine	Agomel- atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
REVIVE	Withdrawal rate due to AEs	5.9% (N=253)	9.5% (N=242)	-	-	-	-
	RR vs. vortioxetine	-	1.60	-	-	-	-
	95% CI	-	[0.86; 3.00]	-	-	-	-
Kasper 2013	Withdrawal rate due to AEs	-	3.7% (N=80)	12.2% (N=96)	-	-	-
	RR vs. agomelatine	-	-	3.33	-	-	-
	95% CI	-	-	[0.97; 11.40]	-	-	-
Rush 2006 (STAR*D)	Withdrawal rate due to AEs	-	-	21.0% (N=238)	21.2% (N=250)	27.2% (N=239)	-
	RR vs. sertraline	-	-	-	1.01	1.29	-
	95% CI	-	-	-	[0.72; 1.42]	[0.94; 1.79]	-
Lenox- Smith 2008	Withdrawal rate due to AEs	-	-	-	5.5% (N=200)	-	5.3% (N=206)
	RR vs. venlafaxine	-	-	-	-	-	0.97
	95% CI	-	-	-	-	-	[0.43; 2.19]

RR: relative risk; CI: confidence interval; N: number of patients; XR : extended release; SR: sustained release

Table 20 shows the withdrawal rates due to AEs estimated by adjusted indirect comparison using relative risks.

Table 20. ITC of withdrawal rates due to AEs: estimates by adjusted indirect comparison using relative risks

	Vortioxetine	Agomel- atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
Direct comparison of agomelatine vs. vortioxetine through REVIVE						
Withdrawal rate due to AEs	5.9%	9.5%	-	-	-	-
RR vs. vortioxetine	-	1.60	-	-	-	-
95% CI	-	[0.86; 3.00]	-	-	-	-
Adjusted indirect comparison of sertraline vs. vortioxetine through REVIVE and Kasper 2013						
Withdrawal rate due to AEs	5.9%	-	31.6%	-	-	-
RR vs. vortioxetine	-	-	5.33	-	-	-
95% CI	-	-	[1.34; 21.21]	-	-	-
Adjusted indirect comparison of venlafaxine XR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Withdrawal rate due to AEs	5.9%	-	-	31.9%	-	-
RR vs. vortioxetine	-	-	-	5.38	-	-
95% CI	-	-	-	[1.30; 22.32]	-	-
Adjusted indirect comparison of bupropion SR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Withdrawal rate due to AEs	5.9%	-	-	-	40.7%	-
RR vs. vortioxetine	-	-	-	-	6.87	-
95% CI	-	-	-	-	[1.66; 28.39]	-
Adjusted indirect comparison of citalopram vs. vortioxetine through REVIVE, Kasper 2013, STAR*D and Lenox-Smith 2008						
Withdrawal rate due to AEs	5.9%	-	-	-	-	30.9%
RR vs. vortioxetine	-	-	-	-	-	5.22
95% CI	-	-	-	-	-	[1.01; 26.88]

RR: relative risk; CI: confidence interval; XR : extended release; SR: sustained release

Using relative risks in the adjusted ITC, the estimated withdrawal rates due to AEs were statistically significantly higher for sertraline, venlafaxine, bupropion and citalopram than vortioxetine. These rates are also higher than those derived using risk difference and odds ratios.

A18. Priority question: Results for the company's ITC are provided for remission and withdrawal rates because of adverse events only.

- a. Please state which efficacy and safety outcomes were excluded from the ITC, and why.

Table B27 of the main submission document reports the primary and additional/secondary endpoints reported in each of the studies included in the network. No endpoints additional to rates of remission and withdrawals due to adverse events were consistently reported across all studies and hence they could not be included in the ITC.

In light of this the response to questions 18b and 18c both have limitations. For the former, no comparison could be made to citalopram as Lenox-Smith (2008) did not report response. For the latter, assumptions have been made to allow comparative analyses of change from baseline symptom scores. These are discussed in further detail below.

- b. Please also provide results from similar analyses using response rate as the outcome.

ITC parameter inputs: response rates

Response rates were extracted from the REVIVE study report and from the Kasper 2013 and Rush 2006 (STAR*D) publications. Different scales were used in each study, and no response data were reported in Lenox-Smith 2008. Hence, comparative response rates could not be calculated versus citalopram.

The following scales and definitions used are summarised below:

Study ID	Scale	Definition
REVIVE	MADRS	At least 50% reduction from baseline MADRS (week 8 data)
Kasper 2013	HAM-D ₁₇	At least 50% reduction from baseline HAM-D ₁₇
Rush 2006 (STAR*D)	QIDS-SR ₁₆	At least 50% reduction from treatment step entry in QIDS-SR ₁₆
Lenox-Smith 2008	No results available on response	

Using the raw response rate data from the three studies, Table 21 shows the calculated risk differences, relative risks and odds ratios of response to support estimation of adjusted response rates in the ITC.

Table 21. ITC of response rates: raw data parameter inputs

Study ID	Parameter	Vortioxetine	Agomel- atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
REVIVE	Remission rate	61.5% (N=252)	47.3% (N=241)	-	-	-	-
	RD vs. vortioxetine	-	-14.2%	-	-	-	-
	95% CI	-	[-22.9; -5.5]	-	-	-	-
	RR vs. vortioxetine	-	0.77	-	-	-	-
	95% CI	-	[0.65; 0.91]	-	-	-	-
	OR vs. vortioxetine	-	0.56	-	-	-	-
	95% CI	-	[0.39; 0.80]	-	-	-	-
Kasper 2013	Remission rate	-	67.5% (N=80)	55.2% (N=96)	-	-	-
	RD vs. agomelatine	-	-	-12.3%	-	-	-
	95% CI	-	-	[-26.6; 2.0]	-	-	-
	RR vs. agomelatine	-	-	0.82	-	-	-
	95% CI	-	-	[0.65; 1.04]	-	-	-
	OR vs. agomelatine	-	-	0.59	-	-	-
	95% CI	-	-	[0.32; 1.10]	-	-	-
Rush 2006 (STAR*D)	Remission rate	-	-	26.7% (N=236)	28.2% (N=248)	26.1% (N=238)	-
	RD vs. sertraline	-	-	-	1.5%	-0.6%	-
	95% CI	-	-	-	[-6.4; 9.5]	[-8.6; 7.3]	-
	RR vs. sertraline	-	-	-	1.06	0.98	-
	95% CI	-	-	-	[0.79; 1.41]	[0.72; 1.32]	-
	OR vs. sertraline	-	-	-	1.08	0.97	-
	95% CI	-	-	-	[0.72; 1.61]	[0.64; 1.46]	-
RD: risk difference; RR: relative risk; OR: odds ratio; CI: confidence interval; N: number of patients; XR : extended release; SR: sustained release							

Table 22 shows the estimated response rates for sertraline, venlafaxine and bupropion by adjusted indirect comparison using risk differences, relative risks and odds ratios as the input statistics.

Table 22. ITC of response rates: estimates by adjusted indirect comparison using risk differences, relative risks and odds ratios

	Vortioxetine	Agomelatine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
Direct comparison of agomelatine vs. vortioxetine through REVIVE						
Response rate	61.5%	47.3%	-	-	-	-
RD vs. vortioxetine	-	-14.2%	-	-	-	-
95% CI	-	[-22.9; -5.5]	-	-	-	-
RR vs. vortioxetine	-	0.77	-	-	-	-
95% CI	-	[0.65; 0.91]	-	-	-	-
OR vs. vortioxetine	-	0.56	-	-	-	-
95% CI	-	[0.39; 0.80]	-	-	-	-
Adjusted indirect comparison of sertraline vs. vortioxetine through REVIVE and Kasper 2013						
Response rate from RD	61.5%	-	35.0%	-	-	-
RD vs. vortioxetine	-	-	-26.5%	-	-	-
95% CI	-	-	[-43.2; -9.8]	-	-	-
Response rate from RR	-	-	38.8%	-	-	-
RR vs. vortioxetine	-	-	0.63	-	-	-
95% CI	-	-	[0.47; 0.84]	-	-	-
Response rate from OR	-	-	34.7%	-	-	-
OR vs. vortioxetine	-	-	0.33	-	-	-
95% CI	-	-	[0.16; 0.68]	-	-	-
Adjusted indirect comparison of venlafaxine XR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Response rate from RD	61.5%	-	-	36.5%	-	-
RD vs. vortioxetine	-	-	-	-25.0%	-	-
95% CI	-	-	-	[-43.5; -6.5]	-	-
Response rate from RR	-	-	-	41.1%	-	-
RR vs. vortioxetine	-	-	-	0.67	-	-
95% CI	-	-	-	[0.45; 1.01]	-	-
Response rate from OR	-	-	-	36.3%	-	-
OR vs. vortioxetine	-	-	-	0.36	-	-
95% CI	-	-	-	[0.16; 0.81]	-	-
Adjusted indirect comparison of bupropion SR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Response rate from RD	61.5%	-	-	-	34.4%	-
RD vs. vortioxetine	-	-	-	-	-27.1%	-
95% CI	-	-	-	-	[-45.7; -8.6]	-
Response rate from RR	-	-	-	-	38.1%	-
RR vs. vortioxetine	-	-	-	-	0.62	-
95% CI	-	-	-	-	[0.41; 0.94]	-
Response rate from OR	-	-	-	-	33.8%	-

	Vortioxetine	Agomel- atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
OR vs. vortioxetine	-	-	-	-	0.32	-
95% CI	-	-	-	-	[0.14; 0.73]	-

RD: risk difference; RR: relative risk; OR: odds ratio; CI: confidence interval; XR : extended release; SR: sustained release

In the adjusted ITC using risk differences, odds ratio and relative risks, the estimated response rates were higher for vortioxetine than sertraline, venlafaxine and bupropion. These differences were statistically significant for all the comparisons using risk difference and odds ratio and for all the comparisons except with venlafaxine when using relative risks. No response rates could be estimated for citalopram due to the absence of response data in Lenox-Smith 2008.

- c. Please also provide results from similar analyses using change in depression rating scales from baseline as the outcome (for example, by performing a standardised mean difference analysis). If possible, please provide results for both frequentist and Bayesian models.

The standardised mean difference (SMD) of change from baseline is not strictly calculable in all of the four studies from the data reported. Lundbeck has attempted to implement these requested analyses with the data available by making assumptions as necessary.

The main role of the SMD is to facilitate combining results from trials which have reported outcomes measured on different continuous scales. Here the results are derived using a different scale for each study. The scales as well as the outcome measures available in the publications are presented in Table 23.

Table 23. Comparison of endpoint measurements in studies included in ITC

Study	Scale	Measure	Time point	Analysis
REVIVE	MADRS	Change from baseline	Week 8	MMRM
Kasper 2013	HAM-D ₁₇	Score at endpoint	Week 6	Descriptive, LOCF
Rush 2006 (STAR*D)	QIDS-SR ₁₆	Score at endpoint	Week 14	Descriptive
Lenox-Smith 2008	HAM-D ₂₁	Change from baseline	Week 12	ANCOVA LOCF

Cohen's d SMD

As the number of patients in each arm is between 80 and 252, SMDs between arms were computed using Cohen's d formula, rather than Hedge's G, as:

$$SMD = \frac{Mean_B - Mean_A}{\sqrt{\frac{(N_B - 1) * SD_B^2 + (N_A - 1) * SD_A^2}{N_B + N_A - 2}}}$$

The corresponding standard deviation (SD) was computed as:

$$SD_{SMD} = \sqrt{\frac{N_B + N_A}{N_B * N_A}} + \frac{SMD^2}{2 * N_B + 2 * N_A}$$

Data inputs

The data inputs used to perform the ITC are described below.

REVIVE data

Using Panel 22 from REVIVE CSR “Analysis of change from baseline in MADRS total score at week 8 (FAS, MMRM)”, the SD per treatment arm was estimated as the product of the SE per treatment arm by the square root of the number of patients in the treatment arm and the effect size can then be computed using the formula described in previous section.

Table 24. Effect size estimation: REVIVE, using MADRS change from baseline

	Vortioxetine	Agomelatine
<i>N</i>	220	190
<i>Change from baseline – mean</i>	-16.53	-14.38
<i>Change from baseline – SE</i>	0.48	0.51
<i>Change from baseline – SD</i>	7.12	7.03
Difference agomelatine vs. vortioxetine		
Mean difference		2.15
Common SD		7.08
Effect size agomelatine vs. vortioxetine		
Effect size		0.304
SE of effect size		0.100
95% CI lower bound		0.109
95% CI upper bound		0.499

Data in *italics* are directly extracted from the source.

Kasper 2013 data

Results on change from baseline are not available from Kasper 2013. However, an SMD was estimated by making the following assumptions, while acknowledging their limitations.

Assumption 1: The patients in both arms have comparable baseline values.

This assumption is supported by the fact that, as expected by the randomisation process, the mean MADRS baseline values on the whole population (Table 2 in Kasper 2010) are very similar with small and similar standard deviation (SD): 26.1 (SD=2.8) and 26.5 (SD=3) for agomelatine and sertraline, respectively.

Assumption 2: The SD of change from baseline = SD of value at endpoint.

This was observed to be the case in the REVIVE trial. The SDs of the MADRS total score at week 8 (FAS, OC cf. Table 31 of REVIVE CSR) are 7.80 and 7.55, respectively, for the vortioxetine and agomelatine arms. The corresponding SDs of change from baseline on MADRS at week 8 (FAS, OC cf. Table 31 of REVIVE CSR) are 7.65 and 7.35.

Let us therefore assume that the SMD of change from baseline is equal to the SMD of value at endpoint.

Using Tables 3 and 4 from Kasper 2013, the effect size is estimated as shown in Table 25.

Table 25. Effect size estimation: Kasper 2013, using HAM-D₁₇ change from baseline

	Agomelatine	Sertraline
<i>N</i>	80	96
<i>Value at endpoint – mean</i>	11.1	13
<i>Value at endpoint – SD</i>	7	8.7
Difference sertraline vs. agomelatine		
Mean difference		1.9
Common SD		7.97
Effect size sertraline vs. agomelatine		
Effect size		0.238
SE of effect size		0.152
95% CI lower bound		-0.059
95% CI upper bound		0.536

Data in *italics* are directly extracted from the source.

Rush 2006 (STAR*D) data

As with Kasper 2013, results on change from baseline are not available in the Rush 2006 publication.

Assumption 1: The patients of both arms have comparable baseline values.

This assumption is supported by the fact that, as expected by the randomisation process, the mean QIDS-SR₁₆ baseline values on the whole population (Table 1 in Rush 2006) are very similar with small and similar SDs : 13.3 (SD=4.7) and 13.1 (SD=5) and 13.2 (SD=4.9) for sertraline, venlafaxine and bupropion, respectively.

Assumption 2: The SD of change from baseline = SD of value at endpoint.

As with the Kasper 2013 data above, this assumption is made by analogy with data from REVIVE.

Let us therefore assume that the SMD of change from baseline is equal to the SMD of value at endpoint. Using data from Rush 2006, the effect size is estimated as shown in Table 26.

Table 26. Effect size estimation: Rush 2006 (STAR*D), using QIDS-SR₁₆ change from baseline

	Sertraline	Venlafaxine	Bupropion
<i>N</i>	237	248	239
<i>Value at endpoint – mean</i>	10.1	10.2	10.5
<i>Value at endpoint – SD</i>	5.9	6.1	6
Difference vs. sertraline			
Mean difference		0.1	0.4
Common SD		6.00	5.95
Effect size vs. sertraline			
Effect size		0.017	0.067
SE of effect size		0.091	0.092
95% CI lower bound		-0.161	-0.113
95% CI upper bound		0.195	0.247

Data in *italics* are directly extracted from the source.

Lenox-Smith 2008 data

In the Lenox-Smith 2008 publication (Efficacy and primary analyses, page 116), only the change from baseline by treatment arm and the P-value of the difference between arms are provided.

Assumption 1: the P-value is assumed to come from a simple *t* test.

The *t* statistic is obtained from the P-value and the degrees of freedom (DF). The standard error of the difference in means is then obtained as:

$SE = MD/t$, where MD is the difference in means.

Assumption 2: The SD of change from baseline for each arm are not provided. It is assumed that the SD of change from baseline in the venlafaxine arm is equal to the SD of change from baseline in the citalopram arm.

The common SD was calculated as follows:

$$SD = \frac{SE}{\sqrt{\frac{1}{N_E} + \frac{1}{N_C}}}$$

Table 27. Effect size estimation: Lenox-Smith 2008 (STAR*D), using HAM-D₂₁ change from baseline

	Venlafaxine	Citalopram
<i>N</i>	<i>194</i>	<i>202</i>
<i>Change from baseline – mean</i>	<i>-17</i>	<i>-16.5</i>
Difference citalopram vs. venlafaxine in change from baseline		
<i>P-value</i>		<i>0.4778</i>
t statistic (DF=394)		<i>0.7105</i>
SE		<i>0.7037</i>
Mean difference		<i>0.5</i>
Common SD		<i>7.0</i>
Effect size citalopram vs. venlafaxine		
Effect size		<i>0.071</i>
SE of effect size		<i>0.101</i>
95% CI lower bound		<i>-0.126</i>
95% CI upper bound		<i>0.269</i>

Data in *italics* are directly extracted from the source.

Summary of inputs

The below tables presents a summary of the inputs for the ITC calculated as described in the previous sections.

Table 28. Standardised mean difference of change from baseline on efficacy assessment scales: inputs

Study ID (scale used)	Parameter	Vortioxetine	Agomelatine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
REVIVE (MADRS)	N	252	241	-	-	-	-
	SMD vs. vortioxetine	-	0.304	-	-	-	-
	95% CI	-	[0.109; 0.499]	-	-	-	-
Kasper 2013 (HAM-D ₁₇)	N	-	80	96	-	-	-
	SMD vs. agomelatine	-	-	0.238	-	-	-
	95% CI	-	-	[-0.059; 0.536]	-	-	-
Rush 2006 (QIDS-SR ₁₆)	N	-	-	237	248	239	-
	SMD vs. sertraline	-	-	-	0.017	0.067	-
	95% CI	-	-	-	[-0.161; 0.195]	[-0.113; 0.247]	-
Lenox-Smith 2008 (HAM-D ₂₁)	N	-	-	-	194	-	202
	SMD vs. venlafaxine	-	-	-	-	-	0.071
	95% CI	-	-	-	-	-	[-0.126; 0.269]

SMD: standardised mean difference. A positive SMD favours the reference treatment. CI: confidence interval; N: number of patients

REVIVE and Kasper report effect sizes above 0.2 (clinically detectable), but only REVIVE leads to a significant difference on SMD between treatments. For the two other studies, differences on SMD between treatments were all below 0.2 and non-significant²⁶.

Results of the ITC using SMDs: frequentist analysis

As for the binary outcomes, Bucher's method was used to perform an adjusted ITC using the estimated SMDs.

Table 29. Adjusted indirect comparison with SMD of change from baseline

	Vortioxetine	Agomelatine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
Direct comparison of agomelatine vs. vortioxetine through REVIVE						
SMD vs. vortioxetine	-	0.304	-	-	-	-
95% CI	-	[0.109; 0.499]	-	-	-	-
Adjusted indirect comparison of sertraline vs. vortioxetine through REVIVE and Kasper 2013						
SMD vs. vortioxetine	-	-	0.542	-	-	-
95% CI	-	-	[0.186; 0.898]	-	-	-
Adjusted indirect comparison of venlafaxine XR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
SMD vs. vortioxetine	-	-	-	0.559	-	-
95% CI	-	-	-	[0.161; 0.957]	-	-
Adjusted indirect comparison of bupropion SR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
SMD vs. vortioxetine	-	-	-	-	0.609	-
95% CI	-	-	-	-	[0.210; 1.008]	-
Adjusted indirect comparison of citalopram vs. vortioxetine through REVIVE, Kasper 2013, STAR*D and Lenox-Smith 2008						
SMD vs. vortioxetine	-	-	-	-	-	0.630
95% CI	-	-	-	-	-	[0.186; 1.074]

SMD: standardised mean difference. A positive SMD favours vortioxetine. CI: confidence interval.

Although the above estimates of SMD are approximations, given the need to make some assumptions where data were missing, statistically significant differences in favour of vortioxetine are observed versus all five included comparators. These differences are seen in spite of the loss of power (squared standard errors add up all along the chain of evidence) resulting from the indirect comparison process.

In terms of magnitude of effect, the difference versus agomelatine exceeds the 0.2 threshold value that normally indicates a clinically detectable difference between treatments, while the difference versus all other treatments exceeds the 0.5 threshold that indicates a “medium” difference between treatments.

Results of the ITC using SMDs: Bayesian analysis

Table 30 summarises the results of the fixed-effect model for SMD of change from baseline comparing vortioxetine to agomelatine, sertraline, venlafaxine, bupropion and citalopram, respectively. The results are consistent with the frequentist analysis undertaken using the Bucher methodology.

Table 30. Bayesian indirect comparison with SMD of change from baseline (fixed effect)

TT1	vs	TT2	Median SMD	95% CrI
Vortioxetine	vs	Agomelatine	-0.304	[-0.499;-0.108]
Vortioxetine	vs	Sertraline	-0.541	[-0.899;-0.182]

TT1	vs	TT2	Median SMD	95% CrI
Vortioxetine	vs	Venlafaxine	-0.558	[-0.957;-0.156]
Vortioxetine	vs	Bupropion	-0.607	[-1.008;-0.208]
Vortioxetine	vs	Citalopram	-0.628	[-1.073;-0.185]

Both the frequentist and Bayesian analyses based on SMDs support the findings from the corresponding analyses on binary outcomes.

A19. Please explain why the TAK318 trial was excluded from the ITC analysis.

TAK318 was designed to explore the impact of treatment on a specific side-effect, treatment-emergent sexual dysfunction (TESD), in otherwise well-controlled patients (mean MADRS, 7.9 and 8.3 for vortioxetine and escitalopram, respectively). REVIVE and other studies in the ITC were designed to explore efficacy in poorly-controlled patients (mean MADRS scores at baseline of 26 to 36). As TAK 318 was intended to explore a completely different question to the ITC, and involved a different population, it did not meet the eligibility criteria for inclusion in the ITC.

Although TAK318 is a “switch” study comparing vortioxetine to an active comparator and is therefore relevant to the STA decision problem, it does not provide information that can readily be incorporated into the economic evaluation. TAK318 is seen rather as stand-alone, supportive evidence for an aspect of the favourable side-effect profile of vortioxetine.

A20. Table B39, last line (page 124 of the company's submission): please clarify how the adjusted indirect comparison estimated rate of withdrawals because of AEs was 18.0% for citalopram, compared with 5.3% in the original publication (Lenox-Smith et al. 2008).

Applying the Bucher method on risk difference to the inputs below implies simple addition of the risk differences between treatments. The analysis results in a withdrawal rate due to adverse events for citalopram of 18%, which is calculated as follows: $5.9 + 3.6 + 8.5 + 0.2 - 0.2$. The most influential driver of this result is the 8.5% difference between agomelatine and sertraline in the Kasper 2013 study.

Table 31. Calculation of risk differences for withdrawal due to AEs by Bucher method

Study	Outcome	Vortioxetine	Agomelatine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
REVIVE	Withdrawal rate	5.9% (N=253)	9.5% (N=242)	-	-	-	-
	Diff vs vortioxetine	-	3.6%	-	-	-	-
	CI 95%	-	[-1.1; 8.3]	-	-	-	-
Kasper 2013	Withdrawal rate	-	3.7% (N=80)	12.2% (N=96)	-	-	-
	Difference vs.	-	-	8.5%	-	-	-

Study	Outcome	Vortioxetine	Agomelatine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
agomelatine							
	CI 95%	-	-	[0.8; 16.2]	-	-	-
STAR*D	Withdrawal rate	-	-	21.0% (N=238)	21.2% (N=250)	27.2% (N=239)	-
	Difference vs. sertraline	-	-	-	0.2%	6.2%	-
	CI 95%	-	-	-	[-7.0; 7.4]	[-1.5; 13.9]	-
Lenox-Smith	Withdrawal rate	-	-	-	5.5% (N=200)	-	5.3% (N=206)
	Difference vs. venlafaxine	-	-	-	-	-	-0.2%
	CI 95%	-	-	-	-	-	[-4.6; 4.2]

A21. Please provide details of the recruitment setting for trials included in the ITC (that is, primary care, secondary care).

Table 32 below gives details on the recruitment setting for the studies included in the ITC. It should be noted that the treatment setting for depression varies between countries. Expert advice suggests that in some countries, for example, Czech Republic and USA, the majority of patients with depression are treated in secondary care whereas in the UK they would be treated in primary care.

Table 32. Recruitment and treatment settings for the studies included in the ITC

Study details	Recruitment and treatment setting
Montgomery 2014 (REVIVE)	Recruitment was undertaken via advertisements (in Austria, Germany, Estonia, Russia, Sweden and the UK) or referrals from general practitioners and hence represent a mix of primary and secondary care patients. Of the patients in the study only 2.8% were inpatients. The treatment setting for the study was secondary care - 71 psychiatric inpatient and outpatient settings in 14 countries (Austria, Belgium, Bulgaria, Czech Republic, Estonia, Germany, Italy, Lithuania, Poland, Romania, Russia, Spain, Sweden and the UK).
Kasper 2010	The published paper reports that patients were outpatients with MDD requiring anti-depressant therapy from France, Germany, Austria, Spain, Italy and Poland.
Rush 2006 (STAR*D)	The study reported the inclusion of outpatients from both primary and psychiatric, public and private practice settings. In total 41 clinical sites across the US, more specifically 18 primary- and 23 psychiatric-care settings (Ref. Rush 2009).
Lenox-Smith 2008	The recruitment setting was not fully defined. Both inpatients and outpatients were eligible to be included in the study, however the summary states 'participants were adult outpatients'. This therefore implies that only outpatients were recruited.

Clear descriptions of the study settings were not given in Kasper 2010 and Lenox-Smith 2008. The following websites were searched to try to retrieve additional information:

- www.controlled-trials.com
- WHO clinical trials registry

- www.clinicaltrials.gov

Kasper 2010 is listed in www.controlled-trials.com (ISRCTN 49376288) but no details of the study setting are given. No record for Lenox-Smith (2008) could be found in any of the registries.

In the absence of further information on these study settings advice was sought from within Lundbeck's clinical team together with a review of the clinicians involved in the above studies. The clinical team believes most pharmaceutical company sponsored studies in depression (such as Kasper 2010 and Lenox-Smith 2008) are conducted in secondary care, but recruit from both primary and secondary care settings and it is concluded that that is likely to be the case for these two studies.

Adverse events

A22. *Table B44 (page 133 of the company's submission), please provide the number and percentage of patients with a severe adverse event, and the number of discontinuations because of an adverse event per dosage (2.5-10.0 mg; 15-20 mg).*

Data provided in answer to A15.

A23. **Priority question:** *The scope of the literature search for adverse event studies was expanded to include 'non-switch populations' (see Section 6.9.1.2 of the company's submission). Given this, please clarify why most vortioxetine trials listed in Table B4, (page 64 of the company's submission), were not included in this review. If available, please provide summary adverse event data, including severe adverse events and discontinuation because of an adverse event, for all trials of vortioxetine and for all comparator treatment arms (including placebo). For example, by providing relative risks or risk differences between treatments, and results from meta-analyses, if these have been performed.*

As stated in the submission "the relative efficacy of antidepressants cannot be assumed to be constant between initial and switch usage" whereas clinical opinion suggests that tolerability is likely to be. Hence the search was widened to include non-switch populations.

The NICE template states in Section 6.9.1.:

"If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results."

Therefore, the expanded search undertaken to identify the safety studies in the non-switch population focused on those trials which included a safety primary endpoint. Hence the retrieval of only the long-term safety studies rather than all of the studies detailed in Table B4 of the submission.

In any case, the meta-analysed safety and tolerability results for both the short- and long-term pool of studies from the full MDD package are presented in response to question A15 in this document.

Section B: Clarification on cost-effectiveness data**Model time horizon****Table 33. Base case scenario: 12-month horizon (NHS/PSS perspective)**

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Venlafaxine	£964	0.675	-	-	£378	-
Vortioxetine	£971	0.694	£7	0.019	NA	£378
Citalopram	£976	0.664	£5	-0.030	Dominant	Dominated
Sertraline	£977	0.664	£0	-0.001	Dominant	Dominated
Agomelatine	£1,082	0.676	£105	0.012	Dominant	Dominated

B1. It is noted that the recovery period in the company's economic model denotes a period of 4 months where the patient is not at-risk. Please carry out exploratory analyses around the time horizon, and present the cost-effectiveness results for time horizons of 2 and 8 months.

The results of reducing the time horizon to two months increase both the cost and effectiveness of vortioxetine relative to venlafaxine, sertraline and citalopram (ICERs: £1,878, £1,686 and £5,620, respectively, see Table 34). This compares to the base-case analysis, in which the increased costs of vortioxetine at 2 months are offset over the 12-month period in the comparison with citalopram and sertraline (Table 33). Vortioxetine is a dominant strategy compared to agomelatine whether the time horizon is 2 months or 12 months. In the analysis versus venlafaxine, vortioxetine becomes a more cost-effective strategy over a longer time horizon. This analysis also demonstrates that at 2 months citalopram is a preferential strategy compared to sertraline and venlafaxine, as both the latter are dominated. Vortioxetine remains below the £20,000/QALY threshold at two months compared to citalopram.

Table 34. Scenario: 2-month time horizon (NHS/PSS perspective)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Citalopram	£220	0.099	-	-	£5,620	-
Sertraline	£229	0.096	£10	-0.002	£1,686	Dominated
Venlafaxine	£231	0.098	£2	0.002	£1,878	Dominated
Vortioxetine	£239	0.102	£8	0.004	-	£5,620
Agomelatine	£264	0.100	£25	-0.002	Dominant	Dominated

If the time horizon of the model decreases to 8 months (i.e. no recovery phase) vortioxetine continues to be a dominant strategy compared to citalopram, sertraline and agomelatine (Table 35). The gains in QALYs attributable to the final four-month recovery phase in the base case model are now not observed in the eight-month analysis. This is evident from the reduction in total QALYs for all the treatments.

Table 35: Scenario: 8-month time horizon (NHS/PSS perspective)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Venlafaxine	£964	0.440	-	-	£507	-
Vortioxetine	£971	0.454	£7	0.014	-	£507
Citalopram	£976	0.434	£5	-0.020	Dominant	Dominated
Sertraline	£977	0.434	£1	0.000	Dominant	Dominated
Agomelatine	£1,082	0.443	£105	0.009	Dominant	Dominated

B2. According to NICE's guidance on [depression in adults](#) (see NICE Clinical Guideline 90), patients at risk of relapse should be treated with anti-depressants for at least 2 years. Please incorporate an additional scenario in the economic model where this is included and present the revised cost-effectiveness results for vortioxetine compared with each of the comparators.

In this analysis the time horizon of the model increased by one year (i.e. two years). Unlike in the base case, cost of treatment and monitoring are now considered for patients even when they reach the recovery phase.

To extrapolate for a further year, the Markov component of the model was extended by adding additional cycles of two months up to 24 months. This was then reflected in the switch formula in the decision tree. For example, if a patient switched due to lack of efficacy in the maintenance phase (i.e. after 5 months), they would now spend 19 months in the Markov component of the model compared to 7 months in the base-case. In addition, patients who reached recovery now incurred costs associated with treatment and monitoring as it was assumed that, contrary to the base case, patients would continue receiving treatment even after reaching recovery. A discount rate of 3.5% was assumed for the second year for both costs and outcomes.

These changes had an impact on the incremental cost. Although citalopram was associated with the lowest cost, all other treatments (particularly vortioxetine) made greater gains in terms of effectiveness. Vortioxetine now moves from being a dominant strategy in the base case versus citalopram and sertraline to being cost-effective in the two-year model, with ICERs of £4,570 and £4,586 per QALY gained, respectively (see Table 36). The difference in ICERs compared to the base case can be explained by the fact that in this scenario, patients in recovery continue receiving treatment up to two years. In all analyses, the ICER remains well below a threshold of £20,000/QALY.

Table 36. Scenario: 2-year time horizon (NHS/PSS perspective)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Citalopram	£1,127	1.337	-	-	£4,570	-
Sertraline	£1,146	1.341	£20	0.004	£4,586	£4,373
Venlafaxine	£1,215	1.363	£69	0.018	£5,475	£3,234

Vortioxetine for the treatment of MDD [ID583]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Vortioxetine	£1,391	1.395	£176	0.032	-	£5,475
Agomelatine	£1,515	1.360	£124	-0.035	Dominant	Dominated

EQ-5D data

B3. Priority question: *Using results from the REVIVE trial, please provide average baseline and week 8 EQ-5D scores (and associated standard errors) for 'remitters' and 'non-remitters' separately. Please do this separately for those treated with vortioxetine and for those treated with agomelatine, as well as, a combined analysis. Please present the results according to the observed cases [OC], last observation carried forward [LOCF] and mixed model for repeated measures [MMRM] methods (that is, an expanded version of Table B15, page 91 of the company's submission).*

Table 37 to Table 41 below detail EQ-5D scores by remission status for vortioxetine, agomelatine and the total population based on each of the following methods of analysis:

- FAS, MMRM
- FAS, OC
- FAS, LOCF

Please note these are descriptive analyses, so commentary on numerical differences should not be read as statistical inference.

Table 37 shows that EQ-5D scores at week 8 differed according to remission status, with remitters achieving a higher mean score, but that this difference was independent of treatment assignment. This finding suggests that the superiority in mean EQ-5D improvement (as reported in the main submission) for vortioxetine compared with agomelatine was driven by the superior remission rates for patients treated with vortioxetine.

Table 37. EQ-5D summary index (FAS, MMRM): MADRS non-remitters and remitters

Treatment Group	Week	Non-remitters			Remitters		
		N	Mean EQ-5D score	SE	N	Mean EQ-5D score	SE
VOR	8	119	0.68	0.02	101	0.84	0.01
AGO	8	119	0.66	0.02	70	0.84	0.02
Total	8	238	0.67	0.02	171	0.84	0.01

Among the non-remitters, baseline EQ-5D scores were well matched between the treatment groups. However, among the remitters, patients assigned to agomelatine had a slightly greater mean baseline score than those on vortioxetine, as Table 38 to Table 41 illustrate. The pattern of results was insensitive to the choice of analytic method.

Table 38. EQ-5D summary index (FAS, OC): MADRS non-remitters

Treatment Group	Week	N	Mean	SD	SE	Min	Max	Percentiles		
								25%	50%	75%
VOR	0	119	0.53	0.27	0.02	-0.18	0.85	0.27	0.62	0.71
	8	119	0.69	0.21	0.02	0.02	1.00	0.64	0.73	0.81
AGO	0	120	0.53	0.25	0.02	-0.18	0.85	0.38	0.62	0.69
	8	119	0.66	0.24	0.02	-0.16	1.00	0.62	0.71	0.81
Total	0	239	0.53	0.26	0.02	-0.18	0.85	0.32	0.62	0.69
	8	238	0.67	0.23	0.01	-0.16	1.00	0.62	0.73	0.81

Table 39. EQ-5D summary index (FAS, OC): MADRS remitters

Treatment Group	Week	N	Mean	SD	SE	Min	Max	Percentiles		
								25%	50%	75%
VOR	0	101	0.54	0.29	0.03	-0.18	0.88	0.29	0.69	0.81
	8	101	0.84	0.12	0.01	0.59	1.00	0.73	0.85	1.00
AGO	0	70	0.60	0.22	0.03	0.08	0.85	0.38	0.69	0.81
	8	70	0.85	0.16	0.02	0.26	1.00	0.81	0.85	1.00
Total	0	171	0.57	0.26	0.02	-0.18	0.88	0.36	0.69	0.81
	8	171	0.85	0.14	0.01	0.26	1.00	0.76	0.85	1.00

Table 40. EQ-5D Summary Index (FAS, LOCF): MADRS non-remitters

Treatment Group	Week	N	Mean	SD	SE	Min	Max	Percentiles		
								25%	50%	75%
VOR	0	150	0.52	0.28	0.02	-0.18	0.85	0.27	0.62	0.73
	8	140	0.65	0.25	0.02	-0.24	1.00	0.62	0.72	0.81
AGO	0	170	0.53	0.28	0.02	-0.48	0.85	0.29	0.62	0.73
	8	162	0.62	0.27	0.02	-0.18	1.00	0.52	0.69	0.81
Total	0	320	0.52	0.28	0.02	-0.48	0.85	0.27	0.62	0.73
	8	302	0.63	0.26	0.02	-0.24	1.00	0.59	0.69	0.81

Table 41. EQ-5D summary index (FAS, LOCF): MADRS remitters

Treatment Group	Week	N	Mean	SD	SE	Min	Max	Percentiles		
								25%	50%	75%
VOR	0	102	0.54	0.29	0.03	-0.18	0.88	0.26	0.69	0.81
	8	102	0.84	0.12	0.01	0.59	1.00	0.73	0.85	1.00
AGO	0	71	0.60	0.22	0.03	0.08	0.85	0.38	0.69	0.81
	8	71	0.85	0.16	0.02	0.26	1.00	0.81	0.85	1.00
Total	0	173	0.56	0.26	0.02	-0.18	0.88	0.36	0.69	0.81
	8	173	0.85	0.14	0.01	0.26	1.00	0.76	0.85	1.00

B4. *Priority question: Using results from the REVIVE trial, please provide average change in EQ-5D scores from baseline at week 8 (and associated standard errors) for remitters and non-remitters separately. Please do this separately for those treated with vortioxetine and for those treated with agomelatine, as well as, a combined analysis. Please present the results according to the OC, LOCF and MMRM methods.*

Table 42 to Table 45 detail change from baseline EQ-5D scores by remission status defined by MADRS score for vortioxetine, agomelatine and the combined groups based on the following method of analysis:

- FAS, MMRM
- FAS, OC
- FAS, LOCF

Once again, these are descriptive analyses and commentary on numerical differences should not be read as statistical inference.

Both remitters and non-remitters showed increases in mean EQ-5D over 8 weeks of treatment. As expected, the increase was greater among patients who remitted. Among remitters, mean change in EQ-5D score was consistent between treatment groups, but among non-remitters there is a suggestion that patients on vortioxetine achieved slightly greater increases than those on agomelatine. This may possibly be explained by differences in the pattern of adverse events between groups; although the overall incidence of AEs did not differ between groups, fewer patients in the vortioxetine group withdrew due to AEs. No formal analysis of AEs by remission status has been performed, so the above explanation should be regarded as tentative only. The analyses of change were insensitive to the choice of analytic method for remitters, but for the non-remitters the LOCF analysis resulted in smaller estimates of change over 8 weeks than MMRM and OC analyses, which is an unsurprising finding.

Table 42. Changes from baseline in EQ-5D summary index (FAS, MMRM): MADRS non-remitters and remitters

Treatment Group	Week	Non-remitters			Remitters		
		N	Mean EQ-5D score	SE	N	Mean EQ-5D score	SE
VOR	8	119	0.15	0.02	101	0.28	0.01
AGO	8	119	0.13	0.02	70	0.28	0.02
Total	8	238	0.14	0.02	171	0.28	0.01

Table 43. Change from baseline in EQ-5D summary index (FAS, OC): MADRS non-remitters

Treatment Group	Week	N	Mean	SD	SE	Min	Max	Percentiles		
								25%	50%	75%
VOR	8	119	0.16	0.33	0.03	-0.66	1.18	0.00	0.07	0.43
AGO	8	119	0.13	0.28	0.03	-0.71	0.79	0.00	0.04	0.31
Total	8	238	0.15	0.31	0.02	-0.71	1.18	0.00	0.07	0.43

Table 44. Changes from baseline in EQ-5D summary index (FAS, OC): MADRS remitters

Treatment Group	Week	N	Mean	SD	SE	Min	Max	Percentiles		
								25%	50%	75%
VOR	8	101	0.30	0.28	0.03	-0.12	1.18	0.04	0.19	0.52
AGO	8	70	0.25	0.24	0.03	-0.43	0.92	0.07	0.19	0.43
Total	8	171	0.28	0.27	0.02	-0.43	1.18	0.04	0.19	0.49

Table 45. Changes from baseline in EQ-5D summary index (FAS, LOCF): MADRS non-remitters

Treatment Group	Week	N	Mean	SD	SE	Min	Max	Percentiles		
								25%	50%	75%
VOR	8	140	0.12	0.34	0.03	-0.82	1.18	0.00	0.05	0.31
AGO	8	162	0.08	0.30	0.02	-0.83	0.79	0.00	0.00	0.23
Total	8	302	0.10	0.32	0.02	-0.83	1.18	0.00	0.04	0.26

Table 46. Changes from baseline in EQ-5D summary index (FAS, LOCF): MADRS remitters

Treatment Group	Week	N	Mean	SD	SE	Min	Max	Percentiles		
								25%	50%	75%
VOR	8	102	0.30	0.28	0.03	-0.12	1.18	0.04	0.19	0.52
AGO	8	71	0.25	0.24	0.03	-0.43	0.92	0.07	0.19	0.43
Total	8	173	0.28	0.26	0.02	-0.43	1.18	0.05	0.19	0.49

Costs data

B5. It is noted that there is a 'switch cost' associated with changing therapy in the company's economic model. Please justify why this is additional to GP/specialist care visits, and whether switching would take place in primary or secondary care.

In the base case, the cost of an additional visit to a GP to switch treatment was assumed. Data for GP visits during the acute phase were taken from the UK whole population. As switch patients were not differentiated in this population, it was assumed in our model that patients would have an additional GP visit when switching to another treatment

As a sensitivity analysis the model has been run assuming patients requiring a treatment switch do not require an additional GP visit to allow their switch in therapy. The results are shown in the table below. The ICERs in the sensitivity analysis are slightly higher compared to the base case.

Table 47. Results when GP visit for switch set to zero (NHS/PSS perspective)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Venlafaxine	£933	0.675	NA	NA	£553	NA
Vortioxetine	£941	0.664	£8	-0.011	£74	Dominated
Citalopram	£943	0.664	£2	0.000	£25	Dominated
Sertraline	£943	0.694	£0	0.030	NA	£553
Agomelatine	£1,049	0.676	£106	-0.028	Dominant	Dominated

Probabilistic analysis

B6. Priority question: Please clarify how distributions have been assigned to the model parameter inputs in tables B59 and B60, pages 168 and 171 of the company's submission. Please present the data that underpins them, for example, standard deviation, standard error, number of observations etc.

Please refer to commentary in Table 48 and Table 49.

Table 48. Model parameter inputs: utility values

Event	Input utility value	Distribution	Comment	Source	
Acute phase					
Depression at baseline	0.54			} REVIVE	
Remission	0.85	Beta (α :1,083; β :191)	SE estimated as median utility *0.25/1.96		
No remission	0.62	Beta (α :365; β :223)	Weighted average of non-responders and responding non-remitters at 8 weeks; SE = 0.02		
Maintenance phase					
Remission	0.85	Beta (α :8; β :1)	SE estimated as median utility	} Sapin 2004	
Relapse	0.58	Beta (α :25; β :18)	*0.25/1.96		
Recovery	0.85				
Disutilities of side-effects					
Sexual dysfunction	0.049		} Directly reported by Sullivan	} Sullivan 2004	
Headache	0.115				
Diarrhoea	0.044		} Lundbeck applied Sullivan value reported for drowsiness*		
Somnolence	0.085				
Nausea	0.065		Sullivan assumed average of GI AEs		
Insomnia	0.129		Sullivan assumed equivalent utility to anxiety		
Dry mouth	0†		} No data available	} Dixon 2004, REVIVE CSR	
Dizziness	0†				
Sweating	0†				
Weight gain	0.032		Calculation (see below)		

*Drowsiness is normally considered less severe than somnolence, therefore utility estimate for somnolence may be conservative. †As no utility values were available, no utility decrement was assumed for these AEs in the base-case of the economic evaluation.

Table 49. Model parameter inputs: healthcare resource utilisation

Resource	No. of visits	Distribution	Comments	Proportion of patients with ≥ 1 visit	Distribution	Comments	Source
GP consultations							
Remission 0-8 weeks	2.50	Gamma (α :61.47; β :0.04)		100.0%	Uniform (α :75; β :100)		PERFORM
No remission 0-8 weeks	2.80	Gamma (α :61.47; β :0.05)	SE estimated as mean	100.0%	Uniform (α :75; β :100)	Assumptions as the	PERFORM
Remission after 8 weeks	2.15	Gamma (α :61.47; β :0.03)	visits*0.25/1.96	100.0%	Uniform (α :75; β :100)	proportion was 100%	Byford 2011
Relapse after 8 weeks	2.89	Gamma (α :61.47; β :0.05)		100.0%	Uniform (α :75; β :100)		Byford 2011
Psychiatrist consultations							
Remission 0-8 weeks	0.00	-		0.0%	Beta (α :0; β :71)	n=0; N=71	PERFORM
No remission 0-8 weeks	1.00	Gamma (α :61.47; β :0.02)	SE estimated as mean	1.3%	Beta (α :2; β :152)	n=2; N=152	PERFORM
Remission after 8 weeks	0.23	Gamma (α :61.47; β :0.00)	visits*0.25/1.96	2.9%	Beta (α :60; β :1,997)	SE estimated as mean	Byford 2011
Relapse after 8 weeks	0.23	Gamma (α :61.47; β :0.00)		5.0%	Beta (α :58; β :1,109)	visits*0.25/1.96	Byford 2011
Psychotherapy or counselling							
Remission 0-8 weeks	1.20	Gamma (α :9.00; β :0.13)	SE=0.4	12.7%	Beta (α :9; β :62)	n=9; N=71	PERFORM
No remission 0-8 weeks	2.10	Gamma (α :1.96; β :1.07)	SE=1.5	18.8%	Beta (α :29; β :125)	n=29; N=152	PERFORM
Remission after 8 weeks	0.0	-		0.2%	Beta (α :61; β :30,609)	SE estimated as mean	Byford 2011
Relapse after 8 weeks	0.0	-		0.2%	Beta (α :61; β :30,609)	visits*0.25/1.96	Byford 2011
Psychiatric ward admissions							
Remission 0-8 weeks	0.0	-		0.0%	Beta (α :0; β :71)	n=0; N=71	PERFORM
No remission 0-8 weeks	0.0	-		0.0%	Beta (α :0; β :154)	n=0; N=154	PERFORM
Remission after 8 weeks	0.22	Gamma (α :61.47; β :0.00)	SE estimated as mean	5.2%	Beta (α :58; β :1,061)	SE estimated as mean	Byford 2011
Relapse after 8 weeks	0.23	Gamma (α :61.47; β :0.00)	visits*0.25/1.96	5.7%	Beta (α :58; β :958)	visits*0.25/1.96	Byford 2011
General ward admissions							
Remission 0-8 weeks	0.0	-		0.0%	Beta (α :0; β :0)		PERFORM
No remission 0-8 weeks	1.0	Gamma (α :0.35; β :2.89)	SE=1.7	0.5%	Beta (α :1; β :153)	n=1; N=154	PERFORM
Remission after 8 weeks	0.0	-		0.0%	Beta (α :0; β :0)		Assumption
Relapse after 8 weeks	1.0	Gamma (α :61.47; β :0.02)	SE estimated as mean visits*0.25/1.96	0.5%	Beta (α :61; β :11,924)	SE estimated as mean visits*0.25/1.96	Mean assumed equivalent to acute phase
Accident & Emergency visits							
Remission 0-8 weeks	0.0	-		0.0%	Beta (α :0; β :71)	n=0; N=71	PERFORM
No remission 0-8 weeks	0.0	-		0.0%	Beta (α :0; β :154)	n=0; N=154	PERFORM
Remission after 8 weeks	0.22	Gamma (α :61.47; β :0.00)	SE estimated as mean	3.1%	Beta (α :60; β :1,861)	SE estimated as mean	Byford 2011
Relapse after 8 weeks	0.25	Gamma (α :61.47; β :0.00)	visits*0.25/1.96	3.3%	Beta (α :59; β :1,741)	visits*0.25/1.96	Byford 2011

References to sources: Byford 2011²⁵², PERFORM^{36,45,250}.

Appendix: Rationale for subgroup analysis between US and non-US trials

Over the past 2 to 3 decades, there has been a steady decline worldwide in the antidepressant-placebo difference in clinical studies.¹³⁷ In recent years, this decline appears to be particularly pronounced in studies conducted in the United States, although the reasons for this remain elusive. No single causative factor can be isolated to explain the differences between studies conducted in the United States and those conducted outside the United States. It does seem, however, that issues around study conduct, including patient selection and adherence to the protocol and IMP regimen, are critical. This smaller antidepressant-placebo difference is reflected in the studies in the vortioxetine clinical development programme conducted in the United States. In the population pharmacokinetic analysis of the phase II/III studies, the vortioxetine plasma concentrations were lower and more variable in US patients than in non-US patients (including a higher proportion of samples with plasma concentrations below the lower limit of quantification in US patients). This finding cannot be explained by demographics or other covariates and indicates poorer compliance by US. This finding may partially explain the smaller antidepressant-placebo difference observed in the US. Furthermore, in the pharmacokinetic/pharmacodynamic (PK/PD) analysis, region was a significant covariate, with worse efficacy in the United States than outside the United States.

It was therefore relevant to analyse the effect of vortioxetine based solely on the non-US studies, therefore, a meta-analysis was performed that only included Studies 11492A, 11984A, 305, 13267A, 14122A, and CCT002.

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Single Technology Appraisal (STA)

Vortioxetine for treating major depressive disorder

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CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report
Vortioxetine for treating major depressive disorder

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Rider on responsibility for report

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Contributions of authors

Mark Simmonds and Alexis Llewellyn wrote the clinical effectiveness sections of the report. James Lomas and Marta Soares wrote the cost effectiveness sections of the report and performed the economic modelling. Kath Wright wrote the sections of the report dealing with search strategies and provided information support. Alison Eastwood was an advisor for the clinical effectiveness sections and commented on drafts of the report. Stephen Palmer wrote the critique of manufacturer's definition of decision problem, was an advisor for the cost effectiveness sections, and commented on drafts of the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined

Table of Contents

List of abbreviations	9
1 Summary	10
1.1 Critique of the decision problem in the manufacturer's submission	10
1.2 Summary of clinical effectiveness evidence submitted by the manufacturer	11
1.2.1 Direct evidence in the switch population	11
1.2.2 Indirect evidence in the switch population	13
1.2.3 Evidence syntheses of non-switch populations	13
1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted	15
1.4 Summary of cost effectiveness submitted evidence by the manufacturer	17
1.4.1 Evidence used to inform the decision model	18
1.5 Summary of the ERG's critique of cost effectiveness evidence submitted	19
1.6 ERG commentary on the robustness of evidence submitted by the manufacturer	20
1.7 Weaknesses and areas of uncertainty	20
1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG	21
1.9 Conclusions from ERG analyses	22
2 Background	23
2.1 Critique of manufacturer's description of underlying health problem.	23
2.2 Critique of manufacturer's overview of current service provision	24
3 Critique of manufacturer's definition of decision problem	27
3.1 Population	27
3.2 Intervention	30
3.3 Comparators	32
3.4 Outcomes	37
3.5 Other relevant factors	38
4 Clinical Effectiveness	39
4.1 Critique of the methods of review(s)	40
4.1.1 Searches	40
4.1.2 Inclusion criteria	41
4.1.3 Critique of data extraction	42
4.1.4 Quality assessment	42
4.1.5 Evidence synthesis	42
4.2 Critique of the trials of vortioxetine	44
4.2.1 Critique of the validity of the included trials	44
4.2.2 Quality assessment and risk of bias	45
4.2.3 Characteristics of the REVIVE trial	47

4.2.4	REVIVE trial results	49
4.2.5	Characteristics of the TAK318 trial	53
4.2.6	TAK318 trial results	55
4.2.7	Conclusions from the review of vortioxetine RCTs	57
4.3	Indirect treatment comparison	58
4.3.1	Critique of trials identified and included in the indirect comparison	58
4.3.2	Critique of the network meta-analysis	61
4.3.3	Conclusions of the indirect treatment comparison	65
4.4	Non-RCT evidence	65
4.5	Adverse events	65
4.5.1	Short-term pool of placebo controlled studies	66
4.5.2	Open-label pool of continuation studies	69
4.5.2.1	Conclusions of the review of safety studies	71
4.6	Evidence syntheses of non-switch populations	72
4.6.1	Vortioxetine vs placebo	72
4.6.2	Vortioxetine vs active comparators	74
4.6.2.1	Pae et al.	74
4.6.2.2	Meeker et al.	76
4.6.2.3	PBAC submission	76
4.6.3	Indirect treatment comparison	77
4.7	Conclusions of the clinical effectiveness section	78
5	Cost Effectiveness	82
5.1	ERG comment on manufacturer's review of cost-effectiveness evidence	83
5.1.1	Searches	83
5.1.2	Inclusion/exclusion criteria used for study selection	83
5.1.3	Studies included and excluded in the cost effectiveness review	84
5.1.4	Conclusions of the cost effectiveness review	85
5.2	The manufacturer's economic evaluation compared with the NICE reference case checklist	89
5.3	ERG's summary and critique of manufacturer's submitted economic evaluation	90
5.3.1	Population	90
5.3.2	Model structure	90
5.3.2.1	Response and remission	95
5.3.3	Interventions and comparators	100
5.3.4	Perspective, time horizon and discounting	100
5.3.5	Treatment effectiveness and extrapolation	101
5.3.6	Relapse	104

5.3.7	Adverse events and withdrawals due to adverse events	104
5.3.8	Health related quality of life	106
5.3.9	Resources and costs	109
5.3.9.1	Overview	109
5.3.9.2	Acquisition costs	109
5.3.9.3	Health state costs	111
5.3.10	Discounting	113
5.3.11	Model validation and face validity check	113
5.3.12	Cost effectiveness results	115
5.3.12.1	Results from MS base case	115
5.3.12.2	Results from MS sensitivity analysis	115
5.3.12.3	Results from MS clarification scenarios	120
5.4	Conclusions of the cost effectiveness section	122
6	Impact on the ICER of additional clinical and economic analyses undertaken by the ERG	126
6.1	Overview	126
6.2	ERG initial corrections and adjustments to the manufacturer's base case model	127
6.3	Additional ERG analyses	129
6.3.1	Considering the broader effectiveness evidence	129
6.3.2	Examining alternative assumptions regarding the outcomes with further lines of therapy	135
6.4	Conclusions from ERG analyses	138
7	End of life	140
8	Overall conclusions	141
8.1	Clinical effectiveness	141
8.2	Cost effectiveness	142
8.3	Strengths, weaknesses and areas of uncertainty	144
8.3.1	Strengths	144
8.3.2	Weaknesses	144
8.3.3	Areas of uncertainty	145
8.4	Implications for research	146
9	References	147

Table of Tables

Table 1 RCTs included in the submission	11
Table 2 Summary of the results of the frequentist network meta-analyses	13
Table 3 Indirect treatment comparison by Llorca et al	14
Table 4 MS base-case results	19
Table 5 Alternative scenarios regarding relative effectiveness: cost-effectiveness (with up-titration) 21	
Table 6 Summary of vortioxetine	31
Table 7 Comparators outlined in NICE scope	33
Table 8 RCTs included in the submission	44
Table 9 Manufacturer assessments of quality for vortioxetine trials	47
Table 10 Study 14178A (REVIVE). Baseline characteristics of participants.....	49
Table 11 REVIVE trial results: remission and response.....	50
Table 12 REVIVE trial: Primary and secondary efficacy outcomes: scale score differences in mean change from baseline (MMRM)	52
Table 13 REVIVE trial: summary of adverse events reported over 12-week treatment period	52
Table 14 Study TAK318. Baseline characteristics of participants	55
Table 15 Characteristics of studies included in indirect comparisons	59
Table 16 Summary of outcomes from trials included in the main network meta-analysis	61
Table 17 Summary of the results of the frequentist network meta-analyses	63
Table 18 Summary of the results of the Bayesian network meta-analyses.....	63
Table 19 Summary of network meta-analysis reporting standardised mean differences.....	64
Table 20 Overview of pools for the evaluation of the safety and tolerability of vortioxetine	66
Table 21 Summary of TEAEs by dose (APTS)- Short-term pool	67
Table 22 TEAEs with an incidence of 2% or more by preferred term, core treatment period (APTS) - Short-term pool.....	68
Table 23 Incidence of TEAEs of $\geq 5\%$ in the open-label, long-term pool, core treatment period	70
Table 24 Summary of meta-analyses of vortioxetine vs. placebo	73
Table 25 Summary of results in the PBAC report	77
Table 26 Indirect treatment comparison by Llorca et al.	78
Table 27 NICE reference case checklist	89
Table 28 Time to 3 rd -line switch (Adapted from Table B47 MS).....	98
Table 29 Probability of remission and relapse assumed in the manufacturer model	102
Table 30 Percentage of patient who switch in the decision model (MS, base-case).....	103
Table 31 Percentage of patients who experience treatment-emergent adverse events in the acute phase	105
Table 32 Percentage of patients who withdraw from 2 nd line treatment due to AEs in the decision model (base-case, MS)	105

Table 33 Percentage of patients experiencing long-term adverse events.....	106
Table 34 Utility values derived from REVIVE trial	107
Table 35 Utility scores and clinical response during the study period, adapted from Sapin (2004)...	107
Table 36 Acute phase health utilities by analysis set and method	108
Table 37 Health state utilities for both acute and other phases of the decision model	108
Table 38 Costs and disutilities associated with adverse events	109
Table 39 Acute phase drug acquisition costs	110
Table 40 Post-acute phase drug acquisition costs	110
Table 41 Health state costs, adapted from MS Table B63	111
Table 42 Model outputs by clinical outcomes, for each comparator	114
Table 43 Cost-effectiveness results from MS base-case.....	115
Table 44 MS scenario and structural sensitivity analyses, adapted from MS Table B83	116
Table 45 2-month time horizon scenario results	121
Table 46 8-month time horizon scenario results	121
Table 47 24-month time horizon scenario results	121
Table 48 GP visit for switch set to zero scenario results	122
Table 49 Time to 3 rd -line switch (Adapted from MS Table B47).....	124
Table 50 Corrections to health utilities made by ERG	128
Table 51 Cost-effectiveness results: manufacturer base-case with revised utilities	129
Table 52 Alternative scenarios regarding relative effectiveness: proportion of remitters at 8 weeks	130
Table 53 Short-term adverse events probabilities for duloxetine and escitalopram	131
Table 54 Long-term adverse events probabilities for duloxetine and escitalopram	132
Table 55 Acquisition costs for duloxetine and escitalopram	132
Table 56 Alternative scenarios regarding relative effectiveness: cost-effectiveness (with up-titration)	133
Table 57 Alternative scenarios regarding relative effectiveness: cost-effectiveness (without up- titration)	134
Table 58 Alternative ICER estimates assuming same relapse rate and average remission rate of 2nd line treatments (with up-titration).....	137
Table 59 Alternative ICER estimates assuming same relapse rate and average remission rate of 2nd line with proportionate reduction based on STAR*D (with up-titration).....	138

Table of Figures

Figure 1 Typical course of an MDE (source: MS Figure A3)	24
Figure 2 Interpretation of NICE CG90 guidance, with vortioxetine position highlighted.....	25
Figure 3 Overview of clinical evidence for vortioxetine in adults with MDD (from MS, Figure A2) .	29
Figure 4 Modified treatment pathway from CG90 Guidance showing proposed positioning of vortioxetine.....	34
Figure 5 Pharmacological treatments prescribed for patients diagnosed with depression, by line of therapy (from MS, Figure A10).....	35
Figure 6 Kaplan Meir plot of time to first response (50% reduction in MADRS)	51
Figure 7 Study TAK318. Changes in clinical measures of depressive symptoms over 8 weeks of treatment with vortioxetine and escitalopram.....	56
Figure 8 Base-case network used in indirect treatment comparison.....	62
Figure 9 Forest plot of relative risk of TEAEs with an incidence of 2% or more by preferred term, core treatment period (APTS) - MDD Short-term pool.....	69
Figure 10 Forest plot of standardised mean difference based on data from Pae et al.....	75
Figure 11 Forest plot of response rate based on data from Pae et al.....	75
Figure 12 Forest plot of remission rate based on data from Pae et al.	76
Figure 13 Model schematic diagram (MS Figure B21)	92
Figure 14 Markov state transition diagram for modelled events following switch to third line (MS Figure B22).....	93
Figure 15 Diagrammatic representation of the course of an MDD episode (MS Figure A3, adapted from Bakish).....	93
Figure 16 Markov state transition diagram for modelled events following switch to third line.....	99

List of abbreviations

AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ANCOVA	Analysis of covariance
APTS	All patients treated set
BMI	Body mass index
CGI-I	Clinical Global Impression - Improvement Scale
CGI-S	Clinical Global Impression - Severity Scale
CI	Confidence interval
CSFQ-14	Changes in Sexual Functioning Questionnaire Short-Form
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
EMA	European Medicines Agency. Formerly abbreviated as “EMEA”.
EPAR	European Public Assessment Report
EQ-5D	EuroQoL Questionnaire 5-Dimension
FAS	Full analysis set
FDA	Food and Drug Administration
HAM-A	Hamilton Anxiety Rating Scale
HAM-D ₁₇	Hamilton Depression Rating Scale 17-item
HAM-D ₂₄	Hamilton Depression Rating Scale 24-item
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD-10	International Classification of Diseases
ITC	Indirect treatment comparison
ITT	Intention to treat
LOCF	Last observation carried forward
LREG	Logistic regression
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major depressive disorder
MDE	Major depressive episode
MMRM	Mixed model for repeated measures
OR	Odds ratio
PHQ-9	Patient Health Questionnaire
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SAE	Serious adverse event
SNRI	Serotonin–norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
XR	Extended release

1 Summary

1.1 Critique of the decision problem in the manufacturer's submission

Vortioxetine (brand name Brintellix®) is an antidepressant with a different mechanism of action to other antidepressants such as SSRIs and SNRIs, which has been claimed to act on a number of transmitter systems. The Committee for Medicinal Products for Human Use of the EMA granted marketing authorisation on 18 December 2013 for the treatment of major depressive episodes (MDE) in people with major depressive disorder (MDD).

The manufacturer's decision problem was substantially narrower than that of the NICE scope, primarily in terms of the population considered. The patient population was restricted to a subset of the licensed patient population; namely, only patients who responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who switched to an alternative antidepressant. This was referred to as the "switch population". The manufacturer justified this restriction by stating that the distinct pharmacological profile and favourable tolerability profile of vortioxetine may be particularly suitable in the switch population.

The ERG accepts that vortioxetine may be used in a switch population, however it is our view that presenting evidence only for the switch population represents an important limitation from both a clinical and cost-effectiveness perspective. The ERG considers that the appropriate population and potential position of vortioxetine should have been based on a broader consideration of the evidence for vortioxetine and other comparators.

The restriction to a switch population severely constrained the evidence presented. The submission presented only two trials directly comparing vortioxetine to other antidepressants. These two trials represent only 972 patients of over 7,000 patients included in studies of vortioxetine. Only four trials were included in the primary indirect comparison of treatments.

The final scope issued by NICE identified a wide range of relevant comparators including SSRIs, SNRIs, tri-cyclic antidepressants, other types of antidepressant and augmentation treatments. The restriction in scope to a switch population also meant that comparators were restricted primarily to those most likely to be used as second-line therapies, based on NICE guidelines, including SSRIs, SNRIs and newer-generation antidepressants. The restriction to consider only switch population evidence, and the small number of trials identified, meant that vortioxetine was compared directly only to agomelatine and escitalopram; and indirectly only to agomelatine, sertraline, venlafaxine (XR), bupropion and citalopram. In particular, no comparisons to duloxetine, fluoxetine or mirtazapine were made.

The final NICE scope included a range of relevant outcomes, including response to treatment, remission, relapse, symptoms severity, anxiety, cognitive dysfunction, sleep quality, health-related quality of life and a range of adverse events. The manufacturer reported relevant data for most of these outcomes in the two trials of vortioxetine, but the review of indirect evidence included only two outcomes (remission and withdrawal due to adverse events). This further limited the evidence on the relative efficacy, safety and cost-effectiveness of vortioxetine versus other active comparators.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The manufacturer's submission on clinical effectiveness included four systematic reviews: a review of RCTs of vortioxetine compared to active comparators in the switch population to evaluate efficacy; a review of non-RCT evidence of vortioxetine in the switch population; a review of adverse events of vortioxetine; and a review of indirect comparative evidence, again in the switch population, including an indirect treatment comparison and network meta-analysis of RCTs of other antidepressants, to evaluate efficacy and safety.

In response to the points for clarification, the manufacturer also provided meta-analyses of trials in the non-switch population.

1.2.1 Direct evidence in the switch population

As systematic review of RCTs of vortioxetine compared to active comparators in the switch population to evaluate efficacy was reported. It identified two trials, REVIVE and TAK318, summarised in Table 1. These trials were not combined in a meta-analysis because they were in different populations and used different comparators.

Table 1 RCTs included in the submission

Study	Regimen & duration	Comparator	Design	Follow-up duration	Primary outcome	Patient population
REVIVE (14178A)	Vortioxetine 10mg-20mg flexible dosing, 12 weeks	Agomelatine 25-50mg flexible dosing	Double-blind, international phase IIIb, parallel-group randomised trial	Efficacy: up to 12 weeks from baseline Safety: up to 16 weeks from baseline	Change from baseline in depression severity (MADRS total score) at week 8	Patients who have experienced an inadequate response to an SSRI or SNRI in their current MDE
TAK318	Vortioxetine 10mg-20mg flexible dosing, 8 weeks	Escitalopram 10-20mg flexible dosing	Double-blind, multicentre phase IIIb, parallel-group randomised trial	Efficacy: up to 8 weeks from baseline Safety: up to 12 weeks from baseline	Change from baseline in sexual functioning (CSFQ-14 total score) after 8 weeks of treatment	Patients who are well-controlled on an SSRI but experienced treatment emergent sexual dysfunction

MADRS: Montgomery and Åsberg Depression Rating Scale; CSFQ-14: Changes in Sexual Functioning Questionnaire Short-Form

The REVIVE trial was a well conducted trial comparing vortioxetine with agomelatine. The primary outcome in REVIVE was change in depression scores. Vortioxetine showed statistically significant superiority to agomelatine, reducing symptoms of depression. Average MADRS scores were 2.16 points lower on vortioxetine (95% CI 0.81 to 3.51) than on agomelatine after eight weeks.

Vortioxetine was also superior to agomelatine in terms of response rate using MADRS at 8 weeks (OR 1.81, 95% CI 1.26 to 2.60) and remission rate (OR 1.72, 95% CI 1.17 to 2.52).

Vortioxetine and agomelatine had similar rates of treatment-emergent adverse events (around 54%) and serious adverse events (around 1.5%), but vortioxetine had lower rates of adverse events leading to withdrawal (5.9% vs 9.5%).

The TAK318 trial compared vortioxetine with escitalopram. The primary outcome was sexual functioning measured using the CSFQ-14 scale. At 8 week treatment the mean change from baseline was 8.8 (SE 0.64) in the vortioxetine arm and 6.6 (SE 0.64) in the escitalopram arm. This difference was statistically significant in favour of vortioxetine ($p = 0.013$). The submission also reported difference between arms on the CSFQ-14 subscales; there was statistically significant evidence in favour of vortioxetine on all subscales presented.

No differences between vortioxetine and escitalopram were identified for changes in depression scales, response, relapse or remission rates. Adverse event rates were similar on both treatments.

A systematic review for non-RCT evidence was performed, but no relevant studies were identified.

A systematic review for safety trials in the switch population was performed but no trials were identified. The search was expanded to the general, non-switch population and five open-label extensions of vortioxetine trials were identified. On clarification the manufacturers also supplied adverse event data from 12 short-term placebo controlled trials of vortioxetine.

About 6% of patients had severe adverse events on vortioxetine compared to 4% on placebo in the placebo controlled trials. In the open-label extension trials 8.1% of patients had a serious adverse event. The manufacturer concluded that vortioxetine had a generally good safety profile. No data were submitted comparing adverse events using vortioxetine with other active treatments.

1.2.2 Indirect evidence in the switch population

The submission included a systematic review of treatments other than vortioxetine in the switch population used to perform an indirect treatment comparison with vortioxetine for efficacy and safety. This review identified seven trials. One was excluded on the grounds of poor trial quality. Two were placebo controlled trials not included in the primary network meta-analysis. Four trials were used in the primary network meta-analysis; there was only one trial included for each treatment comparison.

The outcomes of the network meta-analysis were remission rate and withdrawal rate due to adverse events. A range of models were fitted using different assumptions, including the placebo controlled trials and using both frequentist and Bayesian statistical methods. A summary of the results from the main frequentist analysis are shown in Table 2. Results from other analyses were broadly consistent with these results.

Table 2 Summary of the results of the frequentist network meta-analyses

	Remission rate			Withdrawal rate due to adverse events		
	Rate (%)	Risk Difference vs vortioxetine (%)	95% CI	Rate (%)	Risk Difference vs vortioxetine (%)	95% CI
Vortioxetine	40.5	–	–	5.9	–	–
Agomelatine	29.5	-11	-19.4 to -2.6	9.5	3.6	-1.1 to 8.3
Sertraline	26.1	-14.4	-29.9 to 1.1	18.0	12.1	3.1 to 21.1
Venlafaxine	33.3	-7.2	-24.3 to 9.9	18.2	12.3	0.8 to 23.8
Bupropion	29.8	-10.7	-27.8 to 6.4	24.2	18.3	6.4 to 30.1
Citalopram	23.7	-16.8	-41.1 to 7.5	18.0	12.1	-0.3 to 24.5

Vortioxetine had higher rates of remission than all other treatments, but results were only statistically significant for agomelatine. Vortioxetine also had lower rates of withdrawal due to adverse events than all other treatments, but results were only statistically significant for comparisons with sertraline, venlafaxine (XR) and bupropion. Due to the limited number of trials in the network, no assessments of heterogeneity or network inconsistency were performed.

1.2.3 Evidence syntheses of non-switch populations

As discussed in Section 1.1 the ERG questions the validity of restricting the analysis to switch populations. The ERG therefore requested that the manufacturer provide results from trials or meta-analyses of trials comparing vortioxetine to other active treatments and/or placebo in initial use and non-switch use populations. The manufacturer provided meta-analyses of their trials comparing

vortioxetine to placebo, but not for vortioxetine versus active comparators. The manufacturer also reported the existence of two submissions to regulators, four systematic reviews of vortioxetine trials and one indirect comparison of vortioxetine with other antidepressants.

The meta-analyses of trials submitted by the manufacturer and the four identified systematic reviews compared vortioxetine with placebo. There was considerable overlap in the trials included in the meta-analyses, and they reported different outcomes. However, all concluded that vortioxetine was superior to placebo.

Two systematic reviews and one regulatory submission (to the Pharmaceutical Benefits Advisory Committee of Australia) compared vortioxetine to other antidepressants by using active reference arms from placebo controlled trials. Active reference arms are included in trials of antidepressants to ensure that patients are responding to therapy. An active reference should be a drug of proven superiority over placebo, so it can be used to check whether the trial has successfully treated patients by confirming a difference between the active reference and placebo. After reanalysis by the ERG of data from one of these reviews (Pae et al. 2014) vortioxetine was found to be inferior to duloxetine in terms of changes in depression scores, response rate and remission rate. There was no evidence of a difference between vortioxetine and venlafaxine. Results from the other review and the regulatory submission were consistent with these results.

One systematic review (Llorca et al. 2015) performed an indirect comparison of vortioxetine with other antidepressants by analysing all placebo controlled trials of vortioxetine and other antidepressants. The results of the indirect treatment comparison are summarised in Table 3. This analysis found no statistically significant evidence of any difference in efficacy between vortioxetine and other antidepressants (except for agomelatine), but did find evidence that vortioxetine had a lower withdrawal rate due to adverse events than venlafaxine, desvenlafaxine and sertraline.

Table 3 Indirect treatment comparison by Llorca et al

	Results vs vortioxetine (Standard error)						
	Agomelatine	Desvenlafaxine	Duloxetine	Escitalopram	Sertraline	Venlafaxine	Vilazodone
Efficacy at 2 months (SMD: <0 favours vortioxetine)	-0.156 (0.113)	0.025 (0.803)	0.090 (0.419)	-0.054 (0.695)	-0.037 (0.832)	0.124 (0.328)	-0.245 (0.111)
Withdrawal (Odds ratio: <1 favours vortioxetine)	1.769 (0.030) *	0.578 (0.035) *	0.752 (0.262)	0.671 (0.275)	0.299 (0.008) **	0.469 (0.009) **	0.640 (0.181)

Response rate (Odds ratio: >1 favours vortioxetine)	1.045 (0.815)	1.153 (0.364)	0.893 (0.514)	0.843 (0.523)	0.772 (0.575)	0.789 (0.353)	0.975 (0.934)
Remission rate (Odds ratio: >1 favours vortioxetine)	1.220 (0.470) **	1.029 (0.852)	0.894 (0.526)	0.990 (0.981)	NA	0.689 (0.444)	0.983 (0.952)

* *p*-value 0.01 – 0.05; ** *p*-value <0.01

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The restriction to a switch population meant that only two trials comparing the efficacy of vortioxetine with other antidepressants were submitted. The REVIVE trial comparing vortioxetine to agomelatine found vortioxetine had greater short-term reduction in depression scores and lower withdrawal rates due to adverse events, but this result may not be reliable as this was a non-inferiority trial and was not powered to detect superiority of vortioxetine. It should also be noted that agomelatine is not approved for use in the UK as no evidence for its efficacy has been submitted. The TAK318 trial included patients who were switching due to sexual dysfunction but had responded to initial treatment. The ERG notes that this is a very narrow and specific population, so the TAK318 trial provided little information on the broader population who might take vortioxetine. It did find that vortioxetine reduced sexual dysfunction symptoms when compared to escitalopram. However it is not clear whether this finding is specific to vortioxetine, or whether any non-SSRI would have a similar beneficial effect. No efficacy evidence was submitted for the licensed 5mg vortioxetine dose.

Based on the safety evidence presented, vortioxetine appears generally safe and tolerable in patients with MDD. Most adverse were mild to moderate in intensity and there was no conclusive evidence that these were dose dependent. The submission did not present any safety comparisons of vortioxetine with any active comparators, so the safety profile of vortioxetine compared to other antidepressants is uncertain.

The ERG has considerable concerns over the validity of the network analysis because of the high apparent diversity in the populations across trials, with very different included patients and severities of depression. For one trial (Kasper) the analysis used a subset of patients who had been treated in the year prior to enrolment. This is not the same as patients who were switching treatment, so the ERG does not think this trial should have been included. The ERG questions the validity of the indirect treatment comparison, but notes that the analysis found no convincing evidence of difference between vortioxetine and other treatments in terms of remission rate (except for agomelatine). There was some

evidence that vortioxetine may have lower withdrawal rates due to adverse events, but the high apparent heterogeneity across trials means the validity of this finding is questionable.

Given the limited nature of the data in the switch population the ERG considers that data in non-switching and initial-use populations should be considered. Although such data is not in the switch population it is relevant to the broader population of all patients with MDD specified in the NICE scope. The manufacturer justified excluding trials of non-switching populations by claiming that treatment efficacy in a switch population may be different from in initial use. The ERG considers that the evidence submitted to justify this claim is limited and refers only to patients who had previously used an SSRI, where switching to another SSRI may be less effective than a non-SSRI treatment. No evidence was presented to suggest that the relative efficacy of non-SSRIs may vary between initial and switch use, and no evidence was specific to vortioxetine. The ERG therefore concludes that this restriction was inappropriate and evidence on non-switch populations is relevant when examining the efficacy and safety of vortioxetine.

Direct evidence comparing vortioxetine to other active treatments in non-switching populations was only available from short-term placebo controlled trials with active reference arms. The manufacturer has criticised the use of active references because they are not true randomised comparisons and patients known to be non-responsive to the reference are excluded, possibly biasing results in favour of the active reference. While the ERG accepts the potential for such bias it does not consider this potential bias to be substantial enough to exclude these trials. The ERG found no evidence of any difference in efficacy between vortioxetine and venlafaxine, based on two trials. There was evidence that vortioxetine was significantly inferior to duloxetine in terms of reducing depression scores, response and remission. While there is a possibility of bias in favour of duloxetine in these analyses it is not clear whether any bias would be sufficient to completely explain this inferiority.

An indirect treatment comparison in non-switch populations found no evidence of any difference in efficacy between vortioxetine and other treatments, but there was some evidence to suggest that vortioxetine had a lower withdrawal rate due to adverse events than some treatments, including sertraline and venlafaxine. While this is an indirect analysis, and not conducted in a switch population, the number of trials included in this analysis suggests that this may represent the most reliable evidence for comparing the efficacy and tolerability of vortioxetine to other treatments.

The ERG concludes, based on the totality of the evidence, that vortioxetine is likely to be of similar efficacy to other antidepressants, but may be superior to agomelatine and inferior to duloxetine. Vortioxetine appears to have a lower withdrawal rate due to adverse events than other treatments, and so may be more tolerable, however data on adverse events with vortioxetine, particularly when

compared to other antidepressants, are too limited to draw any firm conclusions on the safety of vortioxetine.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The MS presented evidence on the cost-effectiveness of vortioxetine in a primary care setting using only the following comparators: agomelatine, sertraline, citalopram and venlafaxine XR. Other relevant comparators, such as escitalopram or duloxetine, were excluded due to the absence of evidence in the switch population.

To evaluate cost-effectiveness, the MS presented a decision model that evaluated the progression of a single MDE. The model was based on treatment success defined in terms of remission at 8-weeks. It followed up patients for 12 months and considered three stages of disease progression: the acute phase (2 months duration), a maintenance phase (6 months duration), and a recovery phase (4 months duration). The model used a decision-tree to evaluate progression within second-line of treatment, and a separate Markov process to describe further lines of therapy that may subsequently be used.

The initial decision tree-structure was common to all patients during the initial acute phase period (0-2 months). During this period patients may achieve remission or they may withdraw from their current therapy due to short-term side-effects or failure to achieve remission. Patients achieving remission in the initial acute phase period subsequently continue within the main decision-tree structure. Between months 2 and 8, these patients subsequently follow additional pathways (or branches) covering the maintenance phase. During the maintenance phase, patients are assumed to stay on treatment (i.e. sustained remission) or they may stop treatment due to an adverse event or subsequent relapse. If patients sustain remission during the maintenance period, they enter the final part of the decision tree structure representing the recovery phase which covers the final 4 months of the total 12-month time horizon. Importantly, during the recovery period, the therapy is assumed to be discontinued and an assumption is made that patients are no longer at risk of relapse or recurrence.

The manufacturer's model assumed that a proportion of patients withdraw from treatment due to adverse events. In the acute phase, these patients were assumed to be non-remitters. The timing of many events within the decision tree was static – for example, all patients were assumed to withdraw one month into the maintenance phase and relapse three months into this phase. The final phase of the decision tree in the MS is the recovery phase. During this phase patients were no longer assumed to be treated with antidepressants. An important additional assumption was also made that patients no longer face a risk of relapse or incur any other NHS or PSS costs.

The separate Markov process was used to model subsequent lines of therapy, with the model allowing additional lines of treatment (i.e. covering 3rd, 4th and 5th lines line of therapy, since the initial therapy in the switching population is already the 2nd line of treatment in the overall management pathway). The effectiveness of further lines of therapy (3rd, 4th and 5th lines) is independent of the initial treatment strategy. The Markov model uses a 2-month cycle and each time a patient moves to the no remission state (including movements from the same state) they are switched to a further line of treatment.

1.4.1 Evidence used to inform the decision model

The main source of evidence on vortioxetine for the acute phase of treatment in the MS was the REVIVE trial. Because this only provided direct evidence for vortioxetine compared to agomelatine, the MS used an indirect comparison to infer remission and withdrawal rates against other comparators. The probability of relapse for the maintenance phase in 2nd line treatment was assumed to be the same for vortioxetine and all comparators, taken from Limosin (2004).

In the decision model, the probability of withdrawing from treatment in the acute phase due to AEs is informed by the indirect comparison. All patients that withdraw were assumed to be non-remitters. A different source of evidence was used to quantify the incidence of specific adverse events (sexual dysfunction, dry mouth, nausea, sweating, somnolence, headache, diarrhoea, insomnia and dizziness), so that associated costs and utility decrements could be evaluated. For agomelatine and vortioxetine REVIVE was used and for other treatments Cipriani (2010), Cipriani (2012) and pooled Cochrane reviews were used. Long-term adverse events considered were sexual dysfunction, insomnia and weight gain. Their incidence was informed by pooled long-term extension studies. It is assumed that if a patient has an adverse event then they will switch treatment with a probability of 25%.

Remission and relapse with further lines of treatment were informed by the blend of treatments used in STAR*D. This study reported that the probabilities of achieving remission and sustaining remission appear to decline in later lines of treatment, and within the MS these were assumed to be independent of the initial switch treatment received.

The MS considered different sources of evidence for utilities associated with short term health outcomes (up to 8 weeks), where the REVIVE trial was used, and longer term outcomes (after 8 weeks), where Sapin (2004) was used. The decision model considers a number of different resource use categories. Acquisition costs of drugs are taken from standard sources and applied to the dose of the drug (licensed dose in the acute phase and up-titration in the maintenance phase). Other cost categories considered were health state costs related to an MDE, which include GP, psychotherapist and psychiatrist consultations, in addition to hospitalisations.

Brief description of cost effectiveness results in the MS

The cost effectiveness results from the MS base-case are shown in Table 4. These results demonstrate that vortioxetine is both cheaper and more effective than agomelatine. Outcomes are driven by the ability to improve remission and the better adverse event profile assumed for vortioxetine.

Table 4 MS base-case results

	Venlafaxine	Vortioxetine	Citalopram	Sertraline	Agomelatine
Cost effectiveness					
Expected QALYs per patient	0.675	0.694	0.664	0.664	0.676
Expected costs per patient	£964	£971	£976	£977	£1,082
ICER	reference	£378	Dominated	Dominated	Dominated

The manufacturer also conducted a number of sensitivity analyses. The MS base case model was robust to the range of scenarios investigated.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The MS evaluated cost effectiveness for the switch population, and did not consider more fully the broader population and potential position of vortioxetine within current pathways. The MS included only relative effectiveness evidence on the switch population. Given the ERG deems the indirect comparison invalid, cost effectiveness evidence submitted (summarised in Table 4) is only interpretable for the comparison of vortioxetine and agomelatine. The ERG believes a broader evidence-base (including initial use) should have been considered to overcome these limitations.

The ERG has a number of additional significant concerns regarding the model structure employed by the manufacturer. Most importantly, the manufacturer's model does not explicitly consider response to treatment and instead only considers remission at 8 weeks. This does not seem to reflect clinically appropriate definitions of initial treatment success and subsequent clinical decisions.

As to the evidence used to describe further lines of treatment, the STAR*D study, the ERG considers that it includes treatments with limited overlap and that the patient population may not be generalisable. Also, the STAR*D shows a lower probability of achieving remission and a higher relapse rate for subsequent switches than expected in clinical practice. The ERG considers the use of separate sources of HRQoL data for particular inputs in the model appeared inconsistent.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

The submitted evidence examined the effectiveness of several relevant antidepressants compared to vortioxetine in the switch population. The submission covered the key clinical outcomes, including changes in depression scores, remission rate, withdrawal rate and incidence of adverse effects. Appropriate statistical methods were used to perform a network meta-analysis and suitable sensitivity analyses were performed.

The ERG considers the manufacturer presents cost effectiveness evidence for vortioxetine for a restrictive case regarding second line use in a primary care setting. The decision model used by the manufacturer seems to broadly reflect the progression of an MDE, and the ERG considers that the use of 12-month horizon appears reasonable for the 'average' patient given that the average duration of an untreated MDE is considered to be between 5-6 months.

1.7 Weaknesses and areas of uncertainty

The ERGs primary concern with the evidence submitted is related to the manufacturer's decision to restrict the submission to a switch population, rather than all patients with MDD as specified in the scope. This restriction meant that only two trials comparing vortioxetine to other antidepressants were presented. One compared vortioxetine to a drug not licenced in the UK, and the other was focused only on patients with SSRI treatment-emergent sexual dysfunction. Therefore neither appeared representative of most UK patients likely to be switching antidepressant treatments. The trials included in the network meta-analysis were very diverse in both the populations included and in their results. The ERG concludes that, as a result, this analysis did not present reliable evidence on the relative efficacy of vortioxetine compared to other antidepressants.

The manufacturer assumed that the most appropriate position of vortioxetine is as a second-line treatment. The ERG's view is that the manufacturer should have developed a more flexible model which was capable of assessing the value of vortioxetine in alternative positions within current treatment pathways. The manufacturer based their economic analysis on relative effectiveness evidence specifically related to the switch population. The ERG, however, feels that the broader evidence base on initial use of vortioxetine and comparator treatments should have also been considered.

The ERG considers there are significant uncertainties concerning both the decision rule applied and the assumption that only patients who achieve remission at 8 weeks will be continued on their initial therapy, and the use of 8-week data to inform switching decisions at an earlier time point. The ERG suggests that STAR*D may impose a worse prognosis to further lines of therapy (i.e. a lower remission rate and higher relapse rate) than what might be expected for the population of interest.

Also, the ERG considers the use of separate sources of HRQoL data for particular inputs appeared inconsistent and potentially optimistic towards the cost-effectiveness of vortioxetine.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG explored some of the key issues and uncertainties on the manufacturer's cost-effectiveness analysis.

First, the ERG revised the manufacturer base-case to correct issues found with the utility scores, namely the use of a single source of evidence (the REVIVE study). The proposed corrections appear to have only minimal effect on the QALY estimates. The second analyses undertaken by the ERG was to consider the broader evidence base on the relative effectiveness of vortioxetine and comparator treatments using three scenarios: scenario 1 uses placebo controlled trials (Llorca et al.); scenario 2 uses direct evidence (Pae et al.); and scenario 3 assumes equal effectiveness. Table 5 reports the results of these analyses.

Table 5 Alternative scenarios regarding relative effectiveness: cost-effectiveness (with up-titration)

	Costs	QALYs	Incremental Costs	Incremental QALY	ICER	
					w SSRI (incremental analyses, in relation to next best)	w/o SSRI (in relation to ref)
Scenario 1: Llorca						
Venlafaxine (XR)	£885	0.736	Ref	Ref	Ref	ref
Escitalopram	£887	0.729	£3	-0.007	Dominated	--
Vortioxetine	£971	0.733	£83	0.004	Dominated	Dominated
Duloxetine	£1,032	0.730	£61	-0.003	Dominated	Dominated
Agomelatine	£1,069	0.728	£36	-0.002	Dominated	Dominated
Scenario 2: Pae						
Venlafaxine (XR)	£919	0.728	Ref	Ref	Ref	NA
Vortioxetine	£971	0.733	£52	0.006	£9,191	NA
Duloxetine	£1,017	0.737	£46	0.003	£13,393	NA
Agomelatine	£1,088	0.717	£71	-0.020	Dominated	NA
Scenario 3: Equal Effectiveness						
Escitalopram	£889	0.729	ref	Ref	Ref	--
Venlafaxine (XR)	£929	0.725	£40	-0.003	Dominated	ref
Vortioxetine	£971	0.733	£42	0.008	£18,188	£5,318
Duloxetine	£1,039	0.727	£68	-0.006	Dominated	Dominated
Agomelatine	£1,059	0.734	£20	0.007	£128,927	£128,927

The results are clearly sensitive to the assumptions made concerning the relative effectiveness of the alternative treatments in achieving remission. In Scenario 1, venlafaxine (XR) dominates vortioxetine

and the other comparator treatments: the higher remission probabilities assumed for venlafaxine (XR) appear to more than offset any additional benefits attributed to vortioxetine and/or other comparator treatments in terms of adverse events. In Scenario 2, venlafaxine (XR) remains the lowest cost strategy but no longer dominates vortioxetine and duloxetine. The most cost-effective treatment in Scenario 2 is now duloxetine which has an ICER of £13,393 compared to vortioxetine. In Scenario 3, when all treatment are assumed to be equally effective in terms of achieving remission at 8-weeks, the differences are now driven entirely by the different acquisition costs and the assumptions related to adverse events. Within this scenario escitalopram is now the lowest cost strategy and appears to dominate venlafaxine (XR). The ICER of vortioxetine is £18,888 per QALY compared to escitalopram. When escitalopram is excluded from consideration, venlafaxine (XR) is now the cheapest strategy and the ICER of vortioxetine is £5,318 per QALY compared to venlafaxine (XR). These results are, however, sensitive to assumptions related to the effectiveness of subsequent lines of therapies tested by the ERG.

1.9 Conclusions from ERG analyses

The ERG's exploratory analyses have demonstrated the cost-effectiveness results for vortioxetine presented by the manufacturer are contingent on the assumption that vortioxetine is the most effective initial switch treatment in terms of remission. Given the higher acquisition cost of vortioxetine relative to other SSRI therapies and venlafaxine (XR), the cost-effectiveness of vortioxetine was only clearly evident in those scenarios where it was assumed that vortioxetine was more or equally effective in achieving remission. However, when the effectiveness estimates were based on a broader set of trials than those considered by the manufacturer, the cost-effectiveness of vortioxetine was less evident. Across all of scenarios tested by the ERG, differences in terms of tolerability have been assumed, i.e. additional benefits with vortioxetine from improved tolerability and/or reductions in adverse events (short and longer-term).

2 Background

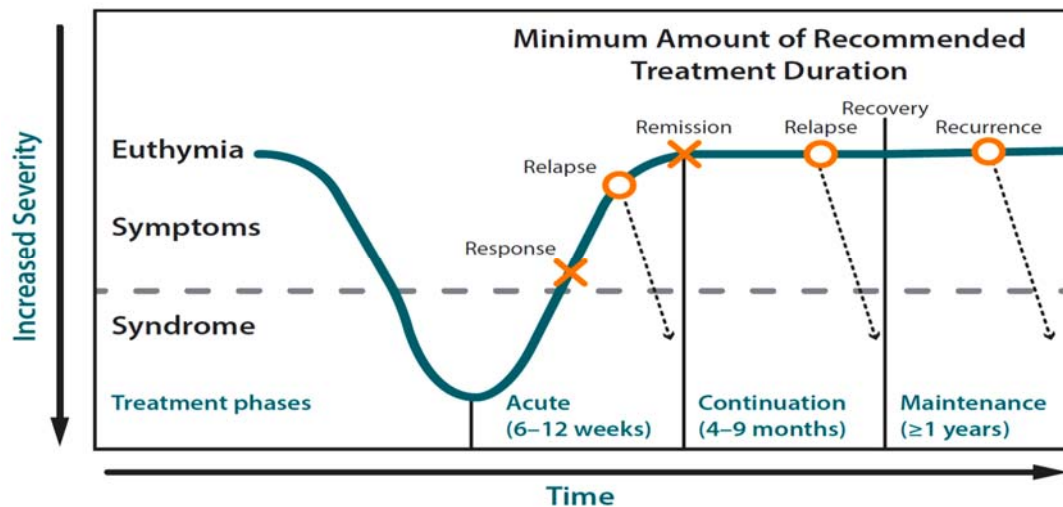
2.1 Critique of manufacturer's description of underlying health problem.

The manufacturer presents a suitable summary of major depressive disorder (MDD) and major depressive episodes (MDE) in manufacturer's submission (MS) sections 2.1 to 2.3; this includes their definition, progression over time, impact on health and quality of life and the impact and cost to the NHS and society in general.

The submission recognises that the terms MDD and MDE are based on standard classifications from the Diagnostic and Statistical Manual of Mental Disorders (DSM); these are used to describe depression in the USA where terminology may differ slightly from that used in the UK, where the terms mild/moderate/severe depression are more commonly used. The submission notes that MDD/MDE are approximately equivalent to moderate to severe depression as defined by NICE guidance.⁽¹⁾ An MDE is defined as the occurrence of depressed mood or a loss of interest or pleasure in life activities for at least two weeks, at least five of the nine core symptoms of depression and at least one significant impairment in social functioning (list provided in submission) occurring almost every day. Left untreated an MDE may last for two months to several years, but this may be greatly reduced by treatment.⁽²⁾ The course of an MDE is characterised by five events: response, remission, recovery, relapse and recurrence,⁽³⁾ as summarised in Figure 1. A patient whose symptoms improve sufficiently on treatment is considered to be responding, and is judged to be in remission when core symptoms of depression cease or are considered very minor. Patients remaining in remission for sufficient time are judged to have recovered. NICE recommends continuing treatment for at least six months following remission, and treatment may be continued for longer (two years or more) in cases of recurrent MDEs.⁽¹⁾ A patient may relapse at any time if symptoms worsen. If symptoms re-occur after recovery this is judged to be a recurrence and constitutes a new MDE. Relapse and lack of response are common, with approximately one-third to one half of patients not responding adequately to treatment,^(4, 5) and at least half of all patients experiencing their first MDE will go on to have at least one more episode within the next ten years.⁽⁶⁾

The submission discusses the potential health impacts of depression, particularly the substantial loss of quality of life and potential reduction in life expectancy, including increased risk of suicide, and its impact on family members. The costs associated with depression are substantial, with 1.24 million people estimated to have depression in England, costing the NHS £1.68 billion, and averaging £2,805 per person.⁽⁷⁾ The submission also noted the substantial wider economic cost of depression due to increased sick leave and absenteeism from work, and reduced productivity.

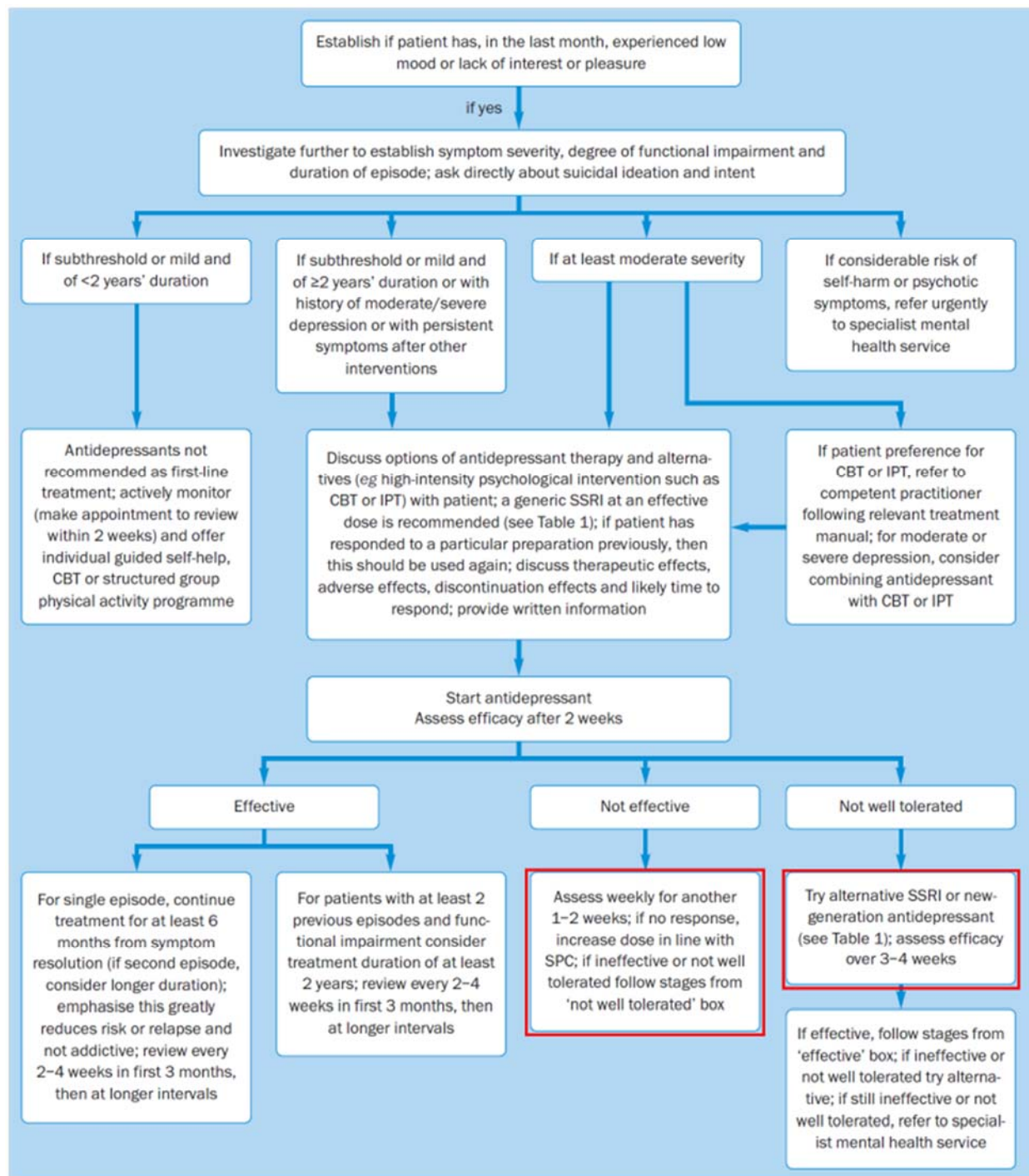
Figure 1 Typical course of an MDE (source: MS Figure A3)



2.2 Critique of manufacturer's overview of current service provision

The submission presents a generally suitable summary in MS sections 2.5 and 2.6 of current clinical practice and service provision with reference to the most recent NICE guidelines, specifically Clinical Guidance 90 (CG90, 2010).(1)

The current NICE guidelines (CG90) are summarised in Figure 2**Error! Reference source not found.** (taken from MS, figure A5). These recommend that patients with moderate or severe depression, but without psychotic symptoms or risk of self-harm, should be offered an SSRI and/or a high-intensity psychological intervention (for example, cognitive behavioural therapy or interpersonal therapy). If the SSRI is not tolerated or has been judged ineffective after at least four weeks of use then patients may switch to another SSRI or to another new-generation antidepressant, or be given the option of increasing their dose if well tolerated and if there is some evidence of initial response. If this second-line treatment is ineffective a third may be tried and/or patients should be referred to a specialist mental health service. As vortioxetine is not an SSRI, the manufacturers have proposed that vortioxetine be considered for this second-line therapy where initial SSRI treatment is unsuccessful (see highlighted section of Figure 2).

Figure 2 Interpretation of NICE CG90 guidance, with vortioxetine position highlighted

Rates of response and remission with antidepressants are low with around 50% response to initial SSRI treatment after eight weeks.⁽⁵⁾ Remission rates decline for second-line, third-line and subsequent treatments. Antidepressants are also associated with high levels of adverse effects, with an estimated 16% of patients on SSRIs experiencing intolerable side effects. Consequently treatment

adherence is poor, with high rates of discontinuation. Many patients also switch treatments due to poor efficacy or side effects, with around 15% of patients on first-line SSRIs switching treatments.(8)

There are currently a wide variety of antidepressant drugs available with a variety of modes of action and varying efficacy and side-effect profiles. Given the low response rates and high rates of side effects, the ERG agrees with the manufacturer's opinion that there is a need for new treatments with favourable efficacy and side-effect profiles for patients who fail initial SSRI therapy.

3 Critique of manufacturer's definition of decision problem

3.1 Population

The population described in the final NICE scope is adults with major depressive disorder, reflecting the licensed population. Vortioxetine has a marketing authorisation in the UK for the treatment of major depressive episodes in adults. However, the patient population considered by the manufacturer was restricted to a subset of the licensed patient population, namely:

“adult patients with moderate-to-severe MDD who are experiencing an MDE, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to alternative antidepressant” (MS, p14).

The manufacturer cites the burden of initial treatment failure on patients, the health service and wider society to highlight the potential unmet clinical and economic need for more effective and better-tolerated options for patients requiring a switch of treatment where initial antidepressant treatment has failed. The manufacturer further justifies this restriction, stating that the distinct pharmacological profile and favourable tolerability profile of vortioxetine may be particularly suitable in the “switch population”. This switch population is further defined by the manufacturer (MS, p38) as:

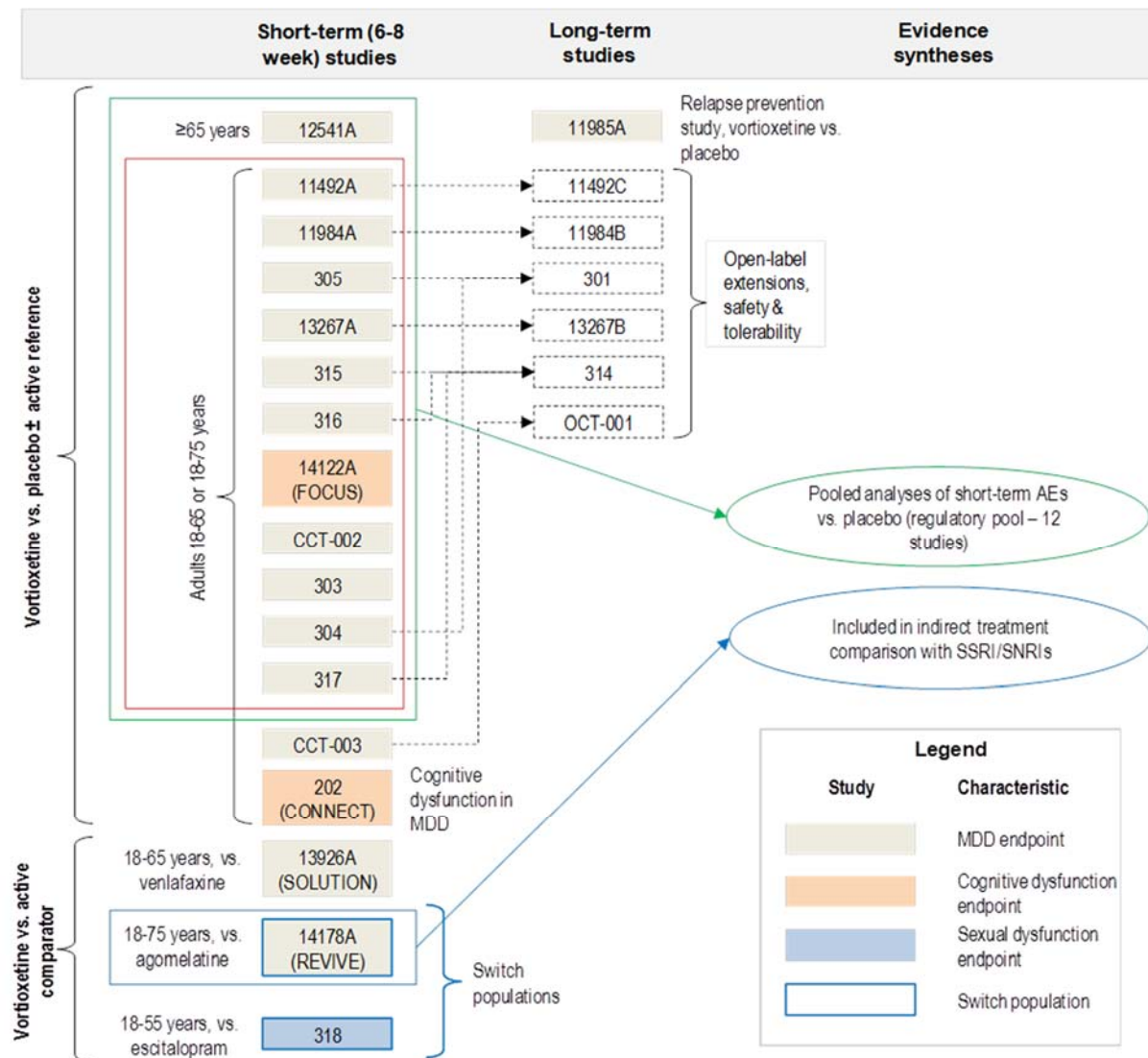
- *Patients who are experiencing a moderate-to-severe MDE, and*
- *whose current episode has been treated initially with an SSRI or SNRI, and*
- *who are candidates for a switch in the clinician's opinion, and*
- *who wish to change antidepressant treatment because of inadequate response or intolerability to the initial treatment.*

Although vortioxetine has been studied in 24 completed trials involving over 7,000 patients, the manufacturer's submission focuses largely on 2 studies considered relevant to the decision problem; Study 14178A (REVIVE) and TAK318. These studies are subsequently used as the basis for short-term efficacy and tolerability data. Longer-term safety studies from a broader population including non-switch patients are also presented in the manufacturer's submission based on the assumption that tolerability and safety data are likely to be generalisable to a switch population. Based on clinical advice, the ERG considers this assumption to be appropriate for safety, but not for tolerability, as patients intolerant of one medication may be more intolerant of others.

The population considered within the manufacturer's submission is thus significantly restricted compared to the broader population stated in the final NICE scope and the licensed indication for vortioxetine. However, such a restriction is potentially consistent with the “Other considerations” section specified in the NICE scope which states that: *“If evidence allows the subgroup of people with*

moderate or severe major depressive disorder will be considered” and “If evidence allows the clinical and cost effectiveness of vortioxetine may be considered in different positions in the treatment pathway.”

Although the ERG acknowledges the justification provided by the manufacturer for restricting the patient population, it is our view that this represents an important limitation from both a clinical and cost-effectiveness perspective. The ERG considers that the appropriate population and potential position of vortioxetine should have been more formally demonstrated by the manufacturer, based on consideration of the full evidence base for vortioxetine and other comparators, rather than restricting the decision population and evidence base from the outset. Figure 3 provides an overview of the existing clinical evidence for vortioxetine that clearly highlights the select evidence base which subsequently underpins the manufacturer’s submission.

Figure 3 Overview of clinical evidence for vortioxetine in adults with MDD (from MS, Figure A2)

The manufacturer assumed that the MDE/MDD population considered within their submission is consistent with the terminology “moderate-to-severe depression” used in NICE CG90. This was justified on the basis that the patients included in the short-term phase III studies of vortioxetine had moderate-to-severe MDD, and that patients in the REVIVE study had a mean MADRS total score at study entry of 29 points (ranging from 22 to 43 points), indicating moderate-to-severe depression. The manufacturer detailed subsequent responses to the EMA based on the assertion in the CHMP that fully responsive patients could have been included in the study, since the severity of depression was not assessed prospectively at the onset of the first monotherapy during the lead-in period. The manufacturer reported that they considered that the absence of a baseline score prior to the initial treatment phase did not invalidate the population definition. They further stated that:

“The requirement of a baseline MADRS total score at study entry ≥ 22 implies that patients fully responsive to previous treatment would need to have a total score ≥ 44 prior to the initiation of the previous treatment. Patients with a MADRS total score ≥ 44 points are very rare: only 0.6% of the patients included in all the short term placebo-controlled studies in the clinical programme in MDD with vortioxetine had such a high MADRS total score” (MS, p23).

3.2 Intervention

The marketing authorisation for vortioxetine licenses it for the treatment of major depressive episodes (MDE) in adults. The marketing authorisation only covers MDEs that are associated with major depressive disorder (MDD), but not with other distinct indications such as bipolar disorder. As previously highlighted, the manufacturer’s decision problem addresses a subset of the population included in the marketing authorisation and the NICE scope.

The CHMP has recently adopted a positive opinion for a Type-II variation related to the update of the SmPC for vortioxetine. The update of the SmPC provides new data on vortioxetine related to its effect on certain aspects of cognitive function and patient functioning. The application was based primarily on data from the recently completed CONNECT trial (referred to in MS, Sections 1.4 and 4), in addition to four clinical studies that were previously submitted as part of the original approval process, as well as a newly completed clinical pharmacology functional magnetic resonance imaging (fMRI) study in remitted patients with depression. The ERG does not consider that this variation has any significant implications for the stated decision problem.

Table 6 provides a summary provided by the manufacturer (MS, Table A1, p.28) regarding the formulation, cost, method of administration, posology and information of length of course (including repeat), dose adjustment and use in special populations. The manufacturer also reported that the EMA has accepted a risk management plan, which includes a non-interventional post-authorisation safety study (PASS) of vortioxetine in Europe.

Table 6 Summary of vortioxetine

Pharmaceutical formulation	Film-coated tablets, 5mg, 10mg, 20mg. (Also approved but not available: 15mg tablets).
Pack sizes	5mg x 28 10mg x 28 20mg x 28
Acquisition cost (excluding VAT)	5mg x 28: £27.72 per pack 10mg x 28: £27.72 per pack 20mg x 28: £27.72 per pack
Method of administration	Oral
Posology	The starting and recommended dose is 10mg once daily in adults less than 65 years of age. The lowest effective dose of 5mg vortioxetine once daily should always be used as the starting dose in patients ≥ 65 years of age.
Average length of a course of treatment	After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response (see SmPC).
Average cost of a course of treatment	Approximately £220 for patients who achieve remission after an acute phase of treatment, assuming treatment is continued for 240 days or 8 months (assumed 8 weeks in acute phase and 6 months' consolidation) in total.
Expected average interval between courses of treatments	According to need, depending on whether remission is sustained through the recommended period of maintenance treatment or whether an MDE recurs. (See section 2.1 for additional information on the course of disease).
Expected number of repeat courses of treatments	According to need, depending on recurrence of MDEs. Recurrence of episodes is a feature of MDD, but the course of disease is highly variable (see section 2.1).
Dose adjustments	Depending on individual patient response, the dose may be increased to a maximum of 20mg once daily or decreased to a minimum of 5mg once daily. Adjustments are normally made early in treatment with assessment of response and tolerability at 2-4 weeks.
Special populations	The lowest effective dose of 5mg vortioxetine once daily should always be used as the starting dose in patients ≥ 65 years of age. Caution is advised when treating patients ≥ 65 years of age with doses higher than 10mg vortioxetine once daily for which data are limited. Dose adjustments may be considered in patients taking concomitant medications that induce or inhibit the P450 cytochrome system (see SmPC for details). The safety and efficacy of vortioxetine in children and adolescents aged less than 18 years has not been established.
Additional tests or investigations needed to identify suitable patients, or particular administration requirements	None.
Monitoring	Usual clinical practice for antidepressants (see Figure A5).

Other therapies likely to be administered at the same time as the intervention as part of a course of treatment	Antidepressant therapy may be provided in combination with a high-intensity psychological intervention, such as cognitive behavioral therapy or interpersonal therapy.

VAT: value-added tax; SmPC: Summary of Product Characteristics; MDE: major depressive episode; MDD: major depressive disorder

The ERG considers that the existing clinical pathways appear a reasonable interpretation of NICE CG90. However, as previously stated by the ERG, uncertainty exists surrounding the optimal position of vortioxetine within these pathways. Although the manufacturer has stated their preferred position of vortioxetine and defined their decision problem accordingly, the ERG considers that the focus on a restricted decision problem from the outset represents an important limitation of the submission. The ERG considers that the appropriate population and potential position of vortioxetine should have been more formally demonstrated by the manufacturer, based on a broader consideration of the evidence base for vortioxetine and other comparators. Consequently, by focusing entirely on the switch-population, the manufacturer subsequently excludes evidence from 22 of the 24 completed studies of vortioxetine, on the basis that these studies were not conducted in the population of interest. As a result, only the REVIVE and TAK318 trials are included on the basis that these provide direct evidence for the efficacy of vortioxetine in patients who switch from an initial SSRI or SNRI within an MDE and therefore address the decision problem. However, these 2 trials represent only 880 patients of the total of over 7,000 patients included within the completed set of vortioxetine studies.

3.3 Comparators

The NICE scope listed a broad set of comparators in line with the marketing authorisation in the UK for vortioxetine, including “SSRIs, tricyclic and tricyclic-related antidepressants, SNRIs, other antidepressant drugs and augmentation treatments”. The full list of comparators included in the NICE scope are summarised in Table 7.

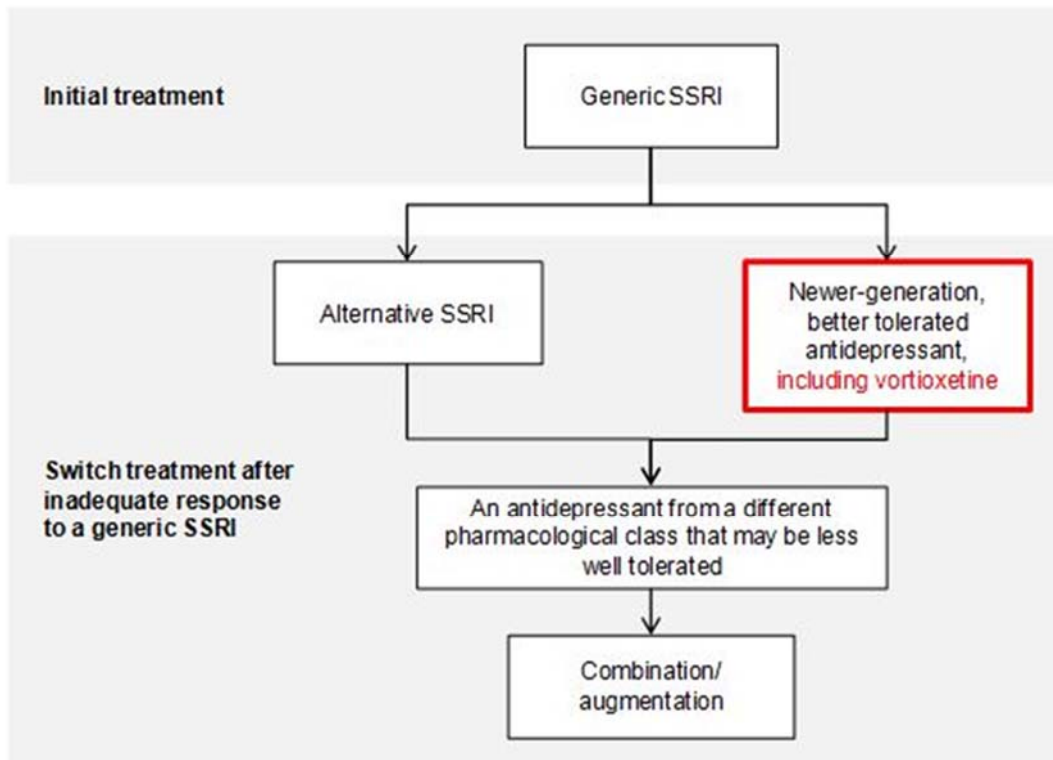
Table 7 Comparators outlined in NICE scope

- | |
|--|
| <ul style="list-style-type: none"> • Selective serotonin reuptake inhibitors (for example citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) • Tricyclic antidepressants (for example clomipramine, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, and amitriptyline) • Tricyclic-related antidepressants (for example mianserin and trazodone) • Serotonin and noradrenaline reuptake inhibitors (for example venlafaxine, duloxetine and levomilnacipran) • Other antidepressant drugs (for example agomelatine, mirtazapine, reboxetine and nonreversible mono-amine oxidase inhibitors [such as phenelzine]) • Augmentation treatments (for example, with an antipsychotic such as quetiapine) |
|--|

The manufacturer significantly restricted the number of eligible comparators only including those which they considered represented alternatives in the proposed switch population (see Section 3.1 above).

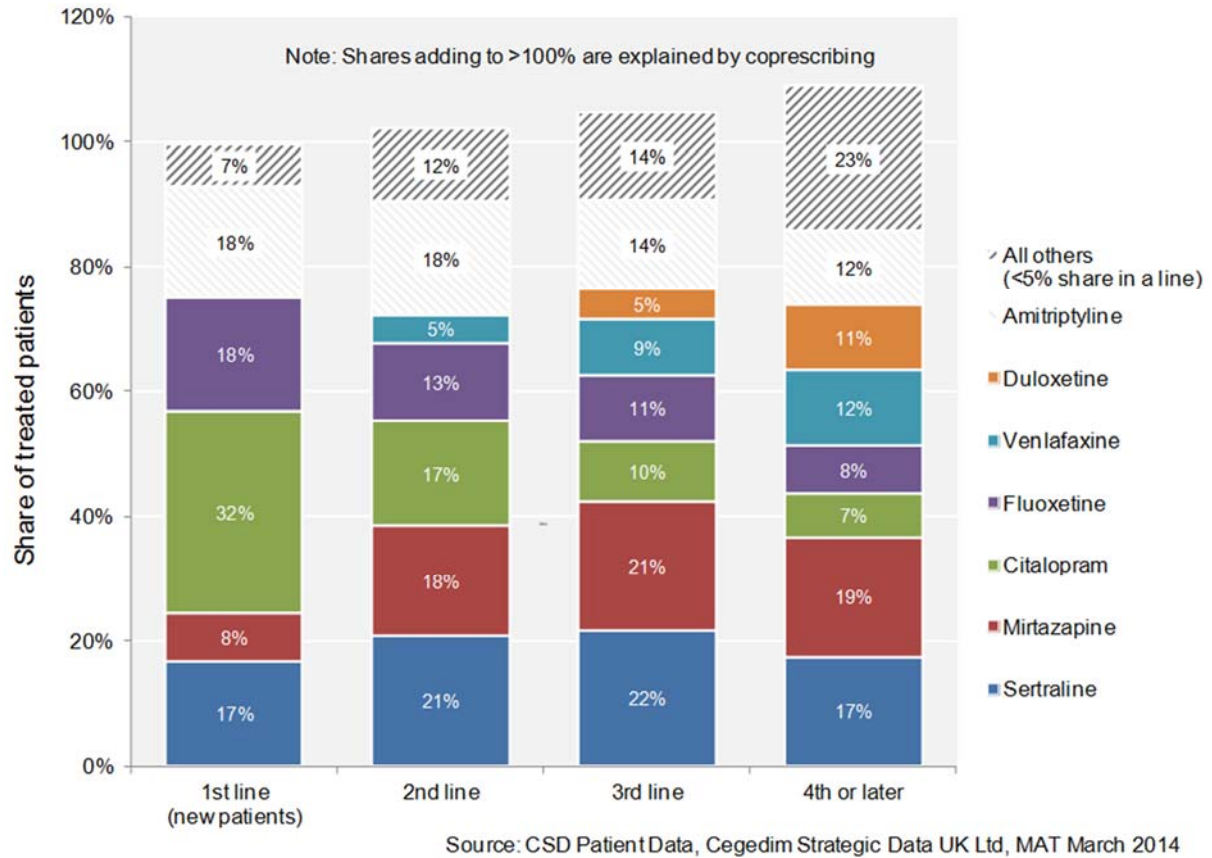
The justification for the choice of comparators provided by the manufacturer was based on the recommendations of NICE clinical guidelines (CG90), clinical opinion and prescribing data in the UK(9), and was reported in MS section 2.7, pp.45-48. Clinical practice recommendations within CG90 state that when switching to another antidepressant, clinicians should consider switching initially to a different SSRI or a better tolerated newer-generation antidepressant and subsequently to an antidepressant of a different pharmacological class that may be less well tolerated, for example venlafaxine, an older TCA (e.g. amitriptyline) or an MAOI (e.g. phenelzine).

The manufacturer stated that the tolerability profile of vortioxetine, supported by the clinical efficacy data available within this population, was consistent with positioning within the category described in CG90 as: “*a better-tolerated newer-generation antidepressant*”. They further stated that proposed positioning of vortioxetine within existing pathways, summarised in Figure 4, also reflects the common practice of switching to an agent with a differing mechanism of action.

Figure 4 Modified treatment pathway from CG90 Guidance showing proposed positioning of vortioxetine

Based on these guidelines, the main comparators for vortioxetine as an initial switch therapy were stated by the manufacturer to be SSRIs and better tolerated, newer-generation antidepressants. The SNRIs (e.g. venlafaxine), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were argued by the manufacturer to be reserved for subsequent switches, as they “*may be less well tolerated*”. Combination/augmentation of antidepressants was not considered to be a relevant comparator in this submission by the manufacturer. These were excluded on the basis that they tend to increase the side-effect and drug interaction burden, and that this strategy should only normally be started in consultation with a consultant psychiatrist.

To further inform the selection of the most relevant comparators in the initial switch position, the manufacturer analysed market share data for the 12-month period April 2013-March 2014 to establish the market share for individual antidepressants by line of treatment. This data is summarised in Figure 5.

Figure 5 Pharmacological treatments prescribed for patients diagnosed with depression, by line of therapy (from MS, Figure A10)

The manufacturer considered that the second-line (i.e. first-switch) data best reflected the initial switch population where the use of vortioxetine is proposed. Based on CG90, market share data and clinical opinion (i.e. the manufacturer concluded that the rates of prescribing for amitriptyline seemed implausibly high), the manufacturer specified the most appropriate comparators as (listed in descending order of second-line market share):

- Sertraline (SSRI)
- Mirtazapine (other)
- Citalopram (SSRI)
- Fluoxetine (SSRI)
- Venlafaxine (SNRI)

The manufacturer conducted systematic reviews (MS, Sections 6.1 and 6.7) to identify data to facilitate direct or indirect comparisons between vortioxetine and these comparators when used as second-line therapy. Studies were identified to support direct comparison with agomelatine (i.e. the comparator treatment in the REVIVE study) and indirect comparison with sertraline, citalopram and venlafaxine. No data were subsequently found to enable a valid comparison with mirtazapine or

fluoxetine in second-line use. While the manufacturer consider their inclusion would be desirable, they concluded that their absence was unlikely to be critical due to efficacy/cost considerations (i.e. they expected that fluoxetine would be dominated by other included SSRIs) and tolerability issues in a second-line setting (mirtazapine).

It is evident in subsequent sections of the ERG report that restricting the trial evidence to switching populations constrains both the evidence base considered as well as subsequent approaches to estimating comparative efficacy data to inform subsequent decisions. Similar concerns regarding the exclusion of potentially relevant evidence were reported by the Cochrane Depression Anxiety and Neurosis group as part of their comments on the draft scope. The group stated that:

“It’s interesting to note that placebo is not mentioned as a comparator. On the one hand we would support this as a goal, as from a policy and clinical perspective, it is important to establish how vortioxetine compares with all other antidepressants. On the other hand, we would expect that excluding placebo controlled studies as comparators will lead to the exclusion of most randomized comparisons. Although we wouldn’t challenge the key comparisons being made here, we do wonder if the scope should be widened to make best use of the available data on Vortioxetine, by considering placebo controlled trials as part of a network meta-analysis. This will enable NICE to consider all the comparative data to inform decision-making.” (Response to consultee and commentator comments on the draft scope, p.4)(10)

No change in scope was proposed in response to these comments on the basis that no treatment (placebo) is not established practice in the UK. However, importantly NICE also stated that:

“Placebo does not need to be included as a comparator in the scope in order for the company to be able to conduct a network meta-analysis including studies that compare the intervention with placebo”. (Response to consultee and commentator comments on the draft scope, p.4)(10)

Importantly the existing clinical guideline (CG90) highlights additional uncertainties surrounding the interpretation of switching trials for comparator treatments as they often either include patients who may be expected to fare poorly on one of the treatments or employ a cross-over design. Furthermore, CG90 also concluded that the evidence for the relative advantage of switching either within or between classes is weak and that evidence from primary efficacy studies of existing treatments should also be considered. Consequently, in summarising the existing evidence and formulating guidance, the guideline group concluded that:

“Given the paucity of evidence from switching studies, evidence from primary efficacy studies in which antidepressants were directly compared were also considered. Caution is required in extrapolating from these studies to those whose illness has not responded to sequential trials of antidepressant drugs. Data from switching studies and head-to-head studies suggest that there may be a very small efficacy advantage for venlafaxine and escitalopram over other antidepressants. This advantage is too small to be clinically meaningful when all people with depression are considered together, but may be large enough to be clinically worthwhile in those who have not benefited from treatment with a first or second antidepressant. However, the current evidence is not sufficiently robust to form the basis of a recommendation”. (NICE CG90, p.479)(1)

The issues are further explored in subsequent sections of the ERG report.

3.4 Outcomes

The outcomes listed in the NICE scope were as follows:

- response to treatment (including response rate and time to response)
- relapse (including relapse rate and time from remission to relapse)
- severity of depression
- cognitive dysfunction
- remission of symptoms
- anxiety
- sleep quality
- hospitalisation
- mortality
- adverse effects of treatment (including adverse effects of treatment discontinuation)
- health-related quality of life

The manufacturer reported relevant data for most of these outcomes in the two trials of vortioxetine (REVIVE and TAK318). However, no data were reported on relapse, cognitive dysfunction, and sleep quality in REVIVE; in TAK318, no data on cognitive dysfunction, anxiety or sleep quality were presented, and no health-related quality of life outcomes, other than related to sexual dysfunction, were reported. The manufacturer stated that data for these outcomes had not been collected.

The primary outcome of the REVIVE trial was change from baseline in depression symptoms severity, which is a relevant outcome to the decision problem, although this was only measured in the short-term. The primary outcome of TAK318 was change from baseline in sexual dysfunction, which is of more limited relevance in the context of this appraisal.

The review of indirect evidence included significantly fewer outcomes, namely remission and withdrawal due to adverse events. The manufacturer stated that no other endpoints could be included in the review of indirect evidence as they were not reported consistently across all included studies. Although this justification appears appropriate, the absence of other outcomes (such as response rates) limits the relevance of the review of evidence comparing vortioxetine with several relevant comparators.

The MS cost-effectiveness model included some, but not all, of the effectiveness outcomes specified in the scope. In particular, the manufacturer did not include response data within the decision model.

3.5 Other relevant factors

The MS stated that no attempts were made to allow for equality considerations issues analytically, such as by applying alternative utility weightings. The MS noted that although people with intellectual disability are more likely to suffer from depressive episodes, this particular population may be at a disadvantage when it comes to receiving a specific diagnosis for depressive symptoms distinct from their other difficulties, and accessing the care they need (MS, Section 3, p.50). The ERG thinks that this approach was likely to be appropriate.

4 Clinical Effectiveness

The manufacturer submitted evidence on clinical effectiveness in the “switch” population based on four systematic reviews. This included three reviews of direct evidence for vortioxetine:

- a) a review of RCTs of vortioxetine compared to active comparators in the switch population (MS, Sections 6.1 to 6.6) to evaluate efficacy;
- b) a review of non-RCT evidence of vortioxetine in the switch population to evaluate efficacy (MS, Section 6.8);
- c) a review of adverse events of vortioxetine (MS, Section 6.9).

Also submitted was a review of indirect comparative evidence, again in the switch population, including an indirect treatment comparison and network meta-analysis of antidepressant RCTs, to evaluate efficacy and safety (MS, Section 6.7).

Section 4.1 below summarises and critiques the methods of all four reviews. The first review identified two RCTs comparing vortioxetine to other active comparators, REVIVE and TAK318; these are critiqued in Section 4.2. The review of indirect treatment comparisons and its associated network meta-analysis are critiqued in Section 4.3. The review of non-RCT evidence did not identify any relevant studies, so this report does not consider this review in any detail (Section 4.4). The review of adverse events is critiqued in Section 4.5.

As discussed in Section 3 above, the ERG considers that the restriction to a switch population only is considerably narrower than the original scope specified and that assessment of the efficacy of vortioxetine should take account of the broader population by including evidence from studies of vortioxetine in non-switch populations. The ERG requested that the manufacturer provide data on all trials of vortioxetine compared to placebo and/or active comparators. The manufacturer supplied efficacy and adverse event data for their placebo controlled trials of vortioxetine. They also identified three published systematic reviews of vortioxetine, two submissions to regulatory authorities and one published indirect comparison of vortioxetine with other antidepressants, sponsored by the manufacturer. The ERG considers this evidence in the wider population to be of relevance when determining the clinical efficacy of vortioxetine; this evidence is critiqued in Section 4.6.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The MS describes the search strategies used to identify direct evidence, indirect comparisons, non-RCT evidence and adverse events on the use of vortioxetine for the treatment of major depressive disorder. The strategies used for identifying the evidence are outlined in the main body of the submission with further details being provided in Section D of the Appendix.

Review of RCTs evidence

The manufacturer reported which bibliographic databases were searched. These include MEDLINE, EMBASE, PsycINFO and the Cochrane Library, among others. Trial registers including clinicaltrials.gov were searched, along with relevant conference websites.

The date when the searches were conducted, the time period covered by the searches and the total number of records identified were also provided. The search strategies used for each of the databases were reported. The search statements were combined appropriately and the correct Boolean notation was used. A PRISMA flowchart showed the total number of records identified and the contribution of each resource.

Reviews of adverse events and non-RCT evidence

The searches described for the review of RCT evidence would have identified RCT evidence, non-RCT evidence and adverse events studies, as no study type filter was applied to the searches. Consequently the comments on that search process apply to these sections too.

Indirect treatment comparison

The manufacturer reported which bibliographic databases were searched. A similar, but more limited, set of databases as in the review of RCT evidence was used. The full search strategies were provided in the appendix and it was noted that the strategy for EMBASE and MEDLINE was based upon a strategy used by a systematic literature review previously undertaken by the Agency for Healthcare Research and Quality (AHRQ), published in April 2012, assessing treatment for depression after unsatisfactory response to SSRIs.(11) The date the searches were conducted is given and it is reported that the search period covered was post 1980 onwards, although the reason for this restriction is not provided.

The ERG considers that the reporting of all search processes was clear, appropriate, and well documented.

4.1.2 Inclusion criteria

Review of RCTs evidence and review of non-RCT evidence

Eligibility criteria for the reviews of RCT and non-RCT evidence are reported in MS sections 6.2.1 and 6.8.1 respectively. Studies evaluating a licensed regimen of vortioxetine (5mg, 10mg, 15mg, or 20mg once daily) were eligible for inclusion. The population of interest was individuals with moderate-to-severe MDD who are experiencing an MDE, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want a switch to an alternative antidepressant. Eligible comparators were any antidepressants. There were no limitations in terms of eligible outcomes, and studies of any duration were eligible for inclusion.

Given the restricted population (see Section 3), the ERG considers the eligibility criteria for the reviews of RCT and non-RCT evidence to be appropriate.

Review of adverse events

Eligibility criteria for the review of adverse events are reported in MS section 6.9.1. Only studies that reported safety as the primary outcome were included. As with the reviews of RCT and non-RCT evidence, all licensed regimens were eligible, antidepressants were eligible as comparators, and the population of interest was switch patients with MDD.

These initial criteria did not lead to the identification of any studies of adverse events within a switch population. Therefore the selection criteria were broadened to include non-switch populations of adults with MDD (of any severity) experiencing an MDE. The manufacturer justified this decision based on the assumption that unlike efficacy, there is no reason to believe that the safety or tolerability of vortioxetine, or any other antidepressant, would differ by treatment line. Based on clinical advice, the ERG considers this assumption to be appropriate for safety, but not for tolerability, as patients intolerant of one medication may be more intolerant of others.

The study selection process and eligibility criteria appeared generally appropriate. However, the review of adverse events excluded studies that evaluated safety but did not report it as a primary outcome. Therefore there is a risk that relevant studies reporting adverse events may have been missed; as the manufacturer did not provide a record for the exclusion of studies, this risk is difficult to assess.

Indirect treatment comparison

The inclusion criteria for trials used in the indirect treatment comparisons were broadly similar to those for trials of vortioxetine. Included were adult patients with major depressive disorder, who for the current major depressive episode had demonstrated inadequate response to a previous treatment

(i.e. the “switch” population). Eighty percent or more of patients had to have received an SSRI or SNRI as first-line treatment. A range of antidepressant treatments (or placebo) were eligible, including all major, widely used treatments (citalopram, venlafaxine, sertraline, mirtazapine etc.). For the network meta-analysis inclusion criteria were more restricted, including only trials judged to be adequately randomised and blinded, based on quality assessment, which compared two or more antidepressants in the “switch” population.

The ERG considers that these inclusion criteria were appropriate.

4.1.3 Critique of data extraction

For all reviews data extracted included details of study design, participant characteristics, data relevant to risk-of bias, details of the treatments, outcomes (including changes in depression scores, response rates, remission rates, withdrawal rates and incidence of adverse events). The data extraction process appeared generally appropriate, although the manufacturer did not state whether attempts were made to minimise the risk of reviewer error and bias (for example, by independent checking or extracting data in duplicate).

4.1.4 Quality assessment

In all reviews the trials included were assessed for quality and risk of bias using seven questions from the NICE quality checklists. The assessment covered randomisation, allocation concealment, similarity of trial arms, blinding, imbalance across groups, outcome reporting and use of intention-to-treat analysis.

The ERG considers this to be an appropriate assessment of trial quality.

4.1.5 Evidence synthesis

Review of RCT evidence

No meta-analysis or evidence synthesis was performed for the trials of vortioxetine in the switch population as presented in the MS. The manufacturers justified this on the basis that only two trials (REVIVE and TAK318) were identified and they used different comparator treatments in different populations, so were unsuitable for synthesis. Instead, the results of the efficacy studies were summarised narratively and in tables. The ERG agrees that these two trials could not be reasonably synthesised and a narrative summary of the trials was appropriate.

Review of adverse events

For the review of safety studies, data from five of the six included studies were presented in aggregate to calculate the incidence of treatment emergent adverse events. No formal meta-analytic methods

were used to pool the safety studies. The ERG notes that this method is not ideal as it ignores differences in populations and characteristics across studies.

Indirect treatment comparison

Trials included in the indirect treatment comparison were pooled using network meta-analysis methods. The submission used two different approaches: a frequentist analysis using the Boucher method and a Bayesian analysis performed using WinBUGS. The ERG recognises that both approaches are standard methods, and have been used appropriately in the submitted analyses.

The ERG has concerns with some of the methods used in the network meta-analysis. The primary outcome was remission rate. No other efficacy outcomes, such as response rate or absolute changes in depression scores were included. On clarification, the manufacturer stated that no other efficacy endpoint was consistently reported across all studies and hence they could not be included in the network meta-analysis. Remission was defined as a HAM-D score of seven or less, or a MADRS score of ten or less. Because different trials reported different depression scales these scales may not be exactly comparable, and some patients may have achieved remission on one scale but not another. Also, one trial (Kasper) did not report remission rates, so this was calculated from HAM-D scores, assuming scores followed either a normal or gamma distribution. Sensitivity analyses were performed to investigate the effect of using both these distributions, which was appropriate. However, remission rates may have been inaccurately estimated if the data did not fit either of these distributions. On clarification, the manufacturer presented results of a network meta-analysis with standardised mean difference in depression scale as the outcome.

The main network analysis excluded trials with a placebo arm. The manufacturer justified this based on clinical advice that patients in placebo-controlled studies may be different from those in active-controlled studies. No further justification was provided. The ERG does not consider this to be a strong justification, because such differences would apply to all placebo-controlled trials, and including such trials would be unlikely to bias the network analysis results as a whole. The manufacturer did provide results of the network including placebo-controlled trials in Appendix 16.

The MS reported results as risk differences between treatments. The ERG does not consider the risk difference to be a suitable measure for comparing treatments as it is very sensitive to any heterogeneity in outcomes across trials. The manufacturers justified this choice because using the risk difference led to more conservative estimates for venlafaxine, bupropion and citalopram. The ERG agrees that results were more conservative in this case, but considers results based on odds ratios or relative risks to be more statistically robust. The manufacturers provided results based on odds ratios in an appendix, and results for relative risks in response to requests for clarification.

4.2 Critique of the trials of vortioxetine

The MS presented PRISMA flow diagrams for the review of effectiveness. Table 8 summarises the two RCTs identified by the review that compared vortioxetine to another antidepressant in the switch population.

Table 8 RCTs included in the submission

Study	Patient population	Regimen & duration	Comparator	Design	Follow-up duration	Primary outcome
REVIVE (14178A)(12)	Patients who have experienced an inadequate response to an SSRI or SNRI in their current MDE	Vortioxetine 10mg-20mg flexible dosing, 12 weeks	Agomelatine 25-50mg flexible dosing	Double-blind, international phase IIIb, parallel-group randomised trial	Efficacy: up to 12 weeks from baseline Safety: up to 16 weeks from baseline	Change from baseline in depression severity (MADRS total score) at week 8
TAK318(13)	Patients who are well-controlled on an SSRI but experienced treatment emergent sexual dysfunction	Vortioxetine 10mg-20mg flexible dosing, 8 weeks ^a	Escitalopram 10-20mg flexible dosing	Double-blind, multicentre phase IIIb, parallel-group randomised trial	Efficacy: up to 8 weeks from baseline Safety: up to 12 weeks from baseline	Change from baseline in sexual functioning (CSFQ-14 total score) after 8 weeks of treatment

^a Participants who completed the 8-week treatment period entered a 1-week, double-blind taper-down period during which they received placebo. Escitalopram arm participants received 10 mg QD escitalopram during the taper-down period. Patients who prematurely discontinued during the double-blind treatment period were also offered taper-down study medication.

MADRS: Montgomery and Åsberg Depression Rating Scale; CSFQ-14: Changes in Sexual Functioning Questionnaire Short-Form

Study details and participant characteristics of vortioxetine trials were presented in section 6.3 of the MS (pp. 66-82), and efficacy results are reported in section 6.5 of the MS (pp. 87-99). Both included studies met the inclusion criteria. Reporting of study and participant characteristics appeared appropriate overall.

The ERG searched clinicaltrials.gov and the WHO ICTRP register and found no relevant ongoing vortioxetine trials in adult MDD switch populations.

4.2.1 Critique of the validity of the included trials

The ERG has several concerns with the validity of the included trials, particularly with how well they represent the UK population likely to receive vortioxetine. Both REVIVE and TAK318 had design

limitations that may have affected their external validity. The ERG has particular concerns regarding the choice of comparator, duration of follow-up and study power.

Comparators

Agomelatine is not currently recommended by NICE. The fact that agomelatine is the only comparator in REVIVE means that, in the context of this appraisal, the relevance of this trial is limited. The use of escitalopram is also limited in UK patients experiencing SSRI-induced sexual dysfunction, which limits the relevance of TAK318 to current UK practice.

Follow-up duration

The 12-weeks follow-up duration of REVIVE is short considering the duration of treatment that is recommended by NICE to achieve and consolidate remission. The manufacturer acknowledged this limitation (MS, p.136), but stated that this shortcoming was mitigated by the results of a relapse-prevention trial (study 11985A)(14) that found significantly lower relapse rates for vortioxetine compared with placebo (13% versus 26%, $p=0.0013$), over 24 weeks after 12 weeks' open-label treatment. The results of study 11985A should be interpreted with caution as it only included patients who were in remission at 10 and 12 weeks of open-label vortioxetine therapy, and therefore excluded responders-only, or patients who may have been in remission following a longer course of therapy. As with REVIVE, TAK318 had a short-term follow-up, therefore evidence of long-term efficacy of vortioxetine in switch populations is uncertain.

Study power

REVIVE was designed as a non-inferiority trial. Sample size calculations were based on a non-inferiority comparison of the treatment groups in the primary outcome, and non-inferiority was considered established if the upper bound of the two-sided 95% confidence interval of the difference between treatment groups in MADRS total score at Week 8 did not exceed 2 MADRS units compared with agomelatine. This means that REVIVE may not have been sufficiently powered to demonstrate that vortioxetine is superior to agomelatine. Therefore any inferences from this trial regarding the superiority of vortioxetine over agomelatine may not be reliable as they may be based on chance.

Additional concerns about the representativeness of the trial populations are reported in sections 4.2.3 (REVIVE) and 4.2.5 (TAK318) of this report.

4.2.2 Quality assessment and risk of bias

The manufacturer provided a quality assessment of the two included trials of vortioxetine (REVIVE and TAK318) in MS section 6.4, Tables B11 and B12 (MS, pp. 83-87). These are summarised in Table 9 below. The ERG mostly concurs with the manufacturer's assessment of quality for the two

trials, although there were minor concerns about baseline imbalances between treatment groups, withdrawal and missing data in both trials.

Prognostic factors were generally comparable across intervention and comparator groups in both trials, although small gender differences between intervention and comparator group were reported in REVIVE and TAK318. In REVIVE, the proportion of female participants was slightly higher in the vortioxetine arm (77.1%) compared with the agomelatine arm (72.3%). In TAK318, the proportion of female participants was slightly lower in the vortioxetine arm (56.9%) compared with the escitalopram group (60.8%). However, the ERG believes that these gender imbalances are relatively small and are unlikely to have introduced significant bias to the results.

In TAK318, ethnicity was also different between the 2 groups: 16.2% of participants reported being Hispanic or Latino in the escitalopram group, compared with 6.2% in the vortioxetine group. However, the ERG believes that this imbalance is unlikely to have a significant impact on the study results, as it is relatively small and involved few individuals.

Overall withdrawal rates were relatively high in REVIVE (23%) and TAK318 (22%). However there were no significant imbalances in withdrawal rates between treatment arms in either trials (21% in the vortioxetine group and 26% in the agomelatine group in REVIVE; 25% in the vortioxetine arm and 19% in the escitalopram arm in TAK318). Reasons for withdrawal were reported. Primary analyses of both trials used a mixed model for repeated measures (MMRM) to address the issue of missing data. Although this approach has limitations (the MMRM assumes that data are missing at random, and may therefore not fully compensate for informative but unobserved missingness), methods used to address missing data appear generally appropriate and the risk of attrition bias is likely to be low.

In REVIVE and TAK318, efficacy analyses were based on a modified intent-to-treat (mITT) analysis, using the full-analysis set (FAS) which comprised all randomised patients who took at least one dose of study medication, had a valid baseline assessment and at least one valid post-baseline assessment of the primary efficacy variable. This is not a strict intention-to-treat analysis according to the Cochrane Collaboration definition which requires the inclusion of all randomised patients. However, relatively few patients randomised in REVIVE (three in the vortioxetine arm and five in the agomelatine arm) and TAK318 (eight in the vortioxetine arm and 15 in the escitalopram arm) were not included in the FAS, therefore the risk of bias associated with the mITT analyses is likely to be low.

Table 9 Manufacturer assessments of quality for vortioxetine trials

	REVIVE	TAK318
1. Was randomisation carried out appropriately?	Yes	Yes
2. Was the concealment of treatment allocation adequate?	Yes	Yes
3. Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

4.2.3 Characteristics of the REVIVE trial

REVIVE was a 12-week, international phase IIIb, non-inferiority, randomised, double-blind, parallel group, flexible-dose, active comparator study, that assessed the efficacy and safety of vortioxetine versus agomelatine in patients with MDD who had failed initial antidepressant therapy.

The patients were randomised equally (1:1) to flexible doses of either vortioxetine (10 to 20mg/day) or agomelatine (25 to 50mg/day). The starting doses were vortioxetine 10mg/day or agomelatine 25mg/day.

Participants were recruited from 71 psychiatric inpatient and outpatient settings in 14 countries (Austria, Belgium, Bulgaria, Czech Republic, Estonia, Germany, Italy, Lithuania, Poland, Romania, Russia, Spain, Sweden and the UK).

The study randomised 501 individuals to vortioxetine (255 participants) or agomelatine (246 participants). Included were adult patients (≥ 18 and ≤ 75 years) who had moderate to severe MDD (MADRS score ≥ 22) at screening and baseline and were candidates for a switch in the investigator's opinion. Patients needed to have responded inadequately to a maximum of one course of antidepressant SSRI or SNRI monotherapy that was prescribed to treat a single episode of MDD or recurrent MDD, according to DSM-IV-TR™ criteria.

A number of exclusion criteria were listed, including: current psychiatric disorder or Axis I disorder (DSM-IV-TR™ criteria), other than generalized anxiety disorder (GAD) and social anxiety disorder (SAD); MDD with post-partum onset or MDD with a seasonal pattern (DSM-IV-TR™ criteria); history of previous treatment resistant MDD; current diagnosis of alcohol or other substance abuse; significant risk of suicide, MADRS Item 10 (suicidal thoughts) score ≥ 5 , or suicide attempt in

previous six months; currently receiving cognitive or behavioural therapy or systematic psychotherapy, or plans to start such therapy during the study. These criteria limit the extent to which the trial population may be representative of the UK switch population with moderate to severe MDD.

The primary outcome of REVIVE was change from baseline in MADRS total score at treatment week 8. Secondary efficacy outcomes included response (defined as $\geq 50\%$ decrease from baseline in MADRS total score, or a CGI-I ≤ 2), and remission (defined as a MADRS total score ≤ 10 , or a CGI-S ≤ 2).

MADRS is a ten-item diagnostic questionnaire used to measure the severity of depressive episodes. The overall score ranges from 0 to 60, with higher scores indicating more severe depression. The CGI-S scale is a seven point scale that rates the severity of a patients' mental illness. Scores range from one (normal) to seven (extremely ill). The CGI-I scale is a seven point scale assessing change relative to a baseline state in patient with mental disorders. Scores range from one (very much improved) to seven (very much worse), with scores of four indicating no change.

Other outcomes measures included safety endpoints (including adverse events and clinical safety laboratory tests), health-related quality of life and overall functioning. Follow-up was up to 12 weeks from baseline for efficacy outcomes, with an additional four weeks safety follow-up. All study outcomes assessed were reported in the submission and the trial CSR. A list of primary and secondary outcome measures is presented in Table B10 (MS, p.76).

Baseline characteristics of participants were reported in Table B8 (MS, p.75) of the submission, which is reproduced below (Table 10). The trial population appeared broadly representative of UK switch population. Baseline MADRS scores ranged from 22 to 43 points, which is consistent with patients experiencing moderate to severe MDD. However, all REVIVE participants (99.8%) were white Caucasian, which is unlikely to be reflective of the UK switch population. Approximately 76% of patients had received an SSRI, and 23% had received an SNRI as initial treatment. This is not representative of UK clinical practice, where first-line SNRI use is negligible, as acknowledged by the manufacturer. Participants from REVIVE were recruited almost entirely (97.2%) from outpatient psychiatric setting. The proportion of UK patients was small (approximately 7%). Variations in healthcare systems and management of MDD across different countries may limit the applicability of the trial results to the UK switch population with moderate to severe MDD.

Table 10 Study 14178A (REVIVE). Baseline characteristics of participants

Baseline characteristic	Vortioxetine	Agomelatine	Total
Number of patients: APTS ¹ , (FAS ²)	253 (252)	242 (241)	495 (493)
Mean (median) age (years) ¹	47.0 (48.0)	45.6 (46.0)	46.3 (47.0)
Sex (% female) ¹	77.1%	72.3%	74.7%
Race (% white) ¹	99.6%	100.0%	99.8%
Mean $\pm$ sd (median) duration of current episode (weeks) ¹	18.6 $\pm$ 10.4 (16.0)	19.2 $\pm$ 10.9 (16.0)	18.9 $\pm$ 10.6 (16.0)
Mean $\pm$ sd (median) number of previous episodes ¹	2.6 $\pm$ 2.1 (2.0)	2.4 $\pm$ 1.8 (2.0)	2.5 $\pm$ 2.0 (2.0)
Mean $\pm$ sd (median) MADRS total baseline score ²	29.1 $\pm$ 4.4 (29.0)	28.7 $\pm$ 4.0 (28.0)	28.9 $\pm$ 4.2 (28.0)
Mean CGI-S $\pm$ sd (median) total baseline score ²	4.4 $\pm$ 0.6 (4.0)	4.4 $\pm$ 0.6 (4.0)	4.4 $\pm$ 0.6 (4.0)
Mean $\pm$ sd (median) HAM-A total baseline score ²	21.6 $\pm$ 6.3 (21.0)	21.4 $\pm$ 6.2 (21.0)	21.5 $\pm$ 6.2 (21.0)

¹ denotes analyses based on APTS (all patients treated set). ² denotes analyses based on FAS (full analysis set). SD: standard deviation. See MS 6.3.6 for definitions of analysis sets

4.2.4 REVIVE trial results

Response and remission

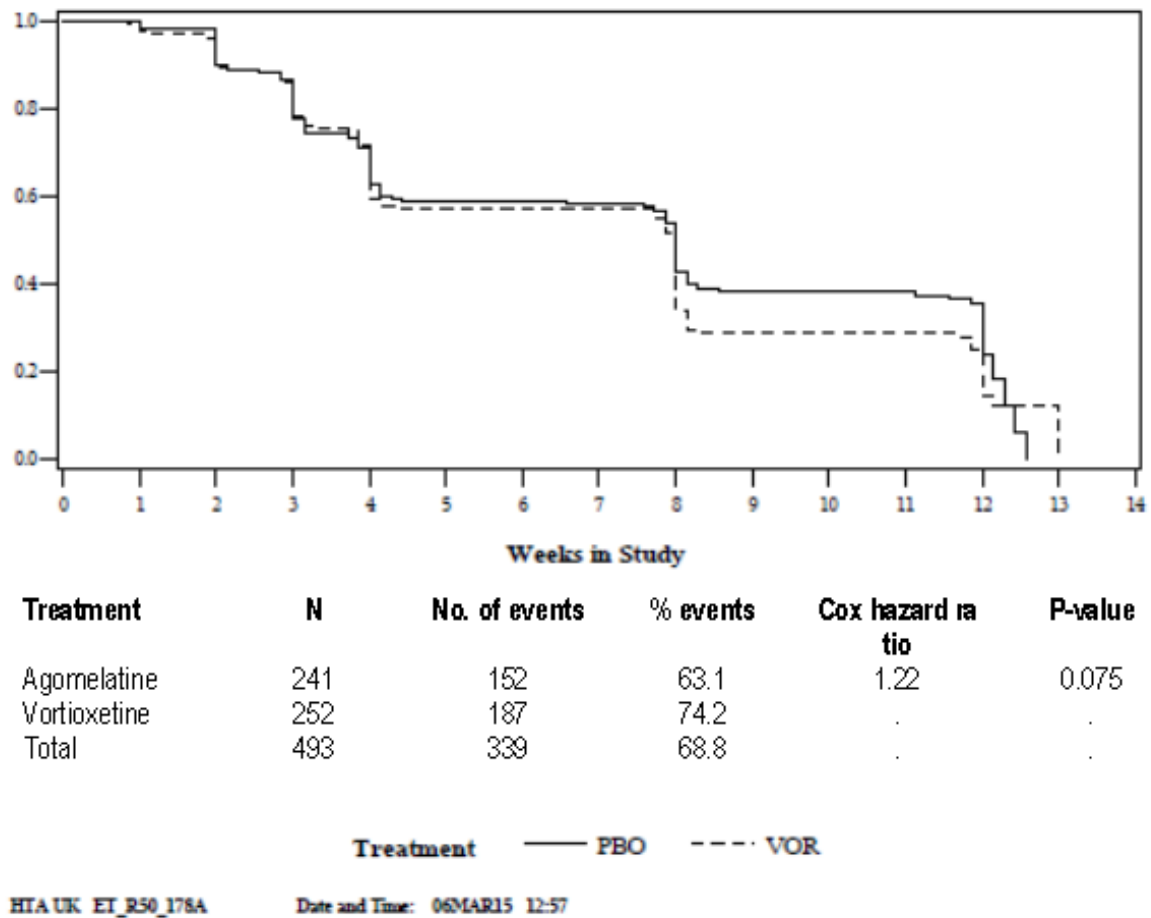
REVIVE results for response and remission were reported in Table B14 (MS, pp.88-89) of the manufacturer submission, with further details presented in the study CSR. Response and remission rates, and corresponding adjusted odds ratios estimates from the manufacturer's logistic regression model are summarised in Table 11 below.

Table 11 REVIVE trial results: remission and response

Endpoint	Week 8				Adjusted OR (95% CI)	Week 12				Adjusted OR (95% CI)
	Vortioxetine		Agomelatine			Vortioxetine		Agomelatine		
	n	%	n	%		n	%	n	%	
Response										
MADRS	155	62%	114	47%	1.81 (1.26 to 2.60)	176	70%	135	56%	1.83 (1.26 to 2.65)
CGI-I	186	74%	140	58%	2.03 (1.38 to 2.96)	187	74%	154	64%	1.62 (1.10 to 2.39)
Remission										
MADRS	102	41%	71	30%	1.72 (1.17 to 2.52)	139	55%	95	39%	2.01 (1.39 to 2.90)
CGI-S	104	41%	78	32%	1.55 (1.07 to 2.25)	140	56%	106	44%	1.63 (1.14 to 2.33)
OR: Odds ratio; CI: Confidence interval										

Table 11 shows that the proportion of MADRS and CGI-I responders was statistically significantly higher in the vortioxetine arm compared with the agomelatine arm at weeks eight and 12. The proportion of MADRS and CGI-S remitters was also statistically significantly higher in the vortioxetine arm compared with the agomelatine arm at weeks eight and 12. Results were consistent across measures and follow-up points. The relatively wide confidence intervals reflect the uncertainty in true magnitude of the difference in efficacy between vortioxetine and agomelatine.

No data on time to response was provided in the submission. On clarification, the manufacturer conducted a post hoc time-to-event analysis of first response in REVIVE, along with a Kaplan-Meier plot of time to first response (defined as a $\geq 50\%$ reduction in MADRS score), presented in Figure 6 below.

Figure 6 Kaplan Meir plot of time to first response (50% reduction in MADRS)

The results of this analysis showed a small separation between groups in favour of vortioxetine from 8 weeks, although the time-to-event analysis yielded a non-statistically significant result ($p=0.075$).

This analysis should be interpreted with caution as it reports time to first response, and does not take into account patients who may have responded at early assessments but did not maintain response until the end of the study, as acknowledged by the manufacturer.

Severity of depression

Table 12 below presents differences in mean change from baseline between vortioxetine and agomelatine and shows that efficacy results were statistically significant across MADRS, CGI-S and CGI-I scores at treatment weeks eight and 12. REVIVE reported a reduction of 16.5 MADRS points (from 29.1 at baseline) in the vortioxetine group, and a reduction of 14.4 points (from 28.66 at baseline) in the agomelatine group, giving a mean difference of -2.16 (95% CI -3.51 to -0.81). The manufacturer stated that non-inferiority was established, as the upper bound of the 95% CI was below

the non-inferiority margin of +2 MADRS points versus agomelatine. The magnitude of the results was also similar between treatment weeks eight and 12 for each measurement scale. The manufacturer reported similar results from sensitivity analyses using LOCF and ANCOVA (Table B13, MS p88).

Table 12 REVIVE trial: Primary and secondary efficacy outcomes: scale score differences in mean change from baseline (MMRM)

Efficacy variables	Vortioxetine: difference to agomelatine	
	Week 8	Week 12
	Mean difference (95% CI)	Mean difference (95% CI)
MADRS total*	-2.16 (3.51 to -0.81)	-2.03 (-3.45 to -0.60)
CGI-S score	-0.30 (-0.48 to -0.11)	-0.27 (-0.47 to -0.07)
CGI-I score	-0.25 (-0.42 to -0.08)	-0.25 (-0.42 to -0.07)

*Primary outcome; MMRM: Mixed model for repeated measures

The ERG notes that MADRS results from MMRM analysis have relatively wide confidence intervals, therefore the magnitude of the mean difference estimate is uncertain.

Adverse effects of treatment

Table 13 presents a summary of adverse data.

Table 13 REVIVE trial: summary of adverse events reported over 12-week treatment period

Event	Vortioxetine (10mg-20mg)	Agomelatine (25mg-50mg)
	n=253	n=242
Adverse event		
Patients with TEAEs, n (%)	137 (54.2%)	127 (52.5%)
Patients with SAEs, n (%)	3 (1.2%)	4 (1.7%)
Patients with AEs leading to withdrawal, n (%)	15 (5.9%)	23 (9.5%)
Patients with TEAEs with an incidence of ≥5% in any treatment group (APTS):		
Nausea (%)	41 (16.2%)	22 (9.1%)
Headache, n (%)	26 (10.3%)	32 (13.2%)
Dizziness, n (%)	18 (7.1%)	28 (11.6%)
Somnolence, n (%)	10 (4.0%)	19 (7.9%)

TEAE: Treatment-emergent adverse event; SAE: serious adverse event; AE: adverse event.

Overall, most patients with TEAEs had TEAEs that were either mild or moderate. The incidence of patients with severe TEAEs was similar between the two treatment groups. The severe adverse events that were considered related to treatment and occurred in at least two patients in any treatment group

were (vortioxetine versus agomelatine): insomnia (4 patients versus 1 patient), headache (1 patients versus 3 patient), anxiety (1 patients versus 2 patient), tremor (2 patients versus 0 patient), and aggression (0 patients versus 2 patients).

The manufacturer stated that the overall incidence of sleep-related TEAEs was similar in the vortioxetine group compared to the agomelatine group (11.1% and 10.7%, respectively). Vortioxetine patients experienced insomnia (4.7%) more frequently than agomelatine patients (1.2%). Somnolence was less frequent in vortioxetine patients (4.0%) compared with agomelatine (7.9%).

The manufacturer did not present data on adverse effects of treatment discontinuation. In clarifications, they stated that the European Medicines Agency reported that there was no evidence of clinically relevant discontinuation symptoms that warranted a dose tapering of vortioxetine. The SPC stated that in short- and long-term placebo controlled studies, there was “no clinically relevant difference to placebo in the incidence or nature of the discontinuation symptoms after either short-term (6-12 weeks) or long-term (24-64 weeks) treatment with vortioxetine”.

Other outcomes

No data on relapse rates, cognitive dysfunction or sleep quality (other than sleep-related adverse events) were presented. There were no deaths during the study and only one patient (in the agomelatine arm) was hospitalised.

Anxiety was measured using the Hamilton Anxiety Rating Scale (HAM-A). REVIVE reported a statistically significant difference in mean change from baseline in HAM-A total scores favouring vortioxetine compared with agomelatine at 8 weeks (MD -1.89; 95% CI -2.98 to -0.80) and 12 weeks (MD -1.93; 95% CI -3.04 to -0.81).

Several health-related quality of life measures were used, including EQ-5D, Sheehan Disability Scale (SDS), Depression and Family Functioning Scale (DFFS) and Work Limitations Questionnaire (WLQ). Statistically significant differences in favour of vortioxetine were reported for all outcomes at week 8 and all except the SDS family life domain and WLQ global score at week 12.

4.2.5 Characteristics of the TAK318 trial

Study TAK318 was a multicentre phase IIb, randomised, double-blind, parallel group, flexible-dose, active comparator study that assessed the efficacy and safety of vortioxetine versus escitalopram in patients with well-treated MDD who were experiencing SSRI-induced sexual dysfunction.

Participants were recruited from psychiatry outpatient settings only, including 57 sites in the US and 9 sites in Canada. The study randomised 447 participants to 10-20mg/day of vortioxetine (225 participants) or 10-20 mg/day of escitalopram (222 participants).

Included were adults patients (≥ 18 and ≤ 55 years) who were currently being treated with SSRI monotherapy (citalopram, paroxetine or sertraline) for at least eight weeks for the treatment of an MDE according to the DSM-IV-TR™ criteria. Patients' depression was well treated and stable (CGI-S score ≤ 3); they were experiencing treatment emergent sexual dysfunction (CSFQ-14 total score ≤ 41 for women and ≤ 47 for men) considered to be attributable to the current SSRI monotherapy, and were suitable for a switch.

A number of exclusion criteria were presented, including: current psychiatric disorder; other comorbid conditions; current alcohol/substance abuse; current diagnosis or history of a psychotic disorder; significant risk of suicide, MADRS Item 10 (suicidal thoughts) score ≥ 5 , or suicide attempt in previous six months; currently receiving cognitive or behavioural therapy or systematic psychotherapy, or plans to start such therapy during the study. The inclusion and exclusion criteria for this trial limit the extent to which the trial population may be representative of the UK switch population of patients with moderate to severe MDD with an inadequate response to initial antidepressant treatment. The primary outcome was change from baseline in sexual dysfunction (CSFQ-14 total score) after eight weeks of treatment. Follow-up was up to eight weeks from baseline for efficacy outcomes, with an additional four weeks safety follow-up. All study outcomes assessed were reported in the submission.

Relevant baseline characteristics of participants were reported in Table B9 (p.76) of MS, which is reproduced below (Table 14). On clarification, the manufacturer reported that 302 (71% of participants in the FAS) were in remission at baseline. Based on the information provided in the submission, it was unclear whether participants had received more than one course of antidepressant before entering the trial.

Table 14 Study TAK318. Baseline characteristics of participants

Participant characteristic	Vortioxetine (n=255)	Escitalopram (n=222)
Age, years	39.3 ± 10.0	40.2 ± 10.0
Mean ± sd (range)	(19–55)	(19–55)
Sex		
Male	97 (43.1%)	87 (39.2%)
Female	128 (56.9%)	135 (60.8%)
Race		
Caucasian	178 (79.1%)	181 (81.5%)
Black	41 (18.2%)	35 (15.8%)
Asian	4 (1.8%)	3 (1.4%)
Other	2 (0.9%)	3 (1.4%)
BMI, kg/m ² , mean ± sd	27.5 ± 4.4	27.9 ± 4.4
CSFQ-14 total score	36.1 ± 0.39	36.0 ± 0.40
Mean ± se (range)	(21–47)	(21–47)
MADRS total scoreMean ± sd (range)	7.9 ± 6.3 (0–34)	8.3 ± 6.5 (0–34)
CGI-S	2.0 ± 0.8	2.0 ± 0.8
Mean ± sd (range)	(1–3)	(1–3)

sd: standard deviation; se: standard error; BMI: body mass index; CGI-S: Clinical Global Impression - Severity Scale; CSFQ-14: Changes in Sexual Functioning Questionnaire Short-Form; MADRS: Montgomery-Åsberg Depression Rating Scale.

4.2.6 TAK318 trial results

Response and remission

No results were reported for response and remission. TAK318 was conducted in switch patients whose MDD was well-treated and stable under previous SSRI treatment. MADRS and CGI-S baseline scores were therefore relatively low, and the lack of response and remission rates data from TAK318 is likely to be of limited relevance.

Relapse

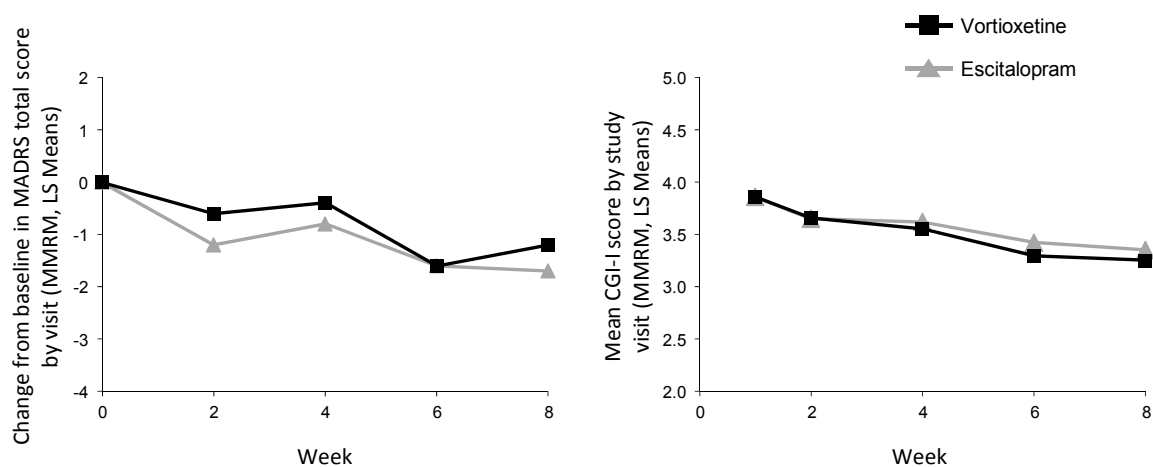
No relapse data were presented as part of the submission. A post-hoc analysis was conducted in response to request for clarification using MADRS score. Relapse was defined as MADRS total score of ≥22. [REDACTED]

Severity of depression

Efficacy results for depression symptoms were assessed using MADRS, CGI-S, CGI-I and POMS total scores. As can be seen from Figure B14 of the MS (reproduced in Figure 7 below), the mean MADRS and CGI-I total scores decreased slightly over time in both treatment groups, suggesting that

the improvement in depressive symptoms achieved with prior SSRI treatment at study entry was maintained or slightly improved overall. Results for CGI-S and POMS total scores were reported in the study CSR and showed a similar trend. Mean MADRS, CGI-S, CGI-I and POMS total scores were not significantly different between vortioxetine and escitalopram treatment groups at eight weeks.

Figure 7 Study TAK318. Changes in clinical measures of depressive symptoms over 8 weeks of treatment with vortioxetine and escitalopram



MMRM: Mixed model for repeated measures; LS: least-squares

Sexual dysfunction

Sexual functioning, measured as change from baseline in CSFQ-14 total score at treatment week eight was the primary outcome. At 8 week treatment the mean change from baseline was 8.8 (SE 0.64) in the vortioxetine arm and 6.6 (SE 0.64) in the escitalopram arm. There was a statistically significant difference in mean change from baseline in CSFQ-14 total score of 2.2 points after eight weeks of treatment which favoured vortioxetine ($p=0.013$).

The number of patients with a shift in CSFQ-14 from abnormal (defined as a CSFQ-14 total score ≤ 41 for women and ≤ 47 for men) at baseline, to normal (defined as >41 for women and >47 for men) was assessed as a secondary outcome. There was no statistically significant difference in the proportion of patients shifting from abnormal to normal CSFQ-14 score in the vortioxetine group (52.1%) compared with escitalopram (44.2%) at week eight (OR 1.37; 95% CI 0.93 to 2.03). The MS also reported a difference between arms on the CSFQ-14 subscales (MS, Figure B13, p98). There was statistically significant evidence in favour of vortioxetine on all subscales presented. Further secondary endpoint results and subgroup analyses were reported in the MS pp. 96-98.

Adverse effects of treatment

Of all participants who were randomized and received at least one dose of double-blind study medication, 283 patients (63.6%) experienced at least one TEAE during the Treatment Period (65.2% for vortioxetine and 62.0% for escitalopram). The overall incidence of TEAEs that caused discontinuation from study drug was 7.9% and lower in the escitalopram group (6.3%) compared with the vortioxetine group (9.4%).

The majority of TEAEs were mild or moderate in intensity. In the vortioxetine arm, the most common TEAE experienced by at least 5% of the participants were nausea (25.0%), headache (9.4%), dizziness (8.0%), and pruritus generalised (5.8%). In the escitalopram group, the most common TEAE were headache (7.7%), irritability (7.2%), anxiety (5.4%), nausea (5.4%) and dizziness (5.0%).

Severe TEAEs were reported for 2.9% of participants overall and occurred with similar incidences in both treatment groups. SAEs were reported for three participants (1.3%) in the vortioxetine group and one individual (0.5%) in the escitalopram group. In clarifications, the manufacturer stated that no adverse event data associated with treatment discontinuation were available from TAK318.

Other outcomes

No deaths or hospitalisations were reported during the trial. No data on cognitive dysfunction, anxiety or sleep quality (other than sleep-related adverse events) were presented. No health-related quality of life outcomes, other than related to sexual dysfunction, were reported.

4.2.7 Conclusions from the review of vortioxetine RCTs

The review of efficacy studies identified two studies. Although both were conducted in switch patients, the populations of these trials differed significantly. REVIVE was conducted in MDD patients switching from initial SRI treatment (SSRI/SNRI) due to lack of efficacy, whereas TAK138 was conducted in patients whose MDD was well-controlled but were switched from an SSRI due to treatment-emergent sexual dysfunction. Therefore each trial only partly covered the switch population as defined by the manufacturer in the decision problem. Due to significant differences in populations, the ERG considers that the manufacturer's decision not to pool these two trials is appropriate.

The manufacturer concluded from the REVIVE trial that in MDD patients with an inadequate response to SSRI/SNRI treatment, switching to vortioxetine resulted in a significant and clinically relevant improvement versus agomelatine in change from baseline in MADRS total score at week eight. They stated that vortioxetine also showed a significant benefit versus agomelatine on the majority of secondary endpoints, and that vortioxetine and agomelatine were well tolerated with few treatment discontinuations.

Based on the TAK318 trial results, the manufacturer stated that vortioxetine is superior to escitalopram in improving sexual functioning in patients with SSRI-induced sexual dysfunction. They stated that both vortioxetine and escitalopram maintained and slightly improved the depressive symptoms seen with the prior SSRI treatment as assessed by MADRS, CGI-S, and CGI-I scores, and that vortioxetine was generally well-tolerated in this study.

REVIVE and TAK318 trials appeared well conducted. However, the designs of both studies raised a number of concerns. As mentioned above (Section 4.2.1), both trials included comparators of limited relevance to UK practice, and there were concerns about the representativeness of the trial participants to the UK switch population. Both studies had short-term follow-up, therefore the long-term efficacy of vortioxetine in switch patients is uncertain based on the evidence presented. In addition, the trials only evaluated the efficacy of vortioxetine 10-20mg/day, therefore the efficacy of the licensed 5mg/day regimen is uncertain. Finally, as REVIVE was designed as a non-inferiority trial, conclusions regarding the superiority of vortioxetine versus agomelatine may not be reliable.

4.3 Indirect treatment comparison

4.3.1 Critique of trials identified and included in the indirect comparison

The systematic review for the indirect comparison analysis identified 27 relevant studies; however 20 were excluded as not being in “switch” populations. The ERG accepts that these studies did not meet the inclusion criteria for the manufacturer’s analysis, but many of these studies may have matched the NICE scope population of adults with MDD.

The seven remaining studies were assessed for study quality. For five studies, all quality components were assessed as either adequate or unclear. One study (Rush 2006(5)) had one component (imbalances between groups) considered to be inadequate. The ERG generally agrees with the manufacturer on their quality assessment of these trials.

One study (Rosso 2012(15)) had two inadequate components (randomisation and blinding). Given the high potential for bias in this trial it was excluded from further analysis. The ERG accepts that assessment of bias was correct and so this exclusion was reasonable, but notes that, as Rosso 2012 was the only study to include duloxetine, this means no evidence comparing vortioxetine to duloxetine has been presented.

Table 15 Characteristics of studies included in indirect comparisons

Study	Interventions	Sample size	Mean age	% Female	Duration of current MDE (median months)	Number of previous MDEs (median)	Baseline HAM-D (mean)	Duration of previous treatment (mean, weeks)	% with prior SSRI/SNRI treatment	Primary outcome	Time of assessment (weeks)
REVIVE (16)	Vortioxetine 10-20mg Agomelatine 25-50mg	501	46	74.7	4.5	1.8	23.3*	24	100	MADRS	8
Kasper 2010(17)	Agomelatine 25-50mg Sertraline 50-100mg	177	44	73.5	3.1	2.0	26.5	NR	87.1	HAM-D ₁₇	6
Olié and Kasper 2007(18)	Agomelatine 25-50mg Placebo	94	44.9	73	2.5	2.6	27.8	NR	81.9	HAM-D ₁₇	6
STAR*D(5)	Bupropion 150-400mg Sertraline 50-200mg Venlafaxine XR 37.5-375mg	727	42	58.7	6.0	7.0	18.9	10	100	HAM-D ₁₇	14
GSK 2009(19)	Bupropion 200-300mg Placebo	325	36	45.3	NR	NR	19	4	100	HAM-D ₁₇	12
Lennox-Smith 2008(20)	Venlafaxine ER 75-300mg Citalopram 20-60mg	112	43	66.5	6.0	1.0	>31	8	100	HAM-D ₂₁	12

* estimated by transforming MADRS; XR: extended release

Baseline characteristics of the six included studies are presented in Table 15. Two trials (Kasper 2010, Olié and Kasper 2007) were not performed specifically in switch populations. Data on switch populations was extracted from a further post-hoc subgroup analysis of both these trials (Kasper 2013).(21) This subgroup analysis was also not strictly in switching patients as the subgroup considered was of previously treated patients, defined as patients who had been treated with antidepressants at least once in the year before randomisation. It was unclear whether all such patients were genuinely switching patients, or whether they had been treated for a prior depressive episode. The ERG considers that the patients are likely to be a mix of these cases, and therefore the eligibility of these two trials for an indirect treatment comparison of switch populations is questionable.

There is considerable diversity in baseline characteristics across trials. Of particular concern are the differences in baseline disease severity. STAR-D and GSK 2009 both have comparatively low baseline depression severity, below the standard threshold for moderate depression in the UK. Lennox-Smith, by contrast had very high baseline depression scores, as the population for this trial was restricted to patients with a HAM-D score over 31. Patients in STAR*D had generally much longer-term MDD, with more previous depressive episodes. As the effectiveness of antidepressants may vary by disease severity these differences could influence the outcomes of the indirect treatment comparison. Similarly the time of assessment varies from 6 to 14 weeks; again remission and withdrawal rates are likely to be time-dependent, so these differences could affect the results. The ERG therefore questions the validity of synthesising these heterogeneous trials as efficacy of treatments may not be consistent across diverse populations.

The primary network meta-analysis performed in the submission excluded the two placebo-controlled trials although these were included in a sensitivity analysis. Results on remission and withdrawal rates from the four remaining studies are presented in Table 16.

Table 16 Summary of outcomes from trials included in the main network meta-analysis

Study	Intervention	Number of patients	Remission			Withdrawal due to AEs		
			Number remitting	Rate (%)	Odds ratio and 95% CI	Number of withdrawals	Rate (%)	Odds ratio and 95% CI
REVIVE	Vortioxetine	252	102	40.5	1.63 (1.12 to 2.37)	15	5.9	0.6 (0.31 to 1.18)
	Agomelatine	241	71	29.5		23	9.5	
Kasper 2010	Agomelatine	80	NR	27.9 / 32.3 *	1.19 (0.61 to 2.24)	NR	2.6	0.28 (0.07 to 1.03)
	Sertraline	96	NR	24.5 / 27.3*		NR	11.3	
STAR*D	Sertraline	238	42	17.6	V vs S 1.54 (0.99 to 2.39)	50	21	V vs S 1.01 (0.65 to 1.56)
	Venlafaxine	250	62	24.8		53	21.2	
	Bupropion	239	51	21.3	B vs S 1.27 (0.80 to 1.99)	65	27.2	B vs S 1.40 (0.92 to 2.14)
Lennox-Smith 2008	Venlafaxine	57 †	21	36.8	1.56 (0.99 to 2.45)	11	5.5	1.03 (0.68 to 1.57)
	Citalopram	55 †	15	27.3		11	5.3	

* Derived from normal/ gamma distribution assumptions; † Patients with MADRS >31

There are considerable differences in results across trials. Remission rates are comparatively low in STAR*D, and are much higher in REVIVE and Lennox-Smith. Similarly withdrawal rates are high in STAR*D and low in both REVIVE and Lennox-Smith. This further suggests that the trials and the populations they recruited may not be comparable.

Only the REVIVE trial found statistically significant evidence of a difference in remission rates between treatments, although comparisons between venlafaxine (XR) and sertraline, and between venlafaxine (XR) and citalopram were almost statistically significant. No trial found any statistically significant differences in withdrawal rates.

4.3.2 Critique of the network meta-analysis

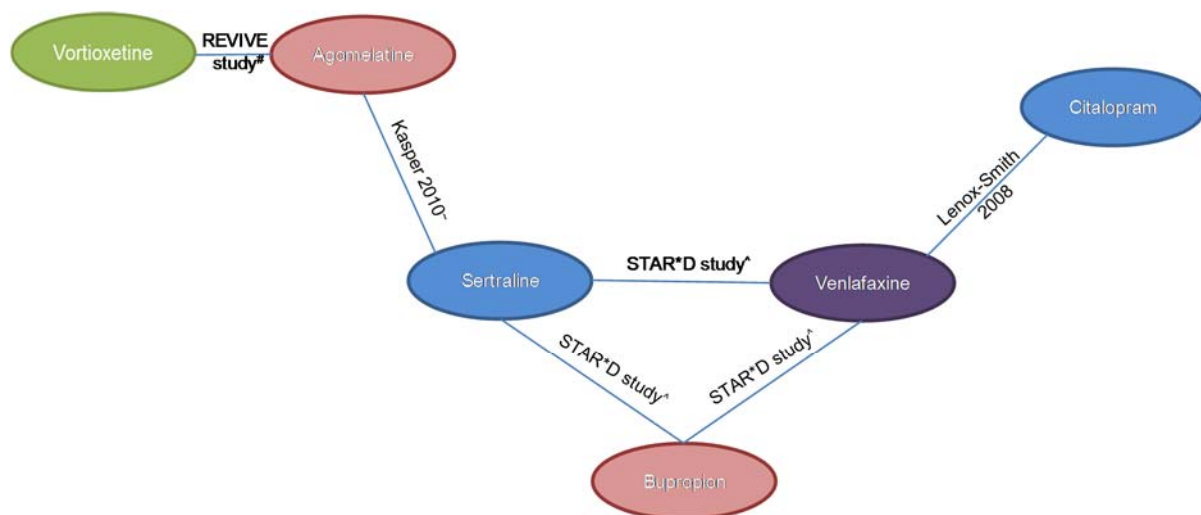
The network considered in the indirect treatment comparison is given in Figure 8 (taken from MS, p. 116). This network is based on only four trials, each arm of the network is informed by only one trial, and there are no “closed loops” in the network. The data for this network are therefore sparse, and comparisons between treatments are driven by the findings in each specific trial, which, as noted in Section 4.3.1, appear to be heterogeneous in their baseline characteristics and outcomes. The limited and heterogeneous nature of the data in the network means its findings may not be reliable.

Only one trial (REVIVE) included vortioxetine, so any comparison of vortioxetine with other treatments will be dependent of the results in that trial. Also only one trial included citalopram, so any

evidence to compare it with vortioxetine is weakened by limited evidence. Agomelatine may have lower efficacy and higher tolerability than other comparators (as suggested by Llorca et al.), (22) which may have biased the efficacy results of the indirect comparisons in favour of vortioxetine, and negatively biased the withdrawal results.

Removing any one trial from this network will leave an unconnected network for which no indirect comparison is possible. Given that the ERG questions whether the subgroup from the Kasper 2010 trial used in the network meets the inclusion criteria (because it does not appear to be specifically in a switch population) and that this trial is an essential link in the network, there is considerably uncertainty around the validity of any findings of this indirect treatment comparison. This should be considered when reading the remainder of this section.

Figure 8 Base-case network used in indirect treatment comparison



^Studies reported remission using HDRS score; *Studies reported remission using MADRS score; ~Remission could be calculated from scores

Vortioxetine: a start point for ITC SSRI SNRI Other non-SSRI

The indirect comparisons were performed for both remission rate and withdrawal rate as outcomes, and using both frequentist and Bayesian network meta-analyses. A summary of the results from the frequentist analysis is presented in Table 17. These results were based on assuming a normal distribution for the remission rate in the Kasper trial. Using a gamma distribution produced similar, but less conservative, results (see MS Appendix Table D49).

Table 17 Summary of the results of the frequentist network meta-analyses

Treatment	Remission rate			Withdrawal rate due to AEs		
	Rate (%)	Risk Difference vs vortioxetine (%)	95% CI	Rate (%)	Risk Difference vs vortioxetine (%)	95% CI
Vortioxetine	40.5	–	–	5.9	–	–
Agomelatine	29.5	-11	-19.4 to -2.6	9.5	3.6	-1.1 to 8.3
Sertraline	26.1	-14.4	-29.9 to 1.1	18.0	12.1	3.1 to 21.1
Venlafaxine	33.3	-7.2	-24.3 to 9.9	18.2	12.3	0.8 to 23.8
Bupropion	29.8	-10.7	-27.8 to 6.4	24.2	18.3	6.4 to 30.1
Citalopram	23.7	-16.8	-41.1 to 7.5	18.0	12.1	-0.3 to 24.5

The ERG considers that basing results on the risk difference is potentially inappropriate because it may be sensitive to heterogeneity across trials. In the appendix the submission also presented results based on the odds ratio using a Bayesian model. These are summarised in Table 18. Results were largely consistent with results based on risk difference.

Table 18 Summary of the results of the Bayesian network meta-analyses

Treatment	Remission rate			Withdrawal rate due to AEs		
	Rate (%)	Odds ratio vs vortioxetine (%)	95% CrI	Rate (%)	Odds ratio vs vortioxetine (%)	95% CrI
Vortioxetine	40.5	–	–	5.9	–	–
Agomelatine	29.5	1.63	1.12 to 2.37	9.5	0.60	0.30 to 1.17
Sertraline	25.9	1.95	0.89 to 4.24	29.5	0.15	0.03 to 0.62
Venlafaxine	35.1	1.26	0.51 to 3.07	29.5	0.15	0.03 to 0.65
Bupropion	30.7	1.54	0.62 to 3.77	38.5	0.10	0.02 to 0.46
Citalopram	25.6	1.98	0.59 to 6.60	29.5	0.15	0.02 to 0.86

The manufacturer also provided results from a Bayesian network meta-analysis which included the two placebo-controlled trials excluded from the main analysis. As the results were broadly similar to those given above (see MS, appendix 10.17.1) this sensitivity analysis is not considered further. On clarification the manufacturer also provided results for analyses based on relative risks. Their findings were similar to the analyses based on odds ratios and risk differences, so they are not discussed further here.

On clarification the manufacturer provided results for analyses based on the standardised mean differences in depression rating scales. These results are summarised in Table 19. These results show efficacy in favour of vortioxetine, although the results are not statistically significant for comparisons with bupropion or citalopram. This finding appears to be dominated by the difference between vortioxetine and agomelatine from the REVIVE trial; other treatments seem broadly of similar efficacy.

Table 19 Summary of network meta-analysis reporting standardised mean differences

Treatment	Standardised mean difference	
	SMD vs vortioxetine	95% CrI
Agomelatine	0.304	0.109 to 0.449
Sertraline	0.542	0.186 to 0.898
Venlafaxine	0.559	0.161 to 0.957
Bupropion	0.609	0.210 to 1.008
Citalopram	0.630	0.186 to 1.074

For remission, frequentist and Bayesian analyses produced broadly similar estimates of remission rates. Neither analysis found any statistically significant evidence that vortioxetine was superior to any other treatment, other than agomelatine (from the REVIVE trial). For withdrawal due to adverse events both analyses found vortioxetine to have statistically significantly lower withdrawal rates than sertraline, venlafaxine (XR) and bupropion. The Bayesian analysis also found vortioxetine to be superior to citalopram. Results from risk difference and odds ratio analyses produced substantially different estimates of withdrawal rates, with the risk difference analysis producing lower rates. This difference suggests that estimates of withdrawal rate are highly sensitive to the method of analysis, and so are likely to be unreliable.

Each arm of the network included only one trial, and the network had no loops, therefore no assessment of heterogeneity or of network inconsistency was possible. The ERG notes that the substantial differences in baseline characteristics and outcomes across trials suggest that heterogeneity is likely to be present, reducing the reliability of the network analysis.

The manufacturer did explore consistency by comparing results from the network meta-analysis to the data from the trials themselves. Remission rates from the analysis and from the original trials are broadly similar, with rates being in general higher than reported in STAR*D, and lower than in Lenox-Smith. Withdrawal rates, however in the analysis were very different from those reported in

the trials. In particular the withdrawal rates on venlafaxine (XR) and citalopram were around 18% in the model (Table 17) but only around 5% in the Lenox-Smith trial (Table 16).

4.3.3 Conclusions of the indirect treatment comparison

The manufacturer concluded that the network meta-analysis showed that vortioxetine is more efficacious and better tolerated than a range of comparator antidepressants.

The ERG does not concur with this conclusion for a variety of reasons. Wide confidence intervals mean that there was little evidence of a statistically significant improvement in efficacy with vortioxetine compared to other treatments. The network meta-analysis used in the indirect treatment comparison was limited to only four trials. Removing any trial would leave the network unconnected. The ERG has concerns as to whether the Kasper trial should have been included as the subgroup analysis used from this trial was not specifically of a switch population.

There is also evidence of substantial heterogeneity in the populations included across the trial, for example in the severity of depression, and apparent heterogeneity in the results of each trial. The limited number of trials meant that formal assessments of heterogeneity and network inconsistency could not be performed. Given these concerns the ERG concludes that the indirect treatment comparison reported in the submission does not provide valid evidence from which any conclusion on the efficacy of vortioxetine may reasonably be drawn.

4.4 Non-RCT evidence

The manufacturers performed a search for evidence other than RCTs but did not identify any relevant studies. The ERG did not find any evidence that relevant non-RCT studies of efficacy in switch patients had been missed.

4.5 Adverse events

The manufacturer performed a search for safety trials of vortioxetine in the “switch” population. None were identified so the search was widened to include all safety trials of vortioxetine. This search identified six studies, of which five were one-year open-label extensions of short-term efficacy trials and were eligible for inclusion in a pooled analysis. This pool included a total of 2,587 patients who continued from short-term, randomised placebo controlled trials and received flexible doses of vortioxetine 2.5 to 20mg/day.

Given that the manufacturer had broadened the scope in the search for adverse event data to all vortioxetine trials, the ERG requested the manufacturer supply adverse event data from all placebo or active control trials they had performed. In response to this request the manufacturer provided data from 12 short-term placebo-controlled phase II/III studies, including one trial (12541A) that was

conducted in patients aged over 65 years. This short-term pool included a total of 3,904 patients treated with vortioxetine.

Table 20 provides a list of studies included in the two pools, and is presented below. None of the studies included were conducted in switch populations. Further details of the pools are presented below.

Table 20 Overview of pools for the evaluation of the safety and tolerability of vortioxetine

Pool	Number of studies included	Study ID
Short-term placebo controlled pool	12	11492A , 11984A, 305, 13267A, 315, 316, 14122A, CCT-002, 303, 304, and 317, and 12541A
Open-label long-term pool	5	11492C, 11984B, 301, 13267B, and 314

4.5.1 Short-term pool of placebo controlled studies

The results of the review of long-term continuation studies of adverse events were reported in a separate document(23) and summarised in clarifications. A summary of incidence of TEAE during the core treatment period (from first dose to last dose in the double-blind treatment period) for vortioxetine and placebo is presented in Table 21 below. The manufacturer stated that the 15mg dose will not be available in the UK, but results for this regimen were presented here for the sake of completion.

The overall incidence of TEAEs was 64.2% in the vortioxetine group, and 57.9% in the placebo group. The Treatment-emergent adverse event (TEAE) with the highest incidence in all the active treatment groups was nausea. The incidence of nausea was 8.1% in the placebo group and 24.1% in the total vortioxetine group (relative risk 3.02; 95% CI 2.57 to 3.55). Headache, which was the TEAE with the highest incidence in the placebo group, had similar incidences in all the treatment groups (approximately 13%).

For the majority of the patients with TEAEs, the TEAEs were mild or moderate. The incidence of severe TEAEs was similar in the placebo group and in the vortioxetine total group (4.4% and 5.5%, respectively). In the vortioxetine dose groups, the incidence of severe TEAEs ranged from 4.1% in the 20mg group to 7.0% in the 5mg group.

The overall incidence of TEAE leading to withdrawal in the vortioxetine total group was higher in the vortioxetine group (6.0%) compared with placebo (4.0%), and higher in 15-20mg doses compared with 5-10mg doses (4.8% [5mg], 5.8% [10mg], 8.0% [15mg], and 7.0% [20mg]). The most common

TEAE leading to withdrawal during the core treatment period was nausea (vortioxetine: 1.1% [5mg], 1.4% [10mg], 3.3% [20mg]; placebo: 0.3%).

Table 21 Summary of TEAEs by dose (APTS)- Short-term pool

	Placebo (n = 1968)	Vortioxetine 5mg (n = 1157)	Vortioxetine 10mg (n = 1042)	Vortioxetine 20mg (n = 812)	Total vortioxetine (n = 3460)
Total adverse events	57.9%	64.7%	61%	65.1%	64.2%
Withdrawal due to adverse event(s)	4%	4.8%	5.8%	7.0%	6.0%
Severe adverse events	4.4%	7%	5.4%	4.1%	5.5%

Table 22 and Figure 9 from the manufacturer response to clarification show the estimated relative risk of adverse events (with 95% confidence intervals) for vortioxetine compared to placebo using the Cochran Mantel-Haenszel approach stratified by study. The analysis included data for vortioxetine 5 to 20mg/day from all studies in the MDD Short-term Pool. The analysis included adverse events with an incidence $\geq 2\%$ for either vortioxetine 5 to 20mg/day or placebo.

Table 22 TEAEs with an incidence of 2% or more by preferred term, core treatment period (APTS) - Short-term pool

Type of treatment emergent adverse event	Percentage with event		Relative risk (95% CI)
	Placebo (n=1968)	Vortioxetine (n=3460)	
Event leading to withdrawal	3.6	5.5	1.54 [1.48 ; 1.59]
Severe AE	4.4	5.5	1.26 [1.22 ; 1.30]
Nausea	24.1	8.1	3.02 [2.57 ; 3.55]
Headache	13.2	12.9	1.06 [0.91 ; 1.22]
Diarrhoea	6.3	5.5	1.24 [0.99 ; 1.55]
Dry mouth	6.1	5.6	1.15 [0.92 ; 1.43]
Dizziness	5.8	5.3	1.14 [0.90 ; 1.44]
Nasopharyngitis	4.6	3.9	1.01 [0.78 ; 1.32]
Constipation	4	2.9	1.42 [1.04 ; 1.94]
Vomiting	3.9	1.1	3.55 [2.25 ; 5.60]
Somnolence	3.1	2.3	1.40 [0.98 ; 1.99]
Fatigue	2.9	2.7	1.11 [0.80 ; 1.55]
Insomnia	2.7	2.5	1.07 [0.76 ; 1.52]

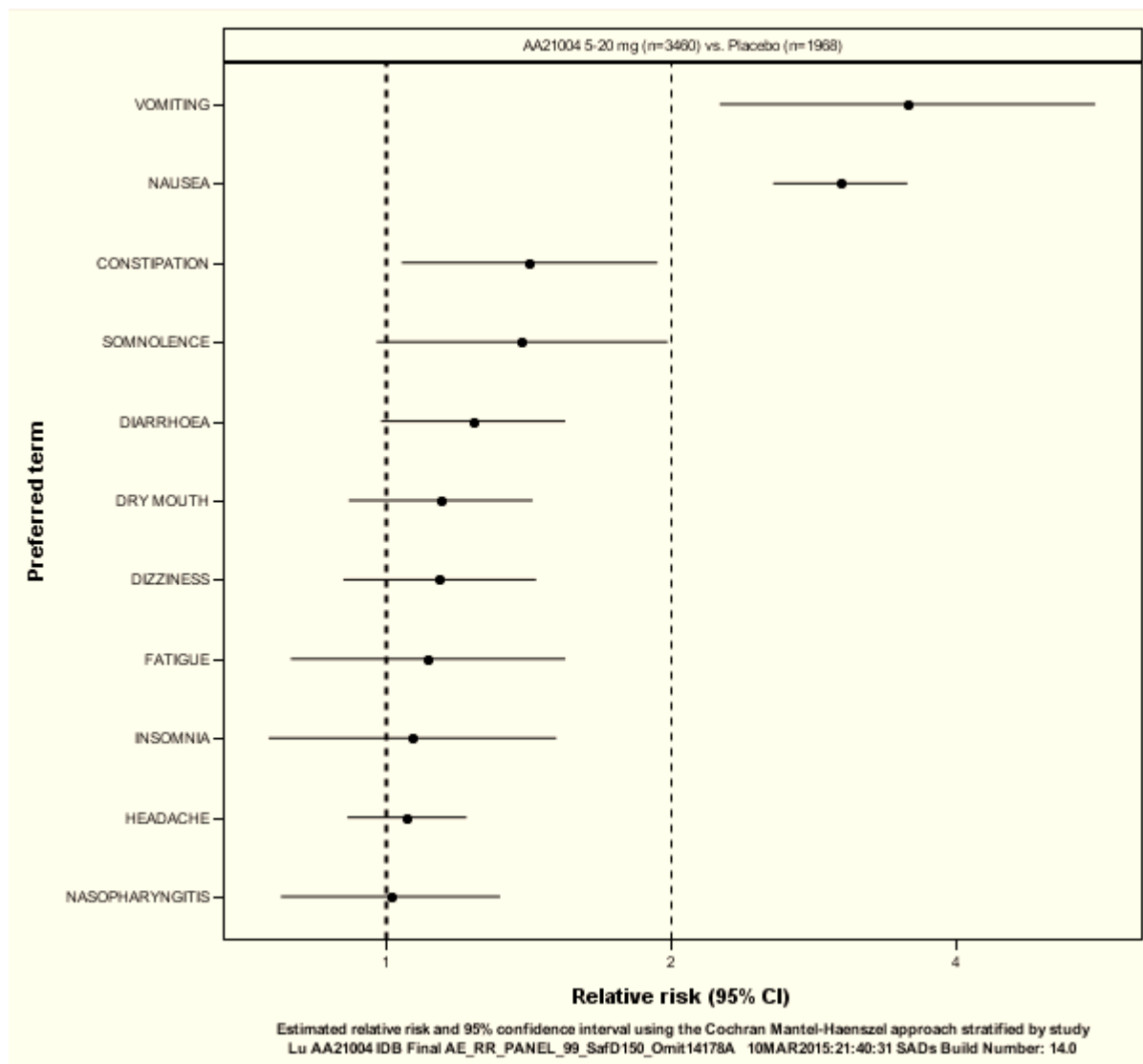


Figure 9 Forest plot of relative risk of TEAEs with an incidence of 2% or more by preferred term, core treatment period (APTS) - MDD Short-term pool

The analysis shows a statistically significant increase in risk of vomiting, nausea and constipation for patients taking vortioxetine. There was no other statistically significant difference in risk between vortioxetine 5 to 20mg/day and placebo in TEAE with an incidence of $\geq 2\%$ in either group.

4.5.2 Open-label pool of continuation studies

The results of the review of long-term continuation studies of adverse events were reported in MS section 6.9.2 (pp.132-133) and in a separate document.(23) The review included six studies of vortioxetine in which safety outcomes were the primary endpoint. All were open-label extensions to short-term efficacy studies and were designed to provide 12-month safety data for regulatory

purposes. Five of those six studies were pooled in an analysis which provided input parameters for long-term side-effects in the economic model, were presented in the submission and in a separate document (“open-label long-term pool”). The sixth trial, which included 120 patients and was conducted in Japan, was excluded from the open-label long-term pool as it had not been completed at the time of the submission. The pool included a total of 2,587 patients who continued from short-term studies and received flexible doses of vortioxetine of 2.5 to 20mg/day. Of these patients, 1,391 (54%) were exposed to vortioxetine for ≥ 52 weeks. A small proportion of the pooled patients were in studies (301 and 11984B) that included a 2.5mg per day dose of vortioxetine. The manufacturer stated that it was not possible to split out the patients who received a 2.5mg dose because study 301 and 11984B were flexible dose studies in which patients received a daily dosage of between 2.5mg and 10mg, but as the proportion of patients receiving this dose was small it is not expected to affect the results.

A summary of incidence of TEAE during the core treatment period (from first dose to last dose of vortioxetine in the treatment period) is presented in Table 23 below. The overall incidence of TEAEs was 74.6%, and was higher in the 15-20mg dose group (78.9%) compared with the 2.5-10mg group (71.2%).

The overall incidence of TEAE leading to withdrawal was 8.1%, and the overall incidence of severe TEAE was 8.9%. The system organ classes (SOCs) with an incidence $\geq 20\%$ were gastrointestinal disorders, infections and infestations, and nervous system disorders. The SOC with the highest incidence in both dose groups was gastrointestinal disorders (33% in the vortioxetine 2.5-10mg group and 42% in the vortioxetine 15-20mg group). The most common TEAE was nausea (20.4%).

Table 23 Incidence of TEAEs of $\geq 5\%$ in the open-label, long-term pool, core treatment period

	Vortioxetine (2.5-10mg)		Vortioxetine (15-20mg)		Vortioxetine (total)	
	n	%	n	%	n	%
Number of patients (APTS)	1,443		1,144		2,587	
Patient-years exposure	1,097		775.4		1,873	
Patients with TEAEs	1,028	71.2	903	78.9	1,931	74.6
Patients with TEAEs leading to withdrawal	89	6.2	120	10.5	209	8.1
Patients with severe TEAEs	135	9.4	95	8.3	230	8.9

Core treatment period: from first dose to last dose of vortioxetine in the treatment period

TEAE: treatment-emergent adverse event.

4.5.2.1 Conclusions of the review of safety studies

No separate conclusions were provided for the review of safety studies, although the manufacturer stated that vortioxetine had a favourable safety profile in an overview of safety in relation to the decision problem (section 6.9.3).

The ERG agrees that based on the evidence presented, vortioxetine appears generally safe and tolerable in patients with MDD. The analysis of the pooled placebo controlled trials and the analysis of the pooled continuation studies included relatively large patient numbers and showed broadly comparable results. Although the incidence of adverse events was high in patients receiving vortioxetine, most AEs were mild to moderate in intensity and there was no conclusive evidence that these were dose-dependent.

However, both pooled analyses had limitations. All analyses from the pool of continuation studies were uncontrolled, and as such they are at high risk of confounding (notably due to the placebo effect). All continuation studies were one-year extensions, and nearly half of patients received vortioxetine for less than one year, which is significantly less than for patients for whom maintenance may be recommended for two years or more. Some relevant studies may have been missed, since only studies that reported safety as a primary outcome were included. Results from the pool of placebo-controlled studies showed that the rate of patients with adverse events was high for vortioxetine (64.2%) as well as for placebo (57.9%), indicating a high placebo effect, although there was a statistically significant higher risk in the incidence of some specific adverse events, particularly nausea and vomiting (approximately 3 and 3.5 times higher than placebo). These results are in line with those of the Pae 2014 review(24), which found that nausea and vomiting were some of the most common AEs reported, and had an incidence that was significantly higher in the vortioxetine than in the placebo group. They also found that nausea was the single most common AE reported as a reason for discontinuation of vortioxetine, and found that its frequency showed a trend toward a dose–response relationship. Compared with placebo, withdrawal due to adverse events was slightly higher for vortioxetine, particularly in higher treatment doses (15-20mg).

The MS and clarifications presented no evidence of adverse events when comparing vortioxetine with active comparators. The ERG concludes that the best data available are that from the two trials (REVIVE, TAK318) discussed above in Section 4.2. The indirect treatment comparisons provided by the manufacturer and in Llorca et al(22) both reported withdrawal due to adverse events, which can be considered a reasonable proxy for adverse events overall. These results are discussed in sections 4.3 and 4.6. Based on these results there is some evidence that vortioxetine has a better adverse event profile than other drugs, including venlafaxine and duloxetine. It may be less safe than agomelatine, although this conflicts with results from REVIVE.

4.6 Evidence syntheses of non-switch populations

As discussed in Section 3 the ERG questions the validity of restricting the analysis to “switch” populations. The evidence to suggest that there is a difference in treatment efficacy between initial use and switch use is limited,(1, 11) and restricted to showing that where patients are switching from an SSRI due to lack of response or intolerance, a non-SSRI may be more effective than another SSRI in these switching patients.(25) There is no evidence currently available to suggest that the relative efficacy of non-SSRIs differs between initial-use and switch populations. The ERG thinks that initial-use trials should be considered as providing relevant supporting evidence, particularly for the relative efficacy of non-SSRIs, given the limited nature of the evidence in the switch population identified by the manufacturer.

The ERG therefore requested that the manufacturer provide results from trials or meta-analyses of trials comparing vortioxetine to other active treatments and/or placebo in initial use and non-switch use populations.

In response the manufacturer:

1. Provided their own meta-analyses of trials comparing vortioxetine to placebo.
2. Reported the existence of two submissions to regulators:
 - Pharmaceutical Benefits Advisory Committee (PBAC, Australia)(26)
 - Canadian Agency for Drugs and Technologies in Health (CADTH)

However, they did not provide these submissions; a redacted version of the PBAC report is in the public domain but the CADTH report has not been made public.

3. Identified four systematic reviews of vortioxetine:
 - Pae et al 2014(24)
 - Berhan and Barker 2014(27)
 - Citrome 2014(28)
 - Meeker et al 2015(29) (this review was published very recently and so was identified by the manufacturer subsequent to the MS and response to clarifications)
4. Identified one indirect treatment comparison sponsored by the manufacturer (Llorca 2015).(22)

The ERG thinks that all these analyses in non-switch populations provide relevant evidence on the efficacy of vortioxetine, and considers this evidence below.

4.6.1 Vortioxetine vs placebo

On request, the manufacturers provided results from meta-analyses of their short-term (6-8 weeks) placebo controlled trials of vortioxetine. The Pae et al.,(24) Berhan and Barker,(27) and Meeker et al.(29) studies were systematic reviews designed to include all placebo controlled randomised trials of vortioxetine. The ERG considers that the search strategy, inclusion criteria and bias assessment processes in these reviews were generally appropriate. All papers reported the results of fixed or random-effects meta-analyses of the trials, for various outcomes. The Citrome paper was also a systematic review of placebo controlled randomised trials of vortioxetine, but did not include a conventional meta-analysis, so it is not considered further here.

There was considerable overlap in the trials included in the meta-analyses, they also reported slightly different outcomes. The manufacturer provided analyses by vortioxetine dose and a subgroup analysis using only non-US trials.

A summary of the results of the meta-analyses is given in Table 24. For data provided by the manufacturer and Meeker et al, results are presented for a 10mg dose of vortioxetine. The results are broadly consistent across analyses, as is to be expected given that they include a similar set of trials. All analyses show that vortioxetine is superior to placebo for all outcomes. Both the manufacturer's analysis and that of Berhan suggest a dose response relationship, with vortioxetine being more effective at higher doses, up to 20mg.

Table 24 Summary of meta-analyses of vortioxetine vs. placebo

Outcome	Meta-analysis (effect estimate and 95%CI)			
	Manufacturer*	Pae et al.(24)	Berhan and Barker(27)	Meeker et al(29)
Mean difference in change in MADRS	-3.53 -4.96 to -2.10	NR	-3.920 -5.258 to -2.581	-3.38 -4.89 to -1.87
Mean difference in change in CGI-I	-0.42 -0.59 to -0.26	NR	NR	NR
Standardised mean difference in depression score	NR	-0.217 -0.313 to -0.122	NR	NR
Response rate (odds/risk ratio)	1.84 1.44 to 2.35	1.652 1.321 to 2.067	NR	1.42 1.21 to 1.67
>50% reduction in MADRS	NR	NR	2.869 2.391 to 3.441	NR
Remission rate (odds/risk ratio)	1.59 1.23 to 2.04	1.399 1.104 to 1.773	NR	1.45 1.18 to 1.77
Discontinuation due to adverse event (odds ratio)	1.58 1.18 to 2.12 ^s	1.530 1.144 to 2.047	NR	NR

*From clarification response, unless otherwise specified; ^s Llorca et al.(22)

4.6.2 Vortioxetine vs active comparators

The submission to PBAC, the Pae and Meeker meta-analyses all considered trials comparing vortioxetine to an active comparator. The trials included in these analyses were generally placebo controlled trials with an active reference arm, except for one randomised trial evaluating vortioxetine and venlafaxine in a head-to-head comparison which was included in the submission to PBAC.⁽³⁰⁾ In the original submission, the manufacturer criticised the use of these active reference arms (MS, Sections 1.4.1 and 2.8.2). Active reference arms are included in trials of antidepressants to ensure that patients are responding to therapy. An active reference should be a drug of proven superiority over placebo, so it can be used to check whether the trial has successfully treated patients by confirming a difference between the active reference and placebo. Patients known to be non-responders to the active reference are excluded from this arm, so the active reference arm may include patients more likely to respond to treatment. The manufacturer therefore claimed that any comparison of vortioxetine with an active reference may be biased towards the active reference.

The ERG recognises the potential for bias because the comparison between vortioxetine and active reference is not truly randomised and there is the potential for patients to differ in likely response to treatment between arms. However, the ERG does not consider this risk of bias to be sufficiently substantial to reject such comparisons altogether, particularly as there is a reasonably large number of such trials. The results of these comparisons discussed in the Pae and Meeker analyses, and the PBAC submission are therefore considered below.

4.6.2.1 Pae et al.

In Pae et al. meta-analyses comparing vortioxetine to active comparator for standardised mean difference, response and remission rates were presented. The analysis did not distinguish between the different comparator treatments. Based on the references in the paper the ERG has reanalysed the data, grouping trials by the comparator included in each trial.

Figure 10 shows the results based on data from the trials in the Pae meta-analysis for standardised mean difference in depression score between arms. Figure 11 shows the results for response rate, and Figure 12 for remission rate. In all three cases vortioxetine is superior to agomelatine based on the trial of Dragheim.⁽³¹⁾ This trial appears to be an early presentation of the results of the REVIVE trial, but this could not be confirmed because the trial was reported only as a conference presentation which the ERG could not access. There is no evidence of a difference between vortioxetine and venlafaxine, based on one trial. Vortioxetine is consistently and statistically significantly inferior to duloxetine for all three outcomes. The potential that results were biased in favour of duloxetine given the potential for bias discussed above must be considered, however there is no evidence of such a bias in favour of venlafaxine.

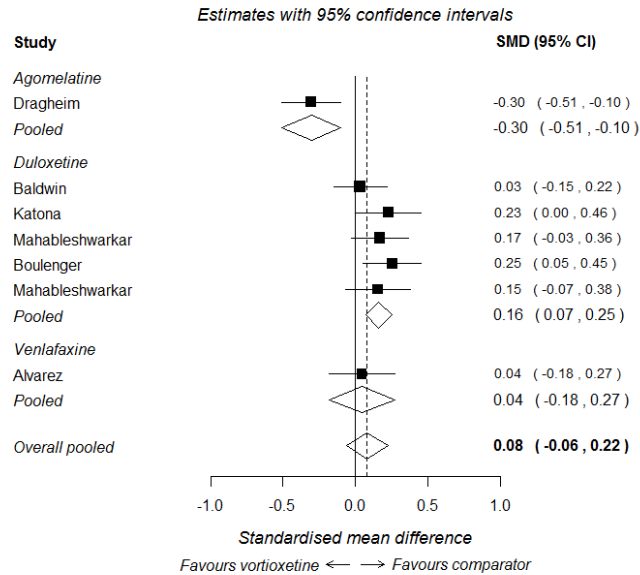
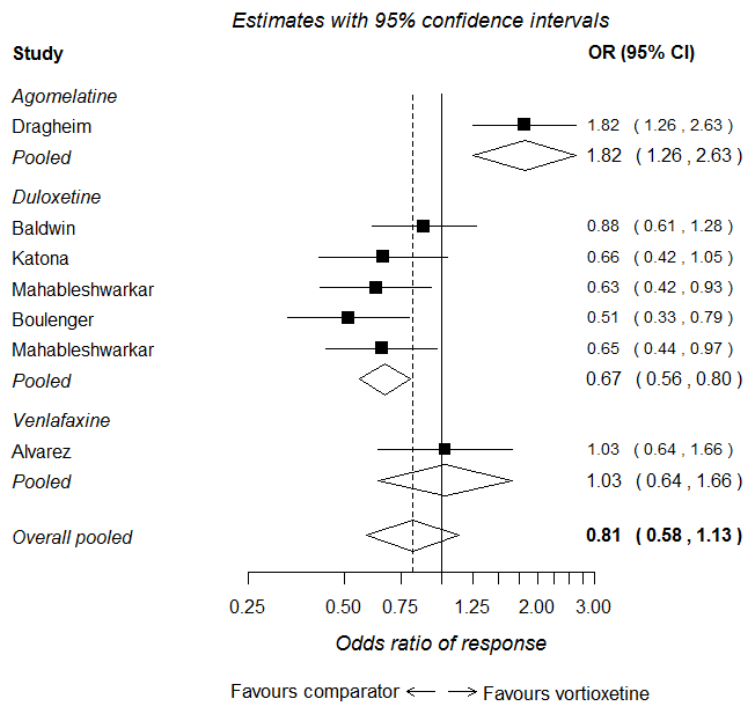
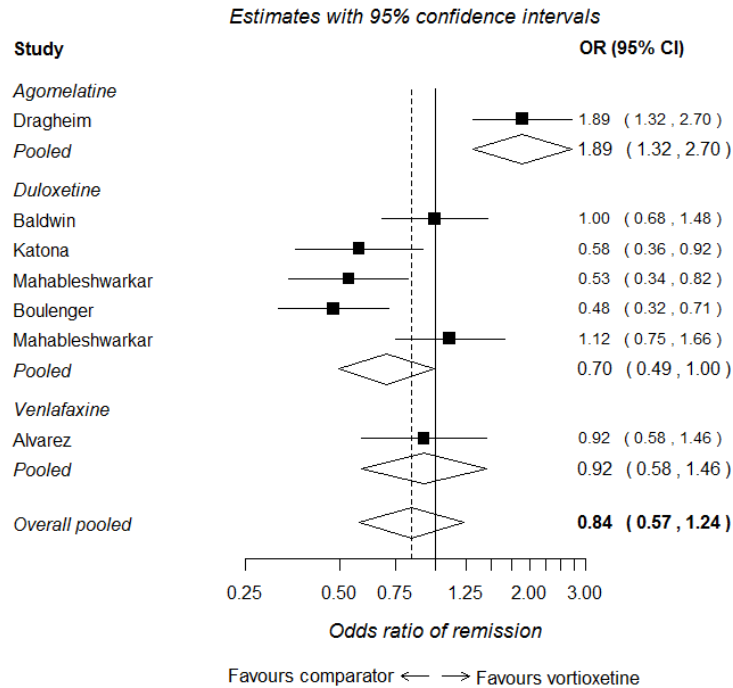
Figure 10 Forest plot of standardised mean difference based on data from Pae et al.**Figure 11 Forest plot of response rate based on data from Pae et al.**

Figure 12 Forest plot of remission rate based on data from Pae et al.

4.6.2.2 Meeker et al.

Meeker et al compared vortioxetine to SNRIs, using a similar set of trials to Pae et al. The paper did not distinguish between different SNRIs and reported results separately for different doses of vortioxetine. Given this, it was not possible to directly compare results from this paper to other analyses, but generally SNRIs were found to have a better response rate than vortioxetine and had greater reductions in MADRS scores. Data on remission were too sparse to draw any conclusions.

At higher doses (15mg and 20mg) vortioxetine had lower rates of withdrawal due to adverse events than SNRIs, but there was no difference in the incidence of serious adverse events.

4.6.2.3 PBAC submission

The submission to PBAC analysed vortioxetine trials with either venlafaxine or duloxetine as active comparators. Two venlafaxine trials were included. Five duloxetine trials were included, but data were redacted for all but one. There was overlap between the trials included in the PBAC submission and Pae et al. Table 25 presents a summary of the results included in the submission.

Table 25 Summary of results in the PBAC report

Outcome	Active comparator (Mean difference and 95% CI)*	
	Venlafaxine (Two trials)(30, 32)	Duloxetine (one trial)(33)
Mean difference in MADRS	-0.44 -2.20 to 1.32	2.50 0.41 to 4.59
Mean difference in HAM-D17	-0.35 -2.07 to 1.37	NR
Mean difference in HAM-D24	-0.22 -2.35 to 1.91	2.10 0.04 to 4.16
*Positive values indicate a difference favouring the active comparator		

As for the Pae et al analysis, there was no evidence of any difference in efficacy between vortioxetine and venlafaxine, but duloxetine was superior to vortioxetine. The PBAC submission reported that treatment withdrawals due to adverse events were significantly more common in the venlafaxine arm than the vortioxetine arms, and found no statistically significant differences between vortioxetine and duloxetine. The PBAC concluded: “the claim of non-inferiority of vortioxetine compared to duloxetine was not adequately supported” (PBAC, p.12),(26) suggesting that the results of redacted duloxetine trials were consistent with that for which data were reported.

The results of the Pae meta-analysis and the PBAC submission appear to be consistent.

4.6.3 Indirect treatment comparison

On request for clarification the manufacturer identified a further indirect treatment comparison (Llorca et al).(22) This was a systematic review and network meta-analysis, sponsored by the manufacturer. The review sought to identify all placebo controlled trials of the following drugs: vortioxetine, agomelatine, desvenlafaxine, duloxetine, escitalopram, sertraline, venlafaxine, vilazodone. The outcomes considered were efficacy (in terms of standardised mean difference in depression scales, remission and response rates) and tolerability (in terms of odds ratio for withdrawal due to adverse effects). Trials were pooled using random-effects meta-analyses for each drug. Indirect treatment comparisons (via placebo) were performed using linear meta-regression models. The ERG considers that the review process and statistical methods used in this review appeared generally appropriate, but notes that no quality assessment of the included trials was reported.

The results of the indirect treatment comparison performed by Llorca et al are given in Table 26.

Table 26 Indirect treatment comparison by Llorca et al.

Outcome	Results vs vortioxetine (Standard error)						
	Agomelatine	Desvenlafaxine	Duloxetine	Escitalopram	Sertraline	Venlafaxine	Vilazodone
Efficacy at 2 months (SMD: <0 favours vortioxetine)	-0.156 (0.113)	0.025 (0.803)	0.090 (0.419)	-0.054 (0.695)	-0.037 (0.832)	0.124 (0.328)	-0.245 (0.111)
Withdrawal (Odds ratio: <1 favours vortioxetine)	1.769 (0.030) *	0.578 (0.035) *	0.752 (0.262)	0.671 (0.275)	0.299 (0.008) **	0.469 (0.009) **	0.640 (0.181)
Response rate (Odds ratio: >1 favours vortioxetine)	1.045 (0.815)	1.153 (0.364)	0.893 (0.514)	0.843 (0.523)	0.772 (0.575)	0.789 (0.353)	0.975 (0.934)
Remission rate (Odds ratio: >1 favours vortioxetine)	1.220 (0.470) **	1.029 (0.852)	0.894 (0.526)	0.990 (0.981)	NA	0.689 (0.444)	0.983 (0.952)

* *p*-value 0.01 – 0.05; ** *p*-value <0.01

This analysis generally found no statistically significant evidence of a difference in efficacy between vortioxetine and any other treatment. The exception was that vortioxetine had a higher remission rate than agomelatine. Vortioxetine generally had a lower withdrawal rate than other treatments, although the results were only statistically significant for desvenlafaxine, sertraline and venlafaxine. Agomelatine had a lower withdrawal rate than vortioxetine.

This analysis was not performed in a “switch” population, however the findings of this analysis are consistent with those from the indirect treatment comparison in the switch population submitted by the manufacturer (except for agomelatine and withdrawal).

4.7 Conclusions of the clinical effectiveness section

The manufacturer’s submission focused on trials in patients who had previously received antidepressants for a current MDE but were switching treatment to vortioxetine due to lack of response or adverse events; the “switch” population. As discussed in Section 3 The ERG notes that this is a substantial restriction when compared to the original scope, which specified a general population of all adults with MDD.

The restriction to a switch population meant that only two trials comparing the efficacy vortioxetine with other antidepressants were submitted. Both trials were generally well conducted but there were a number of issues related to their design and their population which may limit the applicability of their

results to UK practice. The REVIVE trial comparing vortioxetine to agomelatine found vortioxetine had greater reduction in depression scores and lower withdrawal rates due to adverse events, but this result may not be reliable as this was a non-inferiority trial and was not powered to detect superiority of vortioxetine. It should also be noted that agomelatine is not approved for use in the UK as no evidence for its efficacy has been submitted.

The TAK318 trial included patients who were switching due to sexual dysfunction but had responded to initial treatment. The ERG notes that this is a very narrow and specific population, so the TAK318 trial provided little information on the broader population who might take vortioxetine. It did find that vortioxetine reduced sexual dysfunction symptoms when compared to escitalopram. However it is not clear whether this finding is specific to vortioxetine, or whether any non-SSRI would have a similar beneficial effect.

The restriction to switch populations meant that the indirect treatment comparison in the submission included only four trials in its main analysis. The ERG has considerable concerns over the validity of the network analysis because of the high apparent diversity in the populations across trials, including very different patients and severities of depression. For one trial (Kasper) the analysis used a subset of patients who had been treated in the past year. This is not the same as patients who were switching treatment, so the ERG does not think this trial should have been included; without it, there is no connected network, rendering the analysis invalid. As such the ERG does not think the results of the indirect treatment comparison are valid, but notes that the analysis found no convincing evidence of difference between vortioxetine and other treatments in terms of remission rate (except for agomelatine). There was some evidence that vortioxetine may have lower withdrawal rates, but the high apparent heterogeneity across trials means the validity of this finding is questionable.

The manufacturers did not identify any trials reporting safety data in the switch population other than data reported in REVIVE and TAK318. The manufacturers therefore expanded the review of safety data to non-switch populations. This review identified 12 short-term placebo controlled trials and five longer-term open label trials of vortioxetine. In the placebo controlled trials severe adverse event rates and adverse events leading to withdrawal were more common on vortioxetine than placebo. However, based on the evidence presented, vortioxetine appears generally safe and tolerable in patients with MDD. Both the analysis of placebo controlled trials and the analysis of continuation studies included relatively large patient numbers and showed broadly comparable results. Although the incidence of adverse events was high in patients receiving vortioxetine, most AEs were mild to moderate in intensity and there was no conclusive evidence that these were dose-dependent. The manufacturer did not present any safety comparisons of vortioxetine with any active comparators in the broad MDD population, so the safety profile of vortioxetine compared to other antidepressants is uncertain.

Given the limited nature of the data in the switch population the ERG considers that data in non-switching and initial-use populations should be considered. Although such data is not in the switch population it is relevant to the broader population of all patients with MDD specified in the NICE scope. The manufacturer justified excluding trials of non-switching populations by claiming that treatment efficacy in a switch population may be different from in initial use. The ERG considers that the evidence submitted to justify this claim was limited, as it refers only to patients who had previously used an SSRI, where switching to another SSRI may be less effective than a non-SSRI treatment. No evidence was presented to suggest that the relative efficacy of non-SSRIs may vary between initial and switch use, and no evidence was specific to vortioxetine. The ERG therefore concludes that this restriction was inappropriate and evidence on non-switch populations is relevant when examining the efficacy and safety of vortioxetine.

Direct evidence comparing vortioxetine to other active treatments in non-switching populations was primarily available from placebo controlled trials with active reference arms. The manufacturer criticised the use of active references because they are not true randomised comparisons and patients known to be non-responsive to the reference are excluded, possibly biasing results in favour of the active reference. While the ERG accepts the potential for such bias it does not consider this potential bias to be substantial enough to exclude these trials.

Data on trials with active reference arms were available from the meta-analysis of Pae et al, and the manufacturer's submission to PBAC. Both found no evidence of any difference in efficacy between vortioxetine and venlafaxine, based on two trials. There was evidence that vortioxetine was inferior to duloxetine in terms of reducing depression scores, response and remission. While there is a possibility of bias in favour of duloxetine in these analyses it is not clear whether any bias would be sufficient to completely explain this inferiority.

An indirect treatment comparison in non-switch populations was performed by Llorca et al, based on placebo controlled trials of a number of antidepressants. This analysis found no evidence of any difference in efficacy between vortioxetine and other treatments, but there was some evidence to suggest that vortioxetine had a lower withdrawal rate due to adverse events than some treatments, including sertraline and venlafaxine. While this is an indirect analysis, and not conducted in a switch population, the number of trials included in this analysis suggests that this may represent the most reliable evidence for comparing vortioxetine to other treatments.

In summary, the manufacturer's restriction to trials in a "switch" population meant that very limited evidence was presented in the submission and the ERG considers the indirect treatment comparison, in particular, to be unreliable. Trials in the more general, non-switching, population provide more

data, but with the possibility that treatment effects may differ from those patients switching treatments, particularly when comparing vortioxetine to SSRIs. Direct comparisons of vortioxetine to other treatments are limited because they are placebo-controlled trials with active reference arms and so there is potential for bias due to them not being truly randomised. These trials, however, suggested that vortioxetine may be inferior to duloxetine, and this possibility cannot be dismissed entirely even with the potential for bias. Indirect comparisons of treatments suggested that vortioxetine had similar efficacy to other drugs, but with a possibility lower withdrawal rate due to adverse events.

The ERG concludes, based on the totality of the evidence, that vortioxetine is likely to be of similar efficacy to other antidepressants, but may be superior to agomelatine and inferior to duloxetine.

Vortioxetine appears to have a lower withdrawal rate due to adverse events than most other treatments, and so may have a better overall safety profile, however data on adverse events with vortioxetine, particularly when compared to other antidepressants, are too limited to draw any firm conclusions on the safety of vortioxetine.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the manufacturer and the additional information provided in response to the ERG points for clarification. The submission was subject to a critical review on the basis of the manufacturer's report and by direct examination of the electronic version of the economic model. The critical appraisal was conducted to highlight key assumptions and areas of uncertainty. Section 6 presents additional work undertaken by the ERG to further explore these aspects.

The manufacturer's economic submission included:

- A description of the systematic literature review conducted to identify existing published evidence on the cost-effectiveness of vortioxetine relevant to the stated decision problem concerning the management of adults experiencing an inadequate response to a prior SSRI or SNRI for an MDE (MS, Section 7.1).
- A report on the de novo analysis undertaken by the manufacturer. The report described the patient population, the model structure and the associated treatment pathways assumed before and after a possible switch to third and later lines of treatment (MS, Section 7.2); the clinical parameters used in the economic model (MS, Section 7.3); the measurement and valuation of health effects and the quality-of-life data used in the cost-effectiveness analysis (MS, Section 7.4); the resource use identification and the parameters used in the model (MS, Section 7.5); the sensitivity analyses undertaken (MS, Section 7.6); and the cost-effectiveness results for the base-case and sensitivity analyses (MS, Section 7.7).
- An electronic copy of the manufacturer's economic model developed in Microsoft Excel®.

In response to a number of points for clarification raised by the ERG, the manufacturer further submitted:

- Additional exploratory analyses related to the model time horizon and results for alternative time horizons of 2 and 8 months.
- An additional scenario where treatment is assumed to be maintained for at least 2 years for patients at risk of relapse, based on recommendations from NICE Clinical Guideline CG 90.
- Further analyses of the EQ-5D data from the REVIVE trial.
- Additional clarification regarding the ‘switch cost’ applied when patients switched therapy and the distributional assumptions and data used for parameters in the probabilistic sensitivity analysis (PSA).

5.1 ERG comment on manufacturer’s review of cost-effectiveness evidence

Section 7.1 of the MS focusses on identifying evidence specifically on the cost-effectiveness of vortioxetine. The search strategies were briefly described in the main body of the submission, and full details were provided in an appendix. The MS did not attempt to formally identify published evidence on the cost-effectiveness of other antidepressants. However, the manufacturer made reference to the economic model used in NICE CG90 to order to provide a rationale for any differences in model structure proposed within the manufacturer’s de-novo analysis.

5.1.1 Searches

A number of databases were searched, including MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews (CDSR). Reporting of search strategies was generally appropriate. An appropriate economics study-design filter was used in the MEDLINE and EMBASE searches.

The search strategy undertaken for the specific aim of the review presented by the MS is considered appropriate by the ERG.

5.1.2 Inclusion/exclusion criteria used for study selection

The inclusion/exclusion criteria used for study selection can be found on page 141 of the MS and are reproduced below:

- Population: adults with major depressive disorder or experiencing major depressive episodes.
- Intervention: vortioxetine. Evaluations without a vortioxetine-based regimen were excluded.
- Outcomes: results from economic evaluations (including cost-utility, cost-benefit, cost-effectiveness, cost-consequence and cost-minimisation analyses).
- Study designs: economic evaluations and reviews of economic evaluations (to source the original studies).

The ERG considers these criteria to be appropriate to identify existing published evidence specifically on the cost-effectiveness of vortioxetine.

5.1.3 Studies included and excluded in the cost effectiveness review

Twenty-eight potentially relevant studies were identified from the search strategy. However, 26 of these studies were subsequently excluded on the basis of the information reported in the title and abstract. The remaining 2 studies were excluded after a full-text review. Consequently, no previously published studies of the cost-effectiveness of vortioxetine were identified in the MS.

The ERG did not identify any additional published evidence which met the stated inclusion/exclusion criteria. However, the ERG also searched for public documents for the submissions to Pharmaceutical Benefits Advisory Committee (PBAC) in Australia and the Canadian Agency for Drugs and Technologies in Health (CADTH). These submissions were highlighted by the manufacturer in their clarification response to issues raised by the ERG concerning the clinical effectiveness data. Only the public summary document for the PBAC submission was subsequently identified and considered by the ERG.

Only limited details were available in the public summary document for the PBAC assessment and a full review of the submission and approach was not possible. The population considered in the PBAC submission appeared similar to the manufacturer's stated decision problem for NICE, namely "patients who have received and not responded to an initial antidepressant medication or patients who are intolerant of or who have contraindications to other initial antidepressant therapy". The economic submission appears to have been based on a cost-minimisation analysis comparing vortioxetine with desvenlafaxine. Desvenlafaxine is an SNRI based on a synthetic form of the major active metabolite of venlafaxine. The relevance of this study to the NICE decision problem is clearly limited since desvenlafaxine is not commercially available in the UK. However, the ERG considers that the approach and the subsequent responses provided by the Economics Sub-Committee of PBAC were a relevant consideration. The public summary documented stated that:

"By cost-minimising vortioxetine to desvenlafaxine alone, the submission suggested that the price of vortioxetine could be made more commercially viable than a price based on a cost-minimisation listing against venlafaxine or duloxetine which the submission had noted to have been affected by statutory price reductions through generic competition. The ESC considered that this was not reasonable. The economic comparison should have reflected the current range of drugs likely to be displaced by vortioxetine."

The ESC advised that the submission should have used a weighted mean price of the drugs that would actually be displaced by vortioxetine. The ESC noted that the evaluation suggested that this could either be done using a weighted mean of SNRIs, or a weighted mean of all alternative therapies (SSRIs, SNRIs, tricyclic anti-depressants and other anti-depressants)”.

5.1.4 Conclusions of the cost effectiveness review

In the absence of any previously published cost effectiveness studies of vortioxetine for the management of MDE, the de-novo analysis in the MS represents the most relevant evidence for the stated decision problem.

The ERG recognises that the manufacturer has identified and subsequently justified differences between their approach and the model used to inform NICE CG90. However, the ERG also considers that a more formal review of existing economic evaluations for other antidepressants would have been helpful in providing further justification for their approach and to assist with validation (i.e. the extent to which the manufacturer’s model for comparator treatments is consistent with previous models). Such a review could also have provided a helpful conceptual basis for informing and justifying structural choices and assumptions. This seems particularly pertinent since the single study where a comparison is made (NICE CG90) evaluated the cost-effectiveness of 1st line therapy and did not formally include the decision (and associated costs and consequences) of switching therapy.

The ERG identified a previous published systematic review of methodologies used in cost-effectiveness models for evaluating treatments in major depressive disorder.(34) This review identified 37 studies; 29 of these included pharmacological interventions, 9 of which were UK studies. The review highlighted that the model time horizon and associated structure were important aspects in capturing the costs and consequences of the different treatment phases. These phases include acute treatment, during which time the goal is to resolve symptoms; continuation treatment, during which time therapy is continued to ensure complete resolution of the episode and to prevent relapse; and long-term maintenance, where therapy is continued to prevent the development of a new episode.

The majority of the models reviewed used a decision-tree structure (n=28) and most of these had a time horizon of 6 months to 1-year, which was typically separated into two intervals representing the acute and continuation phases of depression.

The review highlighted that 15 of the studies were based largely on 2 alternative structural approaches based on those initially developed by Francois (35) and Casciano.(36)

- The decision-tree structure developed by Francois (35) consisted of two main pathways. Patients with MDD entered the model in the first path representing primary care. Patients with inadequate response in primary care could subsequently titrate to a higher dose or switch treatment. Patients with insufficient response after titration and/or switching were referred to secondary care, which was represented by the second path. In the secondary care path, patients could have their dose titrated, have their treatment switched, receive adjunctive therapy with another agent, or be hospitalised. The model structure also incorporated the risk of suicide and attempted suicide.
- The decision-tree structure developed by Casciano (36) included additional events following treatment failure due to lack of efficacy including titration to maximum dosage, within-class adjunctive therapy, between-class adjunctive therapy, and treatment switch. The model structure did not incorporate the risk of suicide and attempted suicide.

Several key differences were highlighted in the review between these two modelling approaches. Firstly, the models incorporated different treatment options for patients failing first and second lines of treatment, with the Francois structure also including the option of hospitalisation once all treatment options had failed. Secondly, the Casciano structure assumed that successfully treated patients (defined as a 50% or greater improvement in MADRS or HAMD score) would continue on treatment for 6 months and didn't include the risk of a subsequent relapse. In contrast, the Francois structure incorporated a risk of premature treatment discontinuation as well as the risk of a subsequent relapse.

The review also highlighted the significant variation across studies in the measures of treatment success that were used, with measures based on response and/or remission. The lack of consistency in the measures and the definitions of these measures were also noted by the authors. Response was most commonly defined as a 50% or greater improvement in the MADRS score or the HAMD-17 score. However, one model used three definitions for different levels of response based on MADRS scale: response (greater than 50% improvement from baseline), partial response (25%-50% improvement from baseline) and no response (< 25% improvement from baseline).

The review concluded that there appeared general consensus that values of 7 or less on the HAMD and 10 or less for MADRS were indicative of clinical remission. However, of the 14 models using the MADRS-based definition of remission, only two used a cut-off value of ≤ 10 , with the majority of the models using a cut-off value of ≤ 12 .

The systematic review of existing model structures is useful in highlighting the variation that exists both in terms of how initial success is determined (i.e. response and/or remission) and the alternative pathways which are considered following an initial successful or unsuccessful treatment. However,

the review provides limited insight into the appropriateness of using alternative approaches to defining success. The ERG considers this an important limitation since inevitably the criteria applied and the timing of this is an important consideration in ensuring that the model structure appropriately characterises the way in which clinical decisions are made as well as the subsequent pathways followed by patients.

Importantly, while the majority of studies appeared to use either response or remission as the determinant of treatment success (such that subsequent decisions and pathways were then conditioned upon this measure), 4 of the 8 UK studies included both measures. The studies by Benedict (2011) (37) and Lennox-Smith (2008) (20) are particularly insightful since these studies include additional pathways for patients who have responded but not yet achieved remission (i.e. responder/non-remitters). Both models assumed that the initial treatment would be continued in responder/non-remitting patients beyond the initial acute period (8 weeks in both models). This approach contrasts with other published models which typically assumed a single continuation rule based on either response or remission at a single time point. The ERG clinical advisors consider that these additional pathways included by Benedict (2011) and Lennox-Smith (2008) appear more reflective of clinical practice than a single continuation rule based on either response or remission.

Although both Benedict (2011) and Lennox-Smith (2008) allowed patients who have responded but not yet achieved remission to continue therapy beyond 8 weeks, they differ structurally in terms of subsequent pathways and timings. Lennox-Smith (2008) incorporates a single additional 8-week period for this group, such that if these patients do not subsequently achieve full remission over the next 8 weeks (i.e. 16 weeks in total) then their initial therapy will be switched at this point. In contrast, the Markov-structure employed by Benedict (2011) assumes that therapy can be continued in this group for up to 40 weeks (i.e. covering the entire 48 week horizon) as long as the initial response is maintained.

The systematic review is helpful in highlighting the significant variation that exists within existing models and the different approaches employed concerning key structural assumptions. However, it is evident that no clear consensus appears to have emerged on the most appropriate structural assumptions for modelling an MDE and alternative treatment strategies. Despite the lack of consensus, the ERG considers that the review provides an important basis to critique the approach undertaken by the manufacturer in their de-novo analysis for vortioxetine. In particular, the following points are important considerations:

1. The time-horizon should be sufficient to capture the different phases of treatment. Several authors have argued that a horizon of 1-year is appropriate to capture the full recommended course of treatment (6 months after remission) and relapses within a year.
2. Heterogeneity based on the severity of the initial episode (or other characteristics such as number and timing of previous episodes) may mean that different model pathways or structures should be considered. For example, several of the existing models assume different pathways for patients being managed in a primary or secondary care setting. The study by Benedict (2011) assumed that patients with a score of ≥ 25 on the HAMD-17 were likely to be referred to mental health specialists in secondary care.
3. There appears to be significant inconsistency amongst existing studies concerning the appropriate definition of initial treatment success and subsequent clinical decisions. While the majority of existing models use either response or remission (variably defined across studies), several of the more recent publications have incorporated both response and remission as outcomes. These studies have incorporated separate pathways for patients achieving remission during the initial acute period as well as for patients who have responded but not yet achieved full remission. Importantly, those studies which have incorporated these additional pathways have been those in which the decision to switch therapy (and associated pathways) has been a central consideration.
4. There also exists significant variation in subsequent pathways for patients not achieving an initial treatment success. While some models assume that patients are subsequently switched onto another antidepressant medication, other models assume a variety of strategies including titration and augmentation, including both pharmacological and non-pharmacological interventions (e.g. psychotherapy, ECT, hospitalisation).

5.2 The manufacturer's economic evaluation compared with the NICE reference case checklist

Table 27 NICE reference case checklist

Attribute	Reference Case	Included in MS	Comment on whether <i>de novo</i> evaluation meets requirements of NICE reference case
Comparator(s)	Alternative therapies in the NHS, including those currently regarded as current best practice	Partially	The comparators used do not represent the full set of alternative therapies. 18 pharmacological comparators were included in the scope, which were not included in the cost-effectiveness model. These included augmentation therapy as well as competing antidepressant regimens.
Type of economic evaluation	Cost-effectiveness analysis with full incremental analysis	Yes	Yes. The <i>de novo</i> model produced in MS Excel considers pairwise comparisons only, requiring a few simple steps in order to produce full incremental analysis.
Perspective - costs	NHS and Personal Social Services	Yes	The MS also considers a wider societal perspective; where the costs of absenteeism were included through consideration of data relating to reported sick leaves collected as part of PERFORM. These are combined with national average data on wages. A number of wider societal costs are missing and so this is referred to as a partial societal perspective.
Perspective - benefits	All health effects on individuals	Partially	The MS focuses on the achievement of remission in patients, but fails to distinguish between responding non-remitters and non-responding non-remitters. As a result, some health effects may be missed and the structure of the model does not exactly follow the clinical decision problem as discussed in more detail in this section.
Time horizon	Sufficient to capture differences in costs and outcomes	Partially	The ERG considers that the adoption of a 12-month time horizon seems broadly appropriate given the natural history of an MDE for the average patient, but notes that continuation/maintenance therapy for patients with high risk of relapse would require a longer time horizon.
Synthesis of evidence on outcomes	Systematic review	Partially	All searches within systematic reviews are appropriately specified, however, much discussion of the appropriateness of the narrow population being considered is given in sections 3 and 4.
Outcome measure	QALYs	Yes	
Health states for QALY measurement	Described using a standardised and validated instrument	Yes	Health states were described using the MADRS score, which is a validated instrument for MDD. The MS also attempted to synthesise evidence where HAM-D score was used, using appropriate cross-walk procedures.
Benefit valuation	Time Trade Off or Standard Gamble	Yes	Time Trade Off
Source of preference data	Representative sample of the public	Yes	
Discount rate	3.5% for costs and benefits	Yes	Since the time horizon was 12 months, no discounting was required in the base case. In clarifications, the manufacturer supplied results from a 24 month time horizon, where 3.5% discount rates were applied to costs and benefits.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	No additional weighting was given to QALYs.
Sensitivity analysis	Probabilistic sensitivity analysis	Partially	Base case results were based on deterministic model, but probabilistic sensitivity analysis was also presented.

5.3 ERG's summary and critique of manufacturer's submitted economic evaluation

5.3.1 Population

As stated in Section 3.1 above, the patient population considered within the manufacturer's decision problem is restricted to a subset of the licensed patient population, namely:

“adult patients with moderate-to-severe MDD who are experiencing an MDE, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to alternative antidepressant” (MS, p14).

This patient group is referred to in the MS as the “switch population”. No additional patient sub-groups were considered within the MS.

As previously highlighted in Section 3, the restriction to the switch population appears consistent with the “Other considerations” section specified in the NICE scope. However, the ERG also considers that the definition of the “switch population” proposed by the manufacturer imposes a further restriction, in that it focuses entirely on the population in whom a single initial antidepressant medication has failed due to lack of efficacy or tolerability. However, clearly there will also be patients in whom a 2nd or a 3rd line of treatment may have failed and who are not directly considered by the manufacturer's analysis.

Inevitably, the current pathway for patients with MDE potentially involves a series of sequential steps and treatment options with the number of steps and options determined by the success of each prior step or treatment option. The ERG considers that the appropriate population and potential position of vortioxetine within current pathways should have been more formally considered by the manufacturer, based on a broader consideration of the evidence based for vortioxetine and other comparators, rather than restricting the decision population and evidence base from the outset. Furthermore, by only considering the use of vortioxetine as a second line treatment, the MS is not sufficiently flexible to establish the optimal position of vortioxetine within the existing treatment pathway. The ERG considers that the restrictive presentation of the decision problem in the MS prevents a full and appropriate consideration of the optimal position of vortioxetine within an existing sequence of treatment options for the management of patients with an MDE.

5.3.2 Model structure

The MS presents a decision model that evaluates the progression of a single MDE. The model is based on treatment success defined in terms of remission at 8-weeks. The model considers three

stages of disease progression: the acute phase (2 months duration), a maintenance phase (6 months duration), and a recovery phase (4 months duration). Consequently the time horizon of the model is 12 months.

A schematic diagram of the model is presented in Figure 13 below. The model combines a decision-tree structure with a separate Markov process depending upon particular pathways that a patient may follow in the decision-tree.

The initial decision tree-structure is common to all patients during the initial acute phase period (0-2 months). During this period patients may achieve remission or they may withdraw from their current therapy due to short-term side-effects or failure to achieve remission. Patients achieving remission in the initial acute phase period subsequently continue within the main decision-tree structure. Between months 2 and 8, these patients subsequently follow additional pathways (or branches) covering the maintenance phase. During the maintenance phase, patients are subsequently assumed to stay on treatment (i.e. sustained remission) or they may stop treatment due to an adverse event or subsequent relapse. If patients sustain remission during the maintenance period, they enter the final part of the decision tree structure representing the recovery phase which covers the final 4 months of the total 12-month time horizon. Importantly, during the recovery period, the therapy is assumed to be discontinued and an assumption is made that patients are no longer at risk of relapse or recurrence.

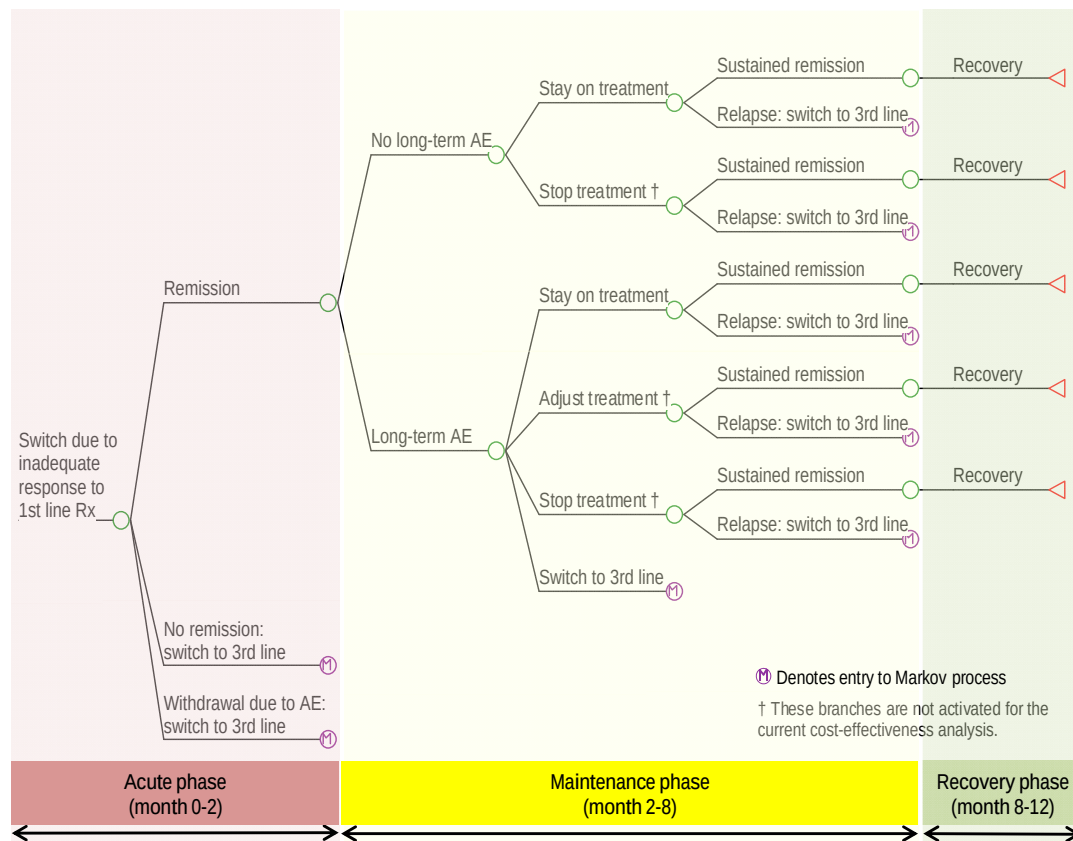


Figure 13 Model schematic diagram (MS Figure B21)

Consequently, the full decision tree is only followed for the entire 12 month period in patients who achieve remission during the acute phase and subsequently maintain this remission during the entire maintenance period. In contrast, all other patients enter into a separate Markov process, with a 2-monthly cycle length. The time at which they enter the Markov process depends upon the phase that the initial therapy is assumed to be stopped (i.e. acute vs maintenance period).

The separate Markov process is then used to model subsequent lines of therapy, with the model allowing up to a maximum of 3 additional lines of treatment (i.e. covering 3rd – 5th lines of therapy, since the initial therapy in the switching population is already the 2nd line of treatment in the overall management pathway).

Figure 14 below illustrates the Markov model schematic in the MS. The Markov model aims to track subsequent patient prognosis in terms of their remission and/or recovery status following additional lines of treatment.

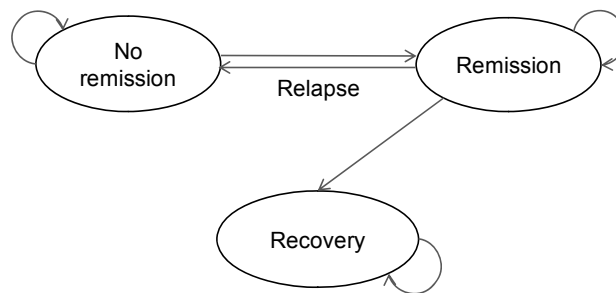


Figure 14 Markov state transition diagram for modelled events following switch to third line (MS Figure B22)

The Markov model uses a 2-month cycle and following every cycle in the no remission state (2 months) an additional switch and further line of treatment is assumed. This means 2 months after initiating a subsequent treatment line patients either achieve remission or switch to an additional line of treatment again.

The manufacturer's structure broadly characterises the progression of a treated MDD episode making reference to a diagrammatic representation (reproduced in Figure 15 below) adapted from Bakish (3).

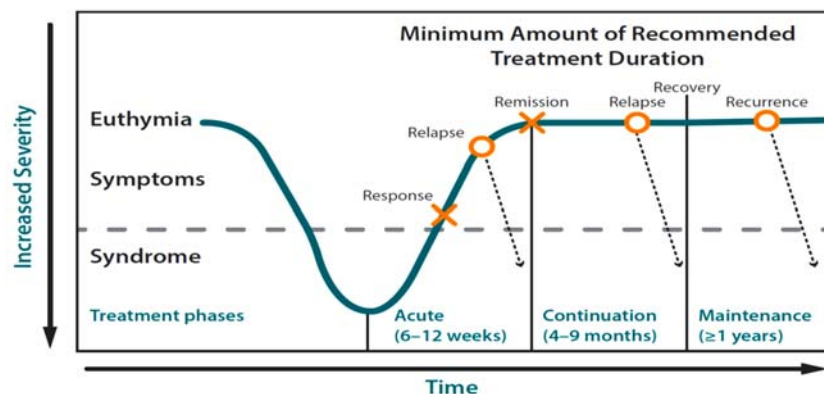


Figure 15 Diagrammatic representation of the course of an MDD episode (MS Figure A3, adapted from Bakish)

This characterisation distinguishes three treatment phases:

1. Acute phase (up to 6 to 8 weeks): the goal is to elicit a response and decrease symptoms to a non-pathologic level
2. Continuation phase (lasting 4 to 9 months): the goal is to maintain the improvements, resolve remaining symptoms and functional impairments and prevent relapse

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Clarifications to Evidence Review Group's report

CRD/CHE University of York

Vortioxetine for treating major depressive disorder

21/04/2015

This document responds to a request for clarification from the manufacturer on some aspects of the additional analysis undertaken by the ERG.

Manufacturer request: *"...we are finding it impossible to replicate the results based only on the changes in utilities that have been specified in Table 50 of their report and the text that accompanies this."*

ERG's Response:

Overview of the rationale for the changes made

- The ERG changed not only the values of inputs, but also modified the way in which inputs were used in the decision model
- Relapse has been defined in the literature as "the return of symptoms meeting the full syndrome criteria that occurs during an asymptomatic period of incomplete recovery from the index episode" [Bakish (2001) with reference to Frank (1991)].
- The ERG made 3 changes to the manufacturer model.
 - i. As part of the ERG corrections, the relapse utility was assumed to be the same as the baseline utility for depression, which the ERG considers to better represent the definition provided above.
 - ii. In the MS, patients achieving remission in the acute phase, but relapsing in the maintenance phase, are assumed to relapse three months into the maintenance phase. The MS, however, assigned these patients the relapse utility for the first three months in maintenance phase, and switched them to the Markov component after that. The ERG modified the MS model by assigning three months utility of remission, rather than utility of relapse, to describe the time before the relapse occurs.
 - iii. In the Markov component of the MS, no distinction is made between patients that have switched due to lack of efficacy and patients that relapsed – in both situations patients are

assigned the utility of relapse. The ERG believes that patients not achieving remission on active therapy will have different utilities to those relapsing. The ERG attempted to reflect this distinction.

Detailed description of the corrections made

- i. The ERG changed the utility values used as inputs, as detailed in table 50 of the ERG report.
- ii. Within the decision tree, patients who relapse after three months were given utility of remission for the first three months in the maintenance phase, before relapsing and entering the Markov component of the model. This was done by editing the cells in column DT in sheets 'DT – Vortioxetine' and 'DT – Comparator'. For instance, the cell DT15 contained the formula ' $=\text{Utility\_remission\_after\_2months}*(3/12)*\$Z15$ ' instead of ' $=\text{Utility\_relapse\_after\_2months}*(3/12)*\$Z15$ '.
- iii. The changes made to the Markov component of the model were as follows:
 - Patients relapsing after three months in the maintenance phase of the decision tree did not enter the sheet 'Markov – switch LOE' and instead entered a newly created sheet 'Markov – switch relapse'. In the first instance, this was simply a copy of 'Markov – switch LOE'.
 - All Markov sheets were edited to reflect that patients entering a 'No remission ...' health state had different utilities depending upon they were relapsing following a remission, or whether they were not remitting.
 - For 'No remission 3rd line' this was a case of editing the Markov utilities tables for the 'Markov – switch LOE' and 'Markov – switch AE' tabs, cells F57:F62 so that they had, for example in cell F57, the formula ' $=(F44/2+F45/2)*\text{Utility\_no\_remission\_8weeks}*2/12$ ' instead of ' $=(F44/2+F45/2)*\text{Utility\_relapse\_after\_2months}*2/12$ '. Note that tabs 'Markov – switch relapse' and 'Markov – switch long term AE' were not changed for 'No remission 3rd line' health state.
 - For 'No remission 4th line' and 'No remission 5th line', the formulae could no longer be based on the Transition matrix table, since the numbers contained in these could contain both relapsers and non-remitters. As a result, it was necessary to multiply the relevant rows and columns of the matrices by hand and assign different utilities to each. See formulae contained within L57, L58, R57 and R58 on 'Markov – switch LOE', 'Markov – switch AE' and 'Markov – switch relapse' tabs, and L59, L60, R59 and R60 of 'Markov – switch long term AE'.

Calculations on total costs and utilities were also modified to reflect the changes above.

For clarity, we also provide the updated Excel model file. Note that this file was not prepared for external use.

Manufacturer request: “Would it be possible to provide further clarification on the exploratory analyses related to efficacy in subsequent lines of treatment (section 6.3.2) that you described on page 136 of the ERG report? “

ERG’s Response:

Exploratory analyses regarding remission and relapse for 3rd, 4th and 5th line treatments

For the exploratory analyses, remission rates in 3rd, 4th and 5th lines were calculated by taking the average of the non-vortioxetine treatments’ remission rates (table 58, ERG report) and also by taking these values and applying a proportionate reduction based on STAR*D (table 59, ERG report). The values used are detailed in the following tables.

Table 1 Remission inputs for Table 58, ERG report

	MS	Llorca	IE	Pae
2nd line	28.15%	42.37%	40.50%	39.43%
3rd line	28.15%	42.37%	40.50%	39.43%
4th line	28.15%	42.37%	40.50%	39.43%
5th line	28.15%	42.37%	40.50%	39.43%

Table 2 Remission inputs for Table 59, ERG report

	MS	Llorca	IE	Pae
2nd line	28.15%	42.37%	40.50%	39.43%
3rd line	12.60%	18.97%	18.13%	17.66%
4th line	11.96%	18.00%	17.21%	16.75%
5th line	11.96%	18.00%	17.21%	16.75%

The relapse rate used was based on Limosin (2004) ¹using a calculation to convert from a 6-month rate to a 2-month rate assuming that the rate is constant:

$$p_{L\ 2-month} = 1 - \exp\left(\frac{\ln(1 - p_{L\ 6-month})}{3}\right)$$

¹ Limosin (2004) was used as an alternative to STAR*D as it was considered to better reflect the population for the decision problem and is consistent with the source employed in the decision tree.

This resulted in a value of $p_{L\ 2-month} = 0.0498$.

**National Institute for Health and Care Excellence
Centre for Health Technology Evaluation**

Pro-forma Response

ERG report

Vortioxetine for the treatment of major depressive disorder in adults [ID583]

You are asked to check the ERG report from the NHS Centre for Reviews & Dissemination and Centre for Health Economics, University of York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by the end of **22 April 2015** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issues 1-7 included within the below proforma are considered major inaccuracies. The remainder are considered moderate-minor and are listed by page number within the ERG report.

Issue 1 Population specified in the decision problem

Description of problem	Description of proposed amendment	Justification for amendment
Lundbeck contests that within the STA process the “optimal position” within a treatment pathway does not have to be demonstrated. It is the manufacturer’s prerogative to present data in a subgroup of the population defined in the scope and the products’ licence. For example: Page 90: “The ERG considers that the restrictive presentation of the decision problem prevents a full and appropriate consideration of the optimal position of vortioxetine within an existing sequence of treatment options for the management of patients with an MDE”.	Removal of statements or explicit recognition at all appropriate points that the manufacturer has the right to identify a subgroup of the population specified within the scope. Statements with a similar sentiment are presented on the following pages and therefore will also require amendment/removal: 10, 20, 28, 32, 39, 58, 95, 123, 125, 126, 142, 144.	Within the STA process a manufacturer is permitted to specify the place in the treatment pathway they wish for a product to be considered regardless of whether this is a subpopulation of the scope or product licence. This point was also raised at the decision problem meeting by the BMJ group (the original ERG for this appraisal). In response to this Elisabeth George reiterated the right/ability of the company to specify their decision problem population. A “demonstration of the most efficient position within the pathway” is therefore not required. In addition, given the high rate of initial treatment failure, the need for efficacious, well tolerated antidepressants in this population is evident. This is recognised within the ERG report and is supported by clinical expert opinion.

Issue 2 Context of the Cochrane Collaboration’s comments on the NICE scope: decision problem vs scope

Description of problem	Description of proposed amendment	Justification for amendment
Page 36: In the ERG’s discussion of the exclusion of placebo controlled trials they	Removal of statements.	Although the statements cited from the Cochrane Collaboration and NICE were

fail to recognise that the Cochrane Depression Anxiety and Neurosis Group were commenting on potential comparators and the value of placebo controlled trials given the scope. As Lundbeck focussed on a subgroup of patients encompassed by the scope (i.e. switch patients), as justified in the submission, the applicability of the placebo controlled trials of vortioxetine was deemed limited to the decision problem.		made, they have been used out of context and therefore the sentiment of the statements may be misconstrued.

Issue 3 Active reference bias recognised by the EMA rather than the manufacturer

Description of problem	Description of proposed amendment	Justification for amendment
On page 16 the ERG report states that “The manufacturer has criticised the use of active references because...”. The current wording of the section reads as if it is only Lundbeck to have recognised the bias associated with active references. In fact the EMA have recognised this in the EPAR for vortioxetine and therefore this should be reflected in the text. A similar statement is made on page 142. This bias should also be recognised when describing the results of Pae 2014 (pg 14).	It should be recognised within the text that within the EPAR for vortioxetine the EMA have stated that comparisons between vortioxetine and active references are invalid. Ensure bias associated with active references is recognised when reporting the results from Pae et al 2014.	Accuracy of reporting to allow an informed interpretation of the results.

In addition, on Page 74 the ERG states: “The potential that results were biased in favour of duloxetine given the potential for bias discussed above must be considered, however there is no evidence of such a bias in favour of venlafaxine”. Lundbeck does not believe this statement can be substantiated. If the ERG accepts the potential of bias being present for the comparison versus duloxetine then it should also accept that the same active reference bias is potentially present for the comparison of vortioxetine versus venlafaxine.		

Issue 4 Incorrect assumption regarding the validity of comparison to active reference

Description of problem	Description of proposed amendment	Justification for amendment
Page 74; ERG states “However, the ERG does not consider this risk of bias to be sufficiently substantial to reject such comparisons altogether, particularly as there is a reasonably large number of such with greater numbers of AR trials.”	Remove “particularly as there is a reasonably large number of such trials” from this sentence.	The ERG assumes that the number of studies affects the selection bias given with the inclusion of non-responders to an active reference. This is an incorrect assumption since the bias would be consistent across the studies and not diluted with increasing number of completed trials. The number of AR trials has no bearing <i>per se</i> on whether the use of AR trials is valid in principle. Indeed, if their use is invalid, as is recognised by the CHMP, then the impact of bias would

		be more serious.

Issue 5 Indirect treatment comparison analyses: outcomes

Description of problem	Description of proposed amendment	Justification for amendment
On page 11 the report states that remission and withdrawals due to adverse events were the only outcomes for which data were presented by Lundbeck. This is true only for the manufacturer's submission. Within the response to the clarification questions data for response and mean change from baseline were also presented as outcomes from the ITC. This should be reflected in the ERG's report.	Include the response and mean change from baseline analyses presented in analyses 18 b and c of Lundbeck's response to clarification questions. The mean change from baseline results show vortioxetine to be statistically significantly better than all comparators included in the analysis (agomelatine, sertraline, venlafaxine and citalopram) in terms of mean change from baseline. The response rate analysis found vortioxetine to be statistically superior to sertraline, venlafaxine and agomelatine (data on response for citalopram was not reported in the Lenox-Smith publication). Similar statements are also presented on the following pages and will also require amendment: 13, 38, 43, 62.	The entirety of the data provided by the manufacturer needs to be reflected accurately. The results for remission and change from baseline should be presented within the ERG report as they allow a fuller understanding of the relative efficacy of vortioxetine when used in the switch population vs the compounds included in the analysis.

Issue 6 Table 27: comments and conclusions in column "Included in MS"

Description of problem	Description of proposed amendment	Justification for amendment
Page 89, Table 27 summarises whether the ERG believes the NICE reference case	Comparators – add comment on the comparators relevant to the switch population with reference to prescribing and clinical	To fairly reflect the decision problem and analyses presented by the manufacturer.

has been adhered to. Lundbeck would like to make comment on the following aspects: • Comparator(s): Comments column states that comparators used do not represent the full set of comparators as defined in the scope. - o Lundbeck contests that given the decision problem population is a subgroup of those defined in the scope the comments column should make reference to the comparators deemed relevant given the decision problem based on those used in the UK and those recommended in NICE CG90 for the treatment of the switch population. • Synthesis of evidence on outcomes: systematic review - o Lundbeck does not consider the rationale for reporting this as “partially” included in the MS to be robust. Given the points highlighted in Issue 1 above, Lundbeck does not believe this to be appropriate. • Sensitivity analysis: probabilistic sensitivity analysis - o Lundbeck is unclear as to why “partially” has been assigned here. The ERG recognise within its comments that probabilistic sensitivity analyses were presented	guidelines. Synthesis of evidence on outcomes – update “partially” to “yes”. Sensitivity analysis: probabilistic sensitivity analysis - update “partially” to “yes”.	

within the submission.		

Issue 7 Power of REVIVE to detect superiority

Description of problem	Description of proposed amendment	Justification for amendment
Page 15: The ERG states that REVIVE may not have been sufficiently powered to demonstrate that vortioxetine is superior to agomelatine. Therefore any inferences from this trial regarding the superiority of vortioxetine over agomelatine may not be reliable as they may be based on chance. This statement is factually inaccurate.	Remove statement as it is incorrect. The following information should be reflected in the ERG report: The MMRM estimates for the mean change from baseline in MADRS total score at Week 8 were -16.5 and -14.4 points in the vortioxetine group and the agomelatine group, respectively, giving a mean difference of -2.16 points in favour of vortioxetine (95% CI: -3.5 to -0.81; $p = 0.002$) (Please refer to study report 14178A- page 66-67 (see Panel 22)). Non-inferiority was established, as the upper bound of the 95% CI for the vortioxetine and agomelatine comparison was -0.81 MADRS points, and therefore clearly below the non-inferiority margin of +2 MADRS points versus agomelatine. As the two-sided 95% CI for the difference between the means excluded zero and was in favour of vortioxetine, vortioxetine was even superior to agomelatine¹. Similar statements are also made on pages 45, 52, 58, 79 and 141 and will also require removal.	It is well recognised for non-inferiority studies that once non-inferiority is established one can move to a superiority test under a closed testing procedure². In addition, an obtained significance can never be disregarded using a 'power' argument since the analyses actually did prove powerful enough to detect the difference. A power argument would typically be used in the absence of an achieved significance. The fact that a non-inferiority study provides statistically significant superiority data does not undermine the data reliability. On the contrary, significant secondary analyses strengthen the reliability of the study and therefore strengthen the evidence of vortioxetine being of superior efficacy compared to agomelatine. 1. EMA 2000 'Points to consider on switching between Superiority and non-inferiority

Issue 8 Comments around agomelatine licence in the UK are misleading

Description of problem	Description of proposed amendment	Justification for amendment
Page, 10: Agomelatine is licensed for the treatment of major depressive episodes in the UK but is not recommended by NICE as no evidence submission was made by the manufacturer. In places the report suggests agomelatine is not licensed in the UK.	Page 15, 1st paragraph – ‘agomelatine is not approved for use in the UK’, should read ‘agomelatine is not recommended for use by NICE.’ Page 20, 3rd paragraph - ‘One compared vortioxetine to a drug not licenced in the UK,’ should read ‘One compared vortioxetine to a drug not recommended for use by NICE’ Amend all additional statements in report. Similar statements are made on pages 79 and 145 and will also require amendment.	Incorrect reporting of agomelatine’s marketing authorisation.

Issue 9 Presentation of short-term adverse event data

Description of problem	Description of proposed amendment	Justification for amendment
Page 12: The ERG states “On clarification the manufacturers also supplied adverse event data from 12 short-term placebo controlled trials of vortioxetine”. These data were provided within an appendix to the main submission (Appendix 15) and also in the clarification question response.	Statement needs to reflect that these data were presented both in the manufacturer’s submission and in response to clarification questions. A similar statement is made on page 65 and will also requirement amendment.	To accurately report the evidence presented by the manufacturer.

Issue 10 Several errors in reporting the results from Llorca et al (2014)

Description of problem	Description of proposed amendment	Justification for amendment
Page 14: there are several errors in the reporting of evidence in table 3 and the sentence preceding the table.	Change following statement is incorrect: “This analysis found no statistically significant evidence of any difference in efficacy between vortioxetine and other antidepressants (except for agomelatine), but did find evidence that vortioxetine had a lower withdrawal rate due to adverse events than venlafaxine, desvenlafaxine and sertraline.” The difference in efficacy with agomelatine is not statistically significant. Vortioxetine had a statistically significantly lower	Inaccurate reporting of figures and incorrect conclusions based on the evidence provided.

	withdrawal rate due to AE than venlafaxine, desvenlafaxine and sertraline. Therefore the sentence should be updated as follows : “This analysis found no statistically significant evidence of any difference in efficacy between vortioxetine and other antidepressants, but did find evidence that vortioxetine had a statistically significantly (p<0.05) lower withdrawal rate due to adverse events than venlafaxine, desvenlafaxine and sertraline.” Corrections to Table 3 : - Results vs vortioxetine (Standard error) to be changed to: Results vs vortioxetine (p-value) - Withdrawal (Odds ratio:<1 favours vortioxetine) to be changed to: Withdrawal due to AE (Odds ratio:<1 favours vortioxetine) - Remission rate results for agomelatine: 1.220 (0.470)**. The asterisks should be deleted. This table is also included on page 78, (Table 26). The same corrections should be applied here.	

Issue 11 Clarification of sources for meta-analyses

Description of problem	Description of proposed amendment	Justification for amendment
Page 14: The ERG states “Two systematic reviews and one regulatory submission (to the Pharmaceutical Benefits Advisory Committee of Australia)...”. The PBAC is not a regulatory authority but rather an HTA agency.	Statement needs updating to reflect that the submission to the PBAC was an HTA submission rather than a regulatory/licencing submission. Similar statements are also presented on the following pages: 14 (bottom of the same paragraph), 39, 72 and will also require amendment.	Inaccurate statement.

Issue 12 Safety comparisons vs active comparators

Description of problem	Description of proposed amendment	Justification for amendment
Page 15 states “The submission did not present any safety comparisons of vortioxetine with any active comparators, so the safety of vortioxetine compared to other antidepressants is uncertain”. This is incorrect. Safety analyses versus active comparators agomelatine and escitalopram were presented from the REVIVE and TAK318 studies respectively.	Remove as incorrect. A similar statement is made on page 71 and will also require removal.	The statement made is factually inaccurate. Data versus escitalopram and agomelatine were reported from head-to-head studies in the switch population.

Issue 13 Applicability of population included in TAK318 to UK patients

Description of problem	Description of proposed amendment	Justification for amendment
Page 15: In reference to the population included in TAK 318 the report states “The ERG notes that this is a very narrow and specific population, so the TAK318 trial provides little information on the broader population who might take vortioxetine”. Lundbeck agrees that the population included in TAK 318 is a subgroup of the licensed population and also of the population addressed in the decision problem. However, the company would contest whether it should be considered “very narrow”. Both the literature and clinical opinion support the incidence of sexual dysfunction is high with many antidepressants and is often cited as one of the most common long-term adverse event triggering treatment switch ^{1,2,3}. 1. Lenderking. W., Samp J., Hanlon J. et al. Factors associated with poor adherence in patients initiating medication for major depressive disorder: Interim results from a	Amend text to: “The ERG notes that this is subpopulation of the population being addressed in the decision problem.” A similar statement is made on page 54 and will also require amending.	Text amended to remove subjective and potentially inaccurate representation of the frequency of sexual dysfunction associated with antidepressant treatment.

prospective, longitudinal study. 16th ISPOR European Congress, 2-6 November 2013, Dublin. Poster PMH48 2013. 2. Lenderking. W., Samp J., Hanlon J. et al. Adherence, switching and discontinuation during the 12 weeks following antidepressant initiation in patients with depressive disorder: Results of a prospective longitudinal study. 16th ISPOR European Congress, 2-6 November 2013, Dublin. Poster PMH49 2013. 3. Hunot VM, Horne R, Leese MN, et al. A cohort study of adherence to antidepressants in primary care: the influence of antidepressant concerns and treatment preferences. Primary care companion to the Journal of clinical psychiatry 2007;9:91.		

Issue 14 Classification of severity of depression

The following statement is included on page 23: "The submission recognises that the terms MDD and MDE are based on standard classifications from the Diagnostic and Statistical Manual of Mental Disorders (DSM); these are used to describe depression in the USA where terminology may differ slightly from that used in the UK, where the terms mild/moderate/severe depression are more commonly used." The manufacturer does not agree that the DSM criteria are not used to classify depression in the UK.	Suggest deleting the second part of the paragraph so it reads: "The submission recognises that the terms MDD and MDE are based on standard classifications from the Diagnostic and Statistical Manual of Mental Disorders (DSM)".	The statement that the DSM criteria are not used in the UK is incorrect. DSM is a globally accepted, widely used diagnostic tool which is also recognised and used in NICE CG90 which states: "After careful review of the diagnostic criteria and the evidence, the Guideline Development Group decided to adopt DSM-IV criteria for this update rather than ICD-10, which was used in the previous guideline (NICE clinical guideline 23). This is because DSM-IV is used in nearly all the evidence reviewed and it provides definitions for atypical symptoms and seasonal depression. Its definition of severity also makes it less likely that a diagnosis of depression will be based solely on symptom counting. In practical terms, clinicians are not expected to switch to DSM-IV but should be aware that the threshold for mild depression is higher than ICD-10 (five symptoms instead of four) and that degree of functional impairment should be routinely assessed before making a diagnosis. Using DSM-IV enables the guideline to target better the use of specific interventions, such as antidepressants, for more severe degrees of depression". Mild/moderate/severe depression is also a distinction made in the DSM, regardless of if the disease is recurrent or not.

Issue 15 Unbalanced comparison of number of chosen trials compared to number of completed trials

Description of problem	Description of proposed amendment	Justification for amendment
Page 27 states “Although vortioxetine has been studied in 24 completed trials involving over 7,000 patients, the manufacturer’s submission focuses largely on 2 studies considered relevant to the decision problem; Study 14178A (REVIVE) and TAK318” The 7,000 patients included in vortioxetine studies also includes studies in healthy volunteers. Therefore this statement provides an unbalanced and inaccurate view on the relative sizes of the overall vortioxetine efficacy package compared with the number of patients included within the two switch studies.	Statement should be deleted. Similar statements are made on page 10 and 32 will also require deletion.	The large number of patients included in clinical trials with vortioxetine does not only encompass efficacy studies but includes studies in healthy volunteers providing an unbalanced description of how much efficacy data and patient data are covered in the two switch-studies.

Issue 16 Scope of systematic review to identify adverse event data

Description of problem	Description of proposed amendment	Justification for amendment
Page 41 states “The study selection process and eligibility criteria appeared generally appropriate. However, the review of adverse events excluded studies that	Remove statement.	The systematic review was limited to trials based on the following text on Page 30 of the Specification for Manufacturer/Sponsor Submission published in June 2012: “If any of the main trials are designed primarily to

evaluated safety but did not report it as a primary outcome. Therefore there is a risk that relevant studies reporting adverse events may have been missed; as the manufacturer did not provide a record for the exclusion of studies, this risk is difficult to assess.” Lundbeck believes that the search undertaken is in line with the instruction provided in the template for manufacturer’s submission published in June 2012 for the identification of adverse event data. In addition, though not identified through the systematic review of adverse events, within Appendix 15 the pooled safety data from the short-term studies of vortioxetine identified in through the systematic review of RCTs were included.		assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results”. From this statement Lundbeck believes that the instruction given in the template can be interpreted as requesting only adverse event data from trials reporting these as a primary endpoint. In addition, Lundbeck reported the remaining adverse event data in Appendix 15 of the Manufacturer’s submission.

Issue 17 Error in Figure 6

Description of problem	Description of proposed amendment	Justification for amendment
Page 51: The key in Figure 6 is incorrect. Instead of reading “PBO” it should read “AGO” as this reports results from REVIVE. Please note, this is an error by Lundbeck which was made in the clarification questions response. Lundbeck have now provided an updated figure to the NICE team.	Please update figure with the updated version as provided by Lundbeck.	The labelling of the key in Figure 6 states the wrong comparator.

Issue 18 Interpretation of CIs in REVIVE results and error in Table 12

Description of problem	Description of proposed amendment	Justification for amendment
Page 50: The ERG states “The relatively wide confidence intervals reflect the uncertainty in true magnitude of the difference in efficacy between vortioxetine and agomelatine.” In addition on page 52, Table 12 there is an error. There is a misprint for the results at week 8 (3.51 should be -3.51).	Remove statement and amend table.	The statement presented is highly subjective and gives no basis for the comparison which underpins the claim of relativity. In addition a MADRS SD=7.6 was observed in the study which is lower than what is typically found in depression studies (SD=9.5). In addition with n>220 per group these confidence intervals in fact narrower than what is typically found.

Issue 19 Threshold for depression severity in the UK

Description of problem	Description of proposed amendment	Justification for amendment
On page 60 it is stated that “there is considerable diversity across trials baseline severity. Of particular concern ...STAR-D and GSK 2009 both have comparatively low baseline disease severity, below the standard threshold for moderate depression in UK.” Lundbeck does not agree that the baseline severity scores in the STAR D study and GSK (2009) – they are above the threshold for moderate depression.	“Below the standard threshold for moderate depression in the UK” should be deleted. Similar statements are made on pages 15 and 141 and will also require amendment.	The statement is incorrect. Baseline HAM-D17 are 18.9 and 19 for STAR-D and GSK (2009) respectively and do correspond to moderate MDD as provided in reference below for HAM-D17¹: - no depression (0-7); - mild depression (8-16); - moderate depression (17-23); and - severe depression (≥24). 1. Zimmerman, Mark et al. (2013). Severity classification on the Hamilton depression

		rating scale Journal of Affective Disorders, Volume 150, Issue 2, 384 – 388.

Issue 20 Erroneous conclusion of bias

Description of problem	Description of proposed amendment	Justification for amendment
Page 62, includes the following sentence: “Agomelatine may have lower efficacy and higher tolerability than other comparators (as suggested by Llorca et al.), (22) which may have biased the efficacy results of the indirect comparisons in favour of vortioxetine, and negatively biased the withdrawal results.” The conclusion of bias here is erroneous. There is no bias within this analysis. The Bucher method has been applied properly, the strength such an analysis over a naïve comparison is the avoidance of the bias of the results.	Remove the statements of bias.	Correctness of the statement.

Issue 21 Incorrect description of differences between agomelatine and vortioxetine safety data

Description of problem	Description of proposed amendment	Justification for amendment
Page 71 includes the following statement: "It may be less safe than agomelatine, although this conflicts with results from REVIVE".	Please rephrase to "It may be less well tolerated than agomelatine, although this conflicts with results from REVIVE".	The indirect comparisons indicate that vortioxetine may have a less favourable tolerability profile than agomelatine based on reported withdrawals due to adverse events, but there are no indications of differences in the compounds' safety profiles.

Issue 22 Unclear description of study types

Description of problem	Description of proposed amendment	Justification for amendment
Page 79: This review identified 12 short-term placebo controlled trials and five longer-term open label trials of vortioxetine.	Change text to: This review identified 12 short-term placebo controlled trials and five longer-term open label extension trials of vortioxetine.	The 5 trials were long-term extension trials to some of the 12 the short term trials and not 5 additional trials.

Issue 23 Concern of misleading conclusion based on available evidence

Description of problem	Description of proposed amendment	Justification for amendment
Page 81: ERG states “The ERG concludes, based on the totality of the evidence, that vortioxetine is likely to be of similar efficacy to other antidepressants, but may be superior to agomelatine and inferior to duloxetine”.	Add statement; “However, the ERG’s conclusion that vortioxetine may be inferior to duloxetine is based on trials in which duloxetine was included as an active reference, and hence depends critically on the ERG’s belief that such a comparison is not substantially biased. It is acknowledged that the CHMP has accepted that comparisons with active references may be invalid”.	ERG’s conclusion vs. duloxetine cannot be reached from the evidence. It requires a strong assumption about the validity of comparison to active references. ERG presents no scientific evidence to support its dismissal of the CHMP’s and Lundbeck’s position on this question.

Issue 24 Incomplete review of sensitivity analysis: differential efficacy

Description of problem	Description of proposed amendment	Justification for amendment
Page 115 and following: No mention is made of the threshold sensitivity analysis performed by Lundbeck on remission rate. This is an error of omission, as the analysis is designed specifically to address the question of uncertainty in differential remission rates arising from the shortcomings of the indirect treatment comparison that informs these model inputs	Include section to appraise section 7.7.10.1 of manufacturer submission: Given that the remission rate at 8 weeks was the most influential driver of cost-effectiveness, a threshold analysis was conducted on this variable, in addition to the DSAs reported above. Remission rates were held constant for the comparators to vortioxetine, while the remission rate for vortioxetine was reduced from the base-case value of 40.5% until the ICER reached thresholds of £20,000 and £30,000 per QALY gained in pairwise comparisons with each comparator. In the base case, vortioxetine and venlafaxine formed the cost-effectiveness frontier; the ICER for vortioxetine vs. venlafaxine was £378 per QALY gained. As Table B1 shows, if the absolute remission rate for vortioxetine is assumed to drop from 40.50% to 30.53%, i.e. a fall of approximately 10% in absolute terms and 25% in relative terms, the ICER for vortioxetine vs. venlafaxine reaches a threshold of approximately £20,000 per QALY gained. Although this assumed remission rate is slightly less than that of venlafaxine, vortioxetine achieves this ICER as a consequence of its superior profile on AEs and withdrawals due to AEs. The table shows the successively lower remission rates at which a similar ICER would result from comparisons with agomelatine, sertraline and citalopram. Corresponding values for a threshold ICER of £30,000 per QALY gained are shown alongside.	The analysis demonstrates the headroom within which vortioxetine is cost-effective in terms of remission rates, an important analysis when ERG does not accept the validity of the remission rates estimated in the ITC.

Table B1. Threshold analysis of remission rates of vortioxetine

Treatment	Remission rate at 8 weeks	£20,000/QALY threshold	Remission at 8 weeks	£30,000/QALY threshold
Vortioxetine (base case)	40.50%		40.50%	
Vortioxetine	30.53%		30.10%	
Venlafaxine	33.30%	£20,009	33.30%	£29,898
Vortioxetine	27.97%		28.54%	
Agomelatine	29.50%	£20,016*	29.50%	£29,973*
Vortioxetine	24.53%		24.00%	
Sertraline	26.10%	£20,075	26.10%	£30,062
Vortioxetine	24.10%		23.55%	
Citalopram	23.70%	£20,027	23.70%	£29,975

Figures in **bold** are base case remission rates.

* Threshold ICERs between vortioxetine and agomelatine are based on lower cost and fewer QALYs for vortioxetine, so the ICERs should be interpreted as willingness to accept QALYs lost, not willingness to pay for QALYs gained.

Issue 25 Missing text

Description of problem	Description of proposed amendment	Justification for amendment
Page 107: There is text missing from the paragraph in bold: last sentence below Table 35. "The purpose of this request was to develop a greater understanding of how the values in..."	Complete text	Error

Issue 26 Source for maintenance phase doses

Description of problem	Description of proposed amendment	Justification for amendment
Page 110: the ERG states that "The manufacturer makes this assumption through observed increases in dosage from REVIVE". Though this was the case for the doses of agomelatine and vortioxetine, the respective trials included in the indirect treatment comparison in switch were used to inform the maintenance phase doses for the remaining comparators.	Update text to read "The manufacturer makes this assumption through observed increases in dosage for each comparator from the respective trials included in the indirect treatment comparison".	Factual accuracy.

Issue 27 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment
In table 52 (page 130) the value associated with venlafaxine in the Pae paper is reported incorrectly.	The value that is reported is 45.52%. However, it should be 42.52%. The correct value has been used by the ERG in the additional analyses that were run. Therefore the typo does not have any further impact.	The value reported is different to the value presented in the source paper.

Evidence Review Group Report

Vortioxetine for the treatment of major depressive disorder in adults [ID583]

Response to factual inaccuracy check

Issue 1

This is not a factual inaccuracy. The ERG report explicitly states that this is the opinion of the ERG.

No changes made.

Issue 2

This is not a factual inaccuracy. The ERG disagrees that statements have been used out of context.

No changes made.

Issue 3

p16: The text: "The manufacturer has criticised the use of active references"

Should read: "The EMA and the manufacturer have criticised the use of active references"

p142: The text: "The manufacturer has criticised the use of active references"

Should read: "The EMA and the manufacturer have criticised the use of active references"

At p14 results are deliberately presented without critique (which is given on p16). No changes made.

p74: The text: "however there is no evidence of such a bias in favour of venlafaxine." should be deleted.

Issue 4

The ERG does not consider this to be a factual inaccuracy as it is an issue of how potentially biased data should be considered, however, for clarity, the following change should be made:

p74: The text: "particularly as there is a reasonably large number of such trials" should be deleted

Issue 5

p11: The text "but the review of indirect evidence"

Should read: "but, in the original MS, the review of indirect evidence"

p13: The text: "network meta-analysis were remission rate"

Should read: "network meta-analysis in the original MS were remission rate"

p38: The text: "The review of indirect evidence included significantly fewer outcomes"

Should read: “The review of indirect evidence presented in the original MS included significantly fewer outcomes”

p43: The text: “absolute changes in depression scores were included.”

Should read: “absolute changes in depression scores were included in the analysis in the original MS.”

p62: The text: “The indirect comparisons were performed for both remission rate”

Should read: “In the original MS, the indirect comparisons were performed for both remission rate”

Issue 6

These are not factual inaccuracies.

The ERG considers that the set of comparators included was too narrow as a consequence of the synthesis undertaken (these issues are discussed elsewhere in the ERG report).

The opinion of the ERG is that while a PSA was performed, there were several issues associated with the conduct and reporting of this:

- ICER results were given using the deterministic model, which gives an incorrect estimate in the case of a non-linear model.
- Additional issues: mean probabilistic inputs not equal to deterministic inputs, potential inconsistencies with parameters modelled as independent when should have been linked in some way.

Issue 7

The ERG considers that it is important to state the REVIVE was designed as a non-inferiority trial, and not a superiority trial, but accepts that there was evidence of superiority.

p15: The text: “but this result may not be reliable as this was a non-inferiority trial and was not powered to detect superiority of vortioxetine”

Should read: “The trial was designed as a non-inferiority trial, and was not designed to detect superiority of vortioxetine”

p45: The text: “Therefore any inferences from this trial regarding the superiority of vortioxetine over agomelatine may not be reliable as they may be based on chance.” should be deleted.

p58: The text: “conclusions regarding the superiority of vortioxetine versus agomelatine may not be reliable.”

Should read: “and was not designed to show superiority of vortioxetine.”

p79: The text: “but this result may not be reliable as this was a non-inferiority trial and was not powered to detect superiority of vortioxetine” should be deleted.

p141: The text: “but this result may not be reliable as this was a non-inferiority trial and was not powered to detect superiority of vortioxetine”

Should read: "The trial was designed as a non-inferiority trial, and was not designed to detect superiority of vortioxetine"

Issue 8

p15: The text: "agomelatine is not approved for use in the UK"

Should read: "agomelatine is not recommended for use by NICE"

p20: The text: "a drug not licenced in the UK"

Should read: "a drug not recommended for use by NICE"

p79: The text: "agomelatine is not approved for use in the UK"

Should read: "agomelatine is not recommended for use by NICE"

p145: The text: "a drug not licenced in the UK"

Should read: "a drug not recommended for use by NICE"

Issue 9

p12: The text: "On clarification the manufacturers also supplied adverse event data from 12 short-term placebo controlled trials of vortioxetine"

Should read: "Adverse event data from 12 short-term placebo controlled trials of vortioxetine were presented in an appendix and in the clarification response."

p65: The text: "In response to this request the manufacturer provided data from 12 short-term placebo-controlled phase II/III studies, including one trial"

Should read: "Data from 12 short-term placebo-controlled phase II/III studies had been provided in an appendix to the MS, some of which was also provided in the clarification response. These trials included one trial"

Issue 10

p14 Table 3 and also p78 Table 26:

- For "(Standard error)", read "(p-value)"
- For "Withdrawal" read "Withdrawal due to AE"
- For "(0.470) ***" read "(0.470)"

p14: The text: "and other antidepressants (except for agomelatine),"

Should read: "and other antidepressants,"

p78: The text: "The exception was that vortioxetine had a higher remission rate than agomelatine." should be deleted.

Issue 11

p14: The text: "one regulatory submission"

Should read: "one HTA submission"

p14: The text: "and the regulatory submission"

Should read: "and the HTA submission"

p39: The text "submissions to regulatory authorities"

Should read: "submissions to regulatory or HTA authorities"

p72: The text: "submissions to regulators"

Should read: "submissions to regulatory or HTA authorities"

Issue 12

p15: The text: "The submission did not present any safety comparisons of vortioxetine with any active comparators"

Should read: "The submission did not present any safety comparisons of vortioxetine with any active comparators, other than as reported in the REVIVE and TAK318 trials"

Issue 13

This is not a factual inaccuracy, but for clarity the following should be changed:

p15: The text: "The ERG notes that this is a very narrow and specific population"

Should read: "The ERG notes that this is a very specific population"

Issue 14

This is not a factual inaccuracy, but for clarity the following should be changed:

p23: The text: "The submission recognises that the terms MDD and MDE are based on standard classifications from the Diagnostic and Statistical Manual of Mental Disorders (DSM); these are used to describe depression in the USA where terminology may differ slightly from that used in the UK, where the terms mild/moderate/severe depression are more commonly used."

Should read: "The submission notes that the terms MDD and MDE are based on standard classifications from the Diagnostic and Statistical Manual of Mental Disorders (DSM). The terms MDE and MDD are used to describe depression in the USA; this terminology differs slightly from that used in the UK, where the terms mild/moderate/severe depression are more commonly used."

Issue 15

This is not a factual inaccuracy, but the ERG is happy to clarify that some trials were healthy volunteer studies. The ERG considers it important to make clear that only a minority of trials have been in switch populations.

p27: The text: "Although vortioxetine has been studied in 24 completed trials involving over 7,000 patients"

Should read: "Although vortioxetine has been studied in 24 completed trials (some of which were healthy volunteer trials) involving over 7,000 patients"

Issue 16

This is not a factual inaccuracy.

No changes made.

Issue 17

The ERG has not been provided with an updated figure. Figure 6 on p51 should be replaced with the corrected version if possible. Otherwise, add a footnote to Figure 6 as follows:

"Erratum to figure: For PBO read Agomelatine; for VOR read Vortioxetine"

Issue 18

This is not a factual inaccuracy.

p52 Table 12: "(3.51 to -0.81)" should read: "(-3.51 to -0.81)"

Issue 19

The ERG notes that there appears to be some discrepancy across sources as how to define moderate depression based on HAM-D. The ERG accepts the citation provided as being up-to-date. The ERG considers there to be diversity in baseline HAM-D scores, even if all patients have at least moderate depression, so statements on pages 15 and 141 are not factually inaccurate.

p60: The text: "both have comparatively low baseline depression severity, below the standard threshold for moderate depression in the UK."

Should read: "both have lower baseline depression severity than other trials."

Issue 20

This is not a factual inaccuracy. The bias here refers to the inclusion of a potentially inferior treatment (agomelatine) at a critical point in the network.

No changes made.

Issue 21

p71: The text: "It may be less safe than agomelatine"

Should read "It may be less well tolerated than agomelatine"

Issue 22

p79: The text: "and five longer-term open label trials of vortioxetine"

Should read: "and five longer-term open label extension trials of vortioxetine"

Issue 23

Not a factual inaccuracy. The ERG notes that the fact that the evidence for duloxetine is based on potentially biased active reference arms is explicit elsewhere in the same section.

No changes made.

Issue 24

Not a factual inaccuracy. The analysis was based on hypothetical assumptions and hence the ERG did not consider that this analysis addressed uncertainties in the differential remission rates.

No changes made

Issue 25

Not a factual inaccuracy. The sentence continues in the following text (not in bold format). A formatting error was the reason for the separation of the text.

Bold text on page 107 should be in normal font, with no paragraph break between "the values in" and "table 34 had been...".

Issue 26

P110: The text: "The manufacturer makes this assumption through observed increases in dosage from REVIVE".

Should read: "The manufacturer makes this assumption through observed increases in dosage for each comparator from the respective trials included in the indirect treatment comparison".

Issue 27

p130 Table 52: The text "45.52%"

Should read "42.52%"

Amended pages of the ERG report are presented below

The final NICE scope included a range of relevant outcomes, including response to treatment, remission, relapse, symptoms severity, anxiety, cognitive dysfunction, sleep quality, health-related quality of life and a range of adverse events. The manufacturer reported relevant data for most of these outcomes in the two trials of vortioxetine, but, in the original MS, the review of indirect evidence included only two outcomes (remission and withdrawal due to adverse events). This further limited the evidence on the relative efficacy, safety and cost-effectiveness of vortioxetine versus other active comparators.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The manufacturer's submission on clinical effectiveness included four systematic reviews: a review of RCTs of vortioxetine compared to active comparators in the switch population to evaluate efficacy; a review of non-RCT evidence of vortioxetine in the switch population; a review of adverse events of vortioxetine; and a review of indirect comparative evidence, again in the switch population, including an indirect treatment comparison and network meta-analysis of RCTs of other antidepressants, to evaluate efficacy and safety.

In response to the points for clarification, the manufacturer also provided meta-analyses of trials in the non-switch population.

1.2.1 Direct evidence in the switch population

As systematic review of RCTs of vortioxetine compared to active comparators in the switch population to evaluate efficacy was reported. It identified two trials, REVIVE and TAK318, summarised in Table 1. These trials were not combined in a meta-analysis because they were in different populations and used different comparators.

Table 1 RCTs included in the submission

Study	Regimen & duration	Comparator	Design	Follow-up duration	Primary outcome	Patient population
REVIVE (14178A)	Vortioxetine 10mg-20mg flexible dosing, 12 weeks	Agomelatine 25-50mg flexible dosing	Double-blind, international phase IIIb, parallel-group randomised trial	Efficacy: up to 12 weeks from baseline Safety: up to 16 weeks from baseline	Change from baseline in depression severity (MADRS total score) at week 8	Patients who have experienced an inadequate response to an SSRI or SNRI in their current MDE
TAK318	Vortioxetine 10mg-20mg flexible dosing, 8 weeks	Escitalopram 10-20mg flexible dosing	Double-blind, multicentre phase IIIb, parallel-group randomised trial	Efficacy: up to 8 weeks from baseline Safety: up to 12 weeks from baseline	Change from baseline in sexual functioning (CSFQ-14 total score) after 8 weeks of treatment	Patients who are well-controlled on an SSRI but experienced treatment emergent sexual dysfunction

MADRS: Montgomery and Åsberg Depression Rating Scale; CSFQ-14: Changes in Sexual Functioning Questionnaire Short-Form

The REVIVE trial was a well conducted trial comparing vortioxetine with agomelatine. The primary outcome in REVIVE was change in depression scores. Vortioxetine showed statistically significant superiority to agomelatine, reducing symptoms of depression. Average MADRS scores were 2.16 points lower on vortioxetine (95% CI 0.81 to 3.51) than on agomelatine after eight weeks. Vortioxetine was also superior to agomelatine in terms of response rate using MADRS at 8 weeks (OR 1.81, 95% CI 1.26 to 2.60) and remission rate (OR 1.72, 95% CI 1.17 to 2.52).

Vortioxetine and agomelatine had similar rates of treatment-emergent adverse events (around 54%) and serious adverse events (around 1.5%), but vortioxetine had lower rates of adverse events leading to withdrawal (5.9% vs 9.5%).

The TAK318 trial compared vortioxetine with escitalopram. The primary outcome was sexual functioning measured using the CSFQ-14 scale. At 8 week treatment the mean change from baseline was 8.8 (SE 0.64) in the vortioxetine arm and 6.6 (SE 0.64) in the escitalopram arm. This difference was statistically significant in favour of vortioxetine ($p = 0.013$). The submission also reported difference between arms on the CSFQ-14 subscales; there was statistically significant evidence in favour of vortioxetine on all subscales presented.

No differences between vortioxetine and escitalopram were identified for changes in depression scales, response, relapse or remission rates. Adverse event rates were similar on both treatments.

A systematic review for non-RCT evidence was performed, but no relevant studies were identified.

A systematic review for safety trials in the switch population was performed but no trials were identified. The search was expanded to the general, non-switch population and five open-label extensions of vortioxetine trials were identified. Adverse event data from 12 short-term placebo controlled trials of vortioxetine were presented in an appendix and in the clarification response.

About 6% of patients had severe adverse events on vortioxetine compared to 4% on placebo in the placebo controlled trials. In the open-label extension trials 8.1% of patients had a serious adverse event. The manufacturer concluded that vortioxetine had a generally good safety profile. No data were submitted comparing adverse events using vortioxetine with other active treatments.

1.2.2 Indirect evidence in the switch population

The submission included a systematic review of treatments other than vortioxetine in the switch population used to perform an indirect treatment comparison with vortioxetine for efficacy and safety. This review identified seven trials. One was excluded on the grounds of poor trial quality. Two were placebo controlled trials not included in the primary network meta-analysis. Four trials were used in the primary network meta-analysis; there was only one trial included for each treatment comparison.

The outcomes of the network meta-analysis in the original MS were remission rate and withdrawal rate due to adverse events. A range of models were fitted using different assumptions, including the placebo controlled trials and using both frequentist and Bayesian statistical methods. A summary of the results from the main frequentist analysis are shown in Table 2. Results from other analyses were broadly consistent with these results.

Table 2 Summary of the results of the frequentist network meta-analyses

	Remission rate			Withdrawal rate due to adverse events		
	Rate (%)	Risk Difference vs vortioxetine (%)	95% CI	Rate (%)	Risk Difference vs vortioxetine (%)	95% CI
Vortioxetine	40.5	–	–	5.9	–	–
Agomelatine	29.5	-11	-19.4 to -2.6	9.5	3.6	-1.1 to 8.3
Sertraline	26.1	-14.4	-29.9 to 1.1	18.0	12.1	3.1 to 21.1
Venlafaxine	33.3	-7.2	-24.3 to 9.9	18.2	12.3	0.8 to 23.8
Bupropion	29.8	-10.7	-27.8 to 6.4	24.2	18.3	6.4 to 30.1
Citalopram	23.7	-16.8	-41.1 to 7.5	18.0	12.1	-0.3 to 24.5

Vortioxetine had higher rates of remission than all other treatments, but results were only statistically significant for agomelatine. Vortioxetine also had lower rates of withdrawal due to adverse events than all other treatments, but results were only statistically significant for comparisons with sertraline, venlafaxine (XR) and bupropion. Due to the limited number of trials in the network, no assessments of heterogeneity or network inconsistency were performed.

1.2.3 Evidence syntheses of non-switch populations

As discussed in Section 1.1 the ERG questions the validity of restricting the analysis to switch populations. The ERG therefore requested that the manufacturer provide results from trials or meta-analyses of trials comparing vortioxetine to other active treatments and/or placebo in initial use and non-switch use populations. The manufacturer provided meta-analyses of their trials comparing

vortioxetine to placebo, but not for vortioxetine versus active comparators. The manufacturer also reported the existence of two submissions to regulators, four systematic reviews of vortioxetine trials and one indirect comparison of vortioxetine with other antidepressants.

The meta-analyses of trials submitted by the manufacturer and the four identified systematic reviews compared vortioxetine with placebo. There was considerable overlap in the trials included in the meta-analyses, and they reported different outcomes. However, all concluded that vortioxetine was superior to placebo.

Two systematic reviews and one HTA submission (to the Pharmaceutical Benefits Advisory Committee of Australia) compared vortioxetine to other antidepressants by using active reference arms from placebo controlled trials. Active reference arms are included in trials of antidepressants to ensure that patients are responding to therapy. An active reference should be a drug of proven superiority over placebo, so it can be used to check whether the trial has successfully treated patients by confirming a difference between the active reference and placebo. After reanalysis by the ERG of data from one of these reviews (Pae et al. 2014) vortioxetine was found to be inferior to duloxetine in terms of changes in depression scores, response rate and remission rate. There was no evidence of a difference between vortioxetine and venlafaxine. Results from the other review and the HTA submission were consistent with these results.

One systematic review (Llorca et al. 2015) performed an indirect comparison of vortioxetine with other antidepressants by analysing all placebo controlled trials of vortioxetine and other antidepressants. The results of the indirect treatment comparison are summarised in Table 3. This analysis found no statistically significant evidence of any difference in efficacy between vortioxetine and other antidepressants, but did find evidence that vortioxetine had a lower withdrawal rate due to adverse events than venlafaxine, desvenlafaxine and sertraline.

Table 3 Indirect treatment comparison by Llorca et al

	Results vs vortioxetine (p-value)						
	Agomelatine	Desvenlafaxine	Duloxetine	Escitalopram	Sertraline	Venlafaxine	Vilazodone
Efficacy at 2 months (SMD: <0 favours vortioxetine)	-0.156 (0.113)	0.025 (0.803)	0.090 (0.419)	-0.054 (0.695)	-0.037 (0.832)	0.124 (0.328)	-0.245 (0.111)
Withdrawal due to AE (Odds ratio: <1 favours vortioxetine)	1.769 (0.030) *	0.578 (0.035) *	0.752 (0.262)	0.671 (0.275)	0.299 (0.008) **	0.469 (0.009) **	0.640 (0.181)

Response rate (Odds ratio: >1 favours vortioxetine)	1.045 (0.815)	1.153 (0.364)	0.893 (0.514)	0.843 (0.523)	0.772 (0.575)	0.789 (0.353)	0.975 (0.934)
Remission rate (Odds ratio: >1 favours vortioxetine)	1.220 (0.470)	1.029 (0.852)	0.894 (0.526)	0.990 (0.981)	NA	0.689 (0.444)	0.983 (0.952)

* p-value 0.01 – 0.05; ** p-value <0.01

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The restriction to a switch population meant that only two trials comparing the efficacy of vortioxetine with other antidepressants were submitted. The REVIVE trial comparing vortioxetine to agomelatine found vortioxetine had greater short-term reduction in depression scores and lower withdrawal rates due to adverse events. The trial was designed as a non-inferiority trial, and was not designed to detect superiority of vortioxetine. It should also be noted that agomelatine is not recommended for use by NICE as no evidence for its efficacy has been submitted. The TAK318 trial included patients who were switching due to sexual dysfunction but had responded to initial treatment. The ERG notes that this is a very specific population, so the TAK318 trial provided little information on the broader population who might take vortioxetine. It did find that vortioxetine reduced sexual dysfunction symptoms when compared to escitalopram. However it is not clear whether this finding is specific to vortioxetine, or whether any non-SSRI would have a similar beneficial effect. No efficacy evidence was submitted for the licensed 5mg vortioxetine dose.

Based on the safety evidence presented, vortioxetine appears generally safe and tolerable in patients with MDD. Most adverse were mild to moderate in intensity and there was no conclusive evidence that these were dose dependent. The submission did not present any safety comparisons of vortioxetine with any active comparators, other than as reported in the REVIVE and TAK318 trials, so the safety profile of vortioxetine compared to other antidepressants is uncertain.

The ERG has considerable concerns over the validity of the network analysis because of the high apparent diversity in the populations across trials, with very different included patients and severities of depression. For one trial (Kasper) the analysis used a subset of patients who had been treated in the year prior to enrolment. This is not the same as patients who were switching treatment, so the ERG does not think this trial should have been included. The ERG questions the validity of the indirect treatment comparison, but notes that the analysis found no convincing evidence of difference between vortioxetine and other treatments in terms of remission rate (except for agomelatine). There was some

evidence that vortioxetine may have lower withdrawal rates due to adverse events, but the high apparent heterogeneity across trials means the validity of this finding is questionable.

Given the limited nature of the data in the switch population the ERG considers that data in non-switching and initial-use populations should be considered. Although such data is not in the switch population it is relevant to the broader population of all patients with MDD specified in the NICE scope. The manufacturer justified excluding trials of non-switching populations by claiming that treatment efficacy in a switch population may be different from in initial use. The ERG considers that the evidence submitted to justify this claim is limited and refers only to patients who had previously used an SSRI, where switching to another SSRI may be less effective than a non-SSRI treatment. No evidence was presented to suggest that the relative efficacy of non-SSRIs may vary between initial and switch use, and no evidence was specific to vortioxetine. The ERG therefore concludes that this restriction was inappropriate and evidence on non-switch populations is relevant when examining the efficacy and safety of vortioxetine.

Direct evidence comparing vortioxetine to other active treatments in non-switching populations was only available from short-term placebo controlled trials with active reference arms. The EMA and the manufacturer have criticised the use of active references because they are not true randomised comparisons and patients known to be non-responsive to the reference are excluded, possibly biasing results in favour of the active reference. While the ERG accepts the potential for such bias it does not consider this potential bias to be substantial enough to exclude these trials. The ERG found no evidence of any difference in efficacy between vortioxetine and venlafaxine, based on two trials. There was evidence that vortioxetine was significantly inferior to duloxetine in terms of reducing depression scores, response and remission. While there is a possibility of bias in favour of duloxetine in these analyses it is not clear whether any bias would be sufficient to completely explain this inferiority.

An indirect treatment comparison in non-switch populations found no evidence of any difference in efficacy between vortioxetine and other treatments, but there was some evidence to suggest that vortioxetine had a lower withdrawal rate due to adverse events than some treatments, including sertraline and venlafaxine. While this is an indirect analysis, and not conducted in a switch population, the number of trials included in this analysis suggests that this may represent the most reliable evidence for comparing the efficacy and tolerability of vortioxetine to other treatments.

The ERG concludes, based on the totality of the evidence, that vortioxetine is likely to be of similar efficacy to other antidepressants, but may be superior to agomelatine and inferior to duloxetine. Vortioxetine appears to have a lower withdrawal rate due to adverse events than other treatments, and

2 Background

2.1 Critique of manufacturer's description of underlying health problem.

The manufacturer presents a suitable summary of major depressive disorder (MDD) and major depressive episodes (MDE) in manufacturer's submission (MS) sections 2.1 to 2.3; this includes their definition, progression over time, impact on health and quality of life and the impact and cost to the NHS and society in general.

The submission notes that the terms MDD and MDE are based on standard classifications from the Diagnostic and Statistical Manual of Mental Disorders (DSM). The terms MDE and MDD are used to describe depression in the USA; this terminology differs slightly from that used in the UK, where the terms mild/moderate/severe depression are more commonly used. The submission notes that MDD/MDE are approximately equivalent to moderate to severe depression as defined by NICE guidance.(1) An MDE is defined as the occurrence of depressed mood or a loss of interest or pleasure in life activities for at least two weeks, at least five of the nine core symptoms of depression and at least one significant impairment in social functioning (list provided in submission) occurring almost every day. Left untreated an MDE may last for two months to several years, but this may be greatly reduced by treatment.(2) The course of an MDE is characterised by five events: response, remission, recovery, relapse and recurrence,(3) as summarised in Figure 1. A patient whose symptoms improve sufficiently on treatment is considered to be responding, and is judged to be in remission when core symptoms of depression cease or are considered very minor. Patients remaining in remission for sufficient time are judged to have recovered. NICE recommends continuing treatment for at least six months following remission, and treatment may be continued for longer (two years or more) in cases of recurrent MDEs.(1) A patient may relapse at any time if symptoms worsen. If symptoms re-occur after recovery this is judged to be a recurrence and constitutes a new MDE. Relapse and lack of response are common, with approximately one-third to one half of patients not responding adequately to treatment,(4, 5) and at least half of all patients experiencing their first MDE will go on to have at least one more episode within the next ten years.(6)

The submission discusses the potential health impacts of depression, particularly the substantial loss of quality of life and potential reduction in life expectancy, including increased risk of suicide, and its impact on family members. The costs associated with depression are substantial, with 1.24 million people estimated to have depression in England, costing the NHS £1.68 billion, and averaging £2,805 per person.(7) The submission also noted the substantial wider economic cost of depression due to increased sick leave and absenteeism from work, and reduced productivity.

3 Critique of manufacturer's definition of decision problem

3.1 Population

The population described in the final NICE scope is adults with major depressive disorder, reflecting the licensed population. Vortioxetine has a marketing authorisation in the UK for the treatment of major depressive episodes in adults. However, the patient population considered by the manufacturer was restricted to a subset of the licensed patient population, namely:

“adult patients with moderate-to-severe MDD who are experiencing an MDE, who have responded inadequately in terms of efficacy or tolerability to initial antidepressant treatment, and who require and want to switch to alternative antidepressant” (MS, p14).

The manufacturer cites the burden of initial treatment failure on patients, the health service and wider society to highlight the potential unmet clinical and economic need for more effective and better-tolerated options for patients requiring a switch of treatment where initial antidepressant treatment has failed. The manufacturer further justifies this restriction, stating that the distinct pharmacological profile and favourable tolerability profile of vortioxetine may be particularly suitable in the “switch population”. This switch population is further defined by the manufacturer (MS, p38) as:

- *Patients who are experiencing a moderate-to-severe MDE, and*
- *whose current episode has been treated initially with an SSRI or SNRI, and*
- *who are candidates for a switch in the clinician's opinion, and*
- *who wish to change antidepressant treatment because of inadequate response or intolerance to the initial treatment.*

Although vortioxetine has been studied in 24 completed trials (some of which were healthy volunteer trials) involving over 7,000 patients, the manufacturer's submission focuses largely on 2 studies considered relevant to the decision problem; Study 14178A (REVIVE) and TAK318. These studies are subsequently used as the basis for short-term efficacy and tolerability data. Longer-term safety studies from a broader population including non-switch patients are also presented in the manufacturer's submission based on the assumption that tolerability and safety data are likely to be generalisable to a switch population. Based on clinical advice, the ERG considers this assumption to be appropriate for safety, but not for tolerability, as patients intolerant of one medication may be more intolerant of others.

The population considered within the manufacturer's submission is thus significantly restricted compared to the broader population stated in the final NICE scope and the licensed indication for vortioxetine. However, such a restriction is potentially consistent with the “Other considerations”

The review of indirect evidence presented in the original MS included significantly fewer outcomes, namely remission and withdrawal due to adverse events. The manufacturer stated that no other endpoints could be included in the review of indirect evidence as they were not reported consistently across all included studies. Although this justification appears appropriate, the absence of other outcomes (such as response rates) limits the relevance of the review of evidence comparing vortioxetine with several relevant comparators.

The MS cost-effectiveness model included some, but not all, of the effectiveness outcomes specified in the scope. In particular, the manufacturer did not include response data within the decision model.

3.5 Other relevant factors

The MS stated that no attempts were made to allow for equality considerations issues analytically, such as by applying alternative utility weightings. The MS noted that although people with intellectual disability are more likely to suffer from depressive episodes, this particular population may be at a disadvantage when it comes to receiving a specific diagnosis for depressive symptoms distinct from their other difficulties, and accessing the care they need (MS, Section 3, p.50). The ERG thinks that this approach was likely to be appropriate.

4 Clinical Effectiveness

The manufacturer submitted evidence on clinical effectiveness in the “switch” population based on four systematic reviews. This included three reviews of direct evidence for vortioxetine:

- a) a review of RCTs of vortioxetine compared to active comparators in the switch population (MS, Sections 6.1 to 6.6) to evaluate efficacy;
- b) a review of non-RCT evidence of vortioxetine in the switch population to evaluate efficacy (MS, Section 6.8);
- c) a review of adverse events of vortioxetine (MS, Section 6.9).

Also submitted was a review of indirect comparative evidence, again in the switch population, including an indirect treatment comparison and network meta-analysis of antidepressant RCTs, to evaluate efficacy and safety (MS, Section 6.7).

Section 4.1 below summarises and critiques the methods of all four reviews. The first review identified two RCTs comparing vortioxetine to other active comparators, REVIVE and TAK318; these are critiqued in Section 4.2. The review of indirect treatment comparisons and its associated network meta-analysis are critiqued in Section 4.3. The review of non-RCT evidence did not identify any relevant studies, so this report does not consider this review in any detail (Section 4.4). The review of adverse events is critiqued in Section 4.5.

As discussed in Section 3 above, the ERG considers that the restriction to a switch population only is considerably narrower than the original scope specified and that assessment of the efficacy of vortioxetine should take account of the broader population by including evidence from studies of vortioxetine in non-switch populations. The ERG requested that the manufacturer provide data on all trials of vortioxetine compared to placebo and/or active comparators. The manufacturer supplied efficacy and adverse event data for their placebo controlled trials of vortioxetine. They also identified three published systematic reviews of vortioxetine, two submissions to regulatory or HTA authorities and one published indirect comparison of vortioxetine with other antidepressants, sponsored by the manufacturer. The ERG considers this evidence in the wider population to be of relevance when determining the clinical efficacy of vortioxetine; this evidence is critiqued in Section 4.6.

were used to pool the safety studies. The ERG notes that this method is not ideal as it ignores differences in populations and characteristics across studies.

Indirect treatment comparison

Trials included in the indirect treatment comparison were pooled using network meta-analysis methods. The submission used two different approaches: a frequentist analysis using the Boucher method and a Bayesian analysis performed using WinBUGS. The ERG recognises that both approaches are standard methods, and have been used appropriately in the submitted analyses.

The ERG has concerns with some of the methods used in the network meta-analysis. The primary outcome was remission rate. No other efficacy outcomes, such as response rate or absolute changes in depression scores were included in the analysis in the original MS. On clarification, the manufacturer stated that no other efficacy endpoint was consistently reported across all studies and hence they could not be included in the network meta-analysis. Remission was defined as a HAM-D score of seven or less, or a MADRS score of ten or less. Because different trials reported different depression scales these scales may not be exactly comparable, and some patients may have achieved remission on one scale but not another. Also, one trial (Kasper) did not report remission rates, so this was calculated from HAM-D scores, assuming scores followed either a normal or gamma distribution. Sensitivity analyses were performed to investigate the effect of using both these distributions, which was appropriate. However, remission rates may have been inaccurately estimated if the data did not fit either of these distributions. On clarification, the manufacturer presented results of a network meta-analysis with standardised mean difference in depression scale as the outcome.

The main network analysis excluded trials with a placebo arm. The manufacturer justified this based on clinical advice that patients in placebo-controlled studies may be different from those in active-controlled studies. No further justification was provided. The ERG does not consider this to be a strong justification, because such differences would apply to all placebo-controlled trials, and including such trials would be unlikely to bias the network analysis results as a whole. The manufacturer did provide results of the network including placebo-controlled trials in Appendix 16.

The MS reported results as risk differences between treatments. The ERG does not consider the risk difference to be a suitable measure for comparing treatments as it is very sensitive to any heterogeneity in outcomes across trials. The manufacturers justified this choice because using the risk difference led to more conservative estimates for venlafaxine, bupropion and citalopram. The ERG agrees that results were more conservative in this case, but considers results based on odds ratios or relative risks to be more statistically robust. The manufacturers provided results based on odds ratios in an appendix, and results for relative risks in response to requests for clarification.

limitations that may have affected their external validity. The ERG has particular concerns regarding the choice of comparator, duration of follow-up and study power.

Comparators

Agomelatine is not currently recommended by NICE. The fact that agomelatine is the only comparator in REVIVE means that, in the context of this appraisal, the relevance of this trial is limited. The use of escitalopram is also limited in UK patients experiencing SSRI-induced sexual dysfunction, which limits the relevance of TAK318 to current UK practice.

Follow-up duration

The 12-weeks follow-up duration of REVIVE is short considering the duration of treatment that is recommended by NICE to achieve and consolidate remission. The manufacturer acknowledged this limitation (MS, p.136), but stated that this shortcoming was mitigated by the results of a relapse-prevention trial (study 11985A)(14) that found significantly lower relapse rates for vortioxetine compared with placebo (13% versus 26%, $p=0.0013$), over 24 weeks after 12 weeks' open-label treatment. The results of study 11985A should be interpreted with caution as it only included patients who were in remission at 10 and 12 weeks of open-label vortioxetine therapy, and therefore excluded responders-only, or patients who may have been in remission following a longer course of therapy. As with REVIVE, TAK318 had a short-term follow-up, therefore evidence of long-term efficacy of vortioxetine in switch populations is uncertain.

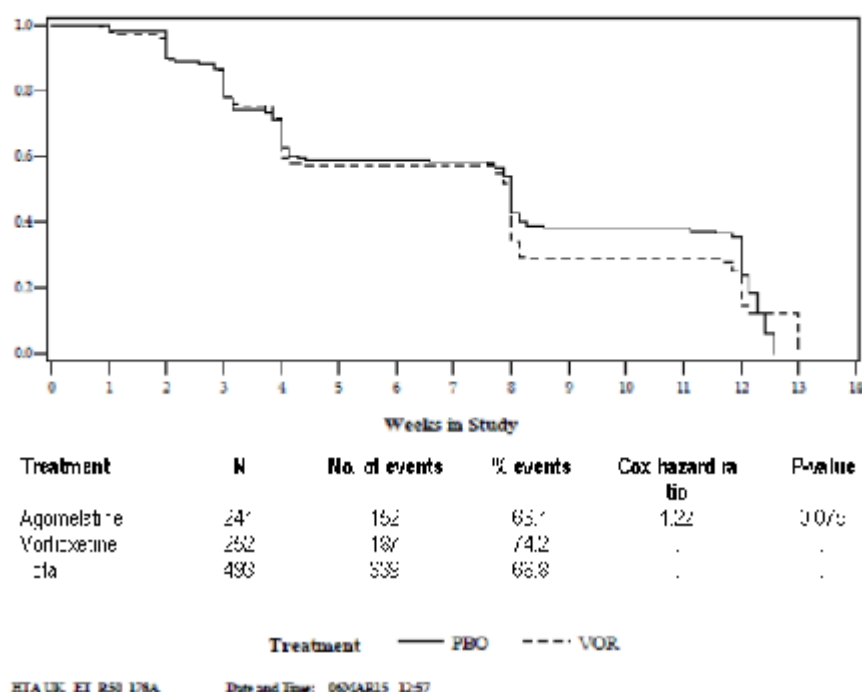
Study power

REVIVE was designed as a non-inferiority trial. Sample size calculations were based on a non-inferiority comparison of the treatment groups in the primary outcome, and non-inferiority was considered established if the upper bound of the two-sided 95% confidence interval of the difference between treatment groups in MADRS total score at Week 8 did not exceed 2 MADRS units compared with agomelatine. This means that REVIVE may not have been sufficiently powered to demonstrate that vortioxetine is superior to agomelatine.

Additional concerns about the representativeness of the trial populations are reported in sections 4.2.3 (REVIVE) and 4.2.5 (TAK318) of this report.

4.2.2 Quality assessment and risk of bias

The manufacturer provided a quality assessment of the two included trials of vortioxetine (REVIVE and TAK318) in MS section 6.4, Tables B11 and B12 (MS, pp. 83-87). These are summarised in Table 9 below. The ERG mostly concurs with the manufacturer's assessment of quality for the two

Figure 6 Kaplan Meir plot of time to first response (50% reduction in MADRS)

Erratum to figure: For PBO read Agomelatine; for VOR read Vortioxetine

The results of this analysis showed a small separation between groups in favour of vortioxetine from 8 weeks, although the time-to-event analysis yielded a non-statistically significant result ($p=0.075$). This analysis should be interpreted with caution as it reports time to first response, and does not take into account patients who may have responded at early assessments but did not maintain response until the end of the study, as acknowledged by the manufacturer.

Severity of depression

Table 12 below presents differences in mean change from baseline between vortioxetine and agomelatine and shows that efficacy results were statistically significant across MADRS, CGI-S and CGI-I scores at treatment weeks eight and 12. REVIVE reported a reduction of 16.5 MADRS points (from 29.1 at baseline) in the vortioxetine group, and a reduction of 14.4 points (from 28.66 at baseline) in the agomelatine group, giving a mean difference of -2.16 (95% CI -3.51 to -0.81). The manufacturer stated that non-inferiority was established, as the upper bound of the 95% CI was below the non-inferiority margin of +2 MADRS points versus agomelatine. The magnitude of the results

Based on the TAK318 trial results, the manufacturer stated that vortioxetine is superior to escitalopram in improving sexual functioning in patients with SSRI-induced sexual dysfunction. They stated that both vortioxetine and escitalopram maintained and slightly improved the depressive symptoms seen with the prior SSRI treatment as assessed by MADRS, CGI-S, and CGI-I scores, and that vortioxetine was generally well-tolerated in this study.

REVIVE and TAK318 trials appeared well conducted. However, the designs of both studies raised a number of concerns. As mentioned above (Section 4.2.1), both trials included comparators of limited relevance to UK practice, and there were concerns about the representativeness of the trial participants to the UK switch population. Both studies had short-term follow-up, therefore the long-term efficacy of vortioxetine in switch patients is uncertain based on the evidence presented. In addition, the trials only evaluated the efficacy of vortioxetine 10-20mg/day, therefore the efficacy of the licensed 5mg/day regimen is uncertain. Finally, as REVIVE was designed as a non-inferiority trial, and was not designed to show superiority of vortioxetine.

4.3 Indirect treatment comparison

4.3.1 Critique of trials identified and included in the indirect comparison

The systematic review for the indirect comparison analysis identified 27 relevant studies; however 20 were excluded as not being in “switch” populations. The ERG accepts that these studies did not meet the inclusion criteria for the manufacturer’s analysis, but many of these studies may have matched the NICE scope population of adults with MDD.

The seven remaining studies were assessed for study quality. For five studies, all quality components were assessed as either adequate or unclear. One study (Rush 2006(5)) had one component (imbalances between groups) considered to be inadequate. The ERG generally agrees with the manufacturer on their quality assessment of these trials.

One study (Rosso 2012(15)) had two inadequate components (randomisation and blinding). Given the high potential for bias in this trial it was excluded from further analysis. The ERG accepts that assessment of bias was correct and so this exclusion was reasonable, but notes that, as Rosso 2012 was the only study to include duloxetine, this means no evidence comparing vortioxetine to duloxetine has been presented.

the trials. In particular the withdrawal rates on venlafaxine (XR) and citalopram were around 18% in the model (Table 17) but only around 5% in the Lenox-Smith trial (Table 16).

4.3.3 Conclusions of the indirect treatment comparison

The manufacturer concluded that the network meta-analysis showed that vortioxetine is more efficacious and better tolerated than a range of comparator antidepressants.

The ERG does not concur with this conclusion for a variety of reasons. Wide confidence intervals mean that there was little evidence of a statistically significant improvement in efficacy with vortioxetine compared to other treatments. The network meta-analysis used in the indirect treatment comparison was limited to only four trials. Removing any trial would leave the network unconnected. The ERG has concerns as to whether the Kasper trial should have been included as the subgroup analysis used from this trial was not specifically of a switch population.

There is also evidence of substantial heterogeneity in the populations included across the trial, for example in the severity of depression, and apparent heterogeneity in the results of each trial. The limited number of trials meant that formal assessments of heterogeneity and network inconsistency could not be performed. Given these concerns the ERG concludes that the indirect treatment comparison reported in the submission does not provide valid evidence from which any conclusion on the efficacy of vortioxetine may reasonably be drawn.

4.4 Non-RCT evidence

The manufacturers performed a search for evidence other than RCTs but did not identify any relevant studies. The ERG did not find any evidence that relevant non-RCT studies of efficacy in switch patients had been missed.

4.5 Adverse events

The manufacturer performed a search for safety trials of vortioxetine in the “switch” population. None were identified so the search was widened to include all safety trials of vortioxetine. This search identified six studies, of which five were one-year open-label extensions of short-term efficacy trials and were eligible for inclusion in a pooled analysis. This pool included a total of 2,587 patients who continued from short-term, randomised placebo controlled trials and received flexible doses of vortioxetine 2.5 to 20mg/day.

Given that the manufacturer had broadened the scope in the search for adverse event data to all vortioxetine trials, the ERG requested the manufacturer supply adverse event data from all placebo or active control trials they had performed. Data from 12 short-term placebo-controlled phase II/III studies had been provided in an appendix to the MS, some of which was also provided in the

clarification response. These trials included one trial (12541A) that was conducted in patients aged over 65 years. This short-term pool included a total of 3,904 patients treated with vortioxetine.

Table 20 provides a list of studies included in the two pools, and is presented below. None of the studies included were conducted in switch populations. Further details of the pools are presented below.

Table 20 Overview of pools for the evaluation of the safety and tolerability of vortioxetine

Pool	Number of studies included	Study ID
Short-term placebo controlled pool	12	11492A, 11984A, 305, 13267A, 315, 316, 14122A, CCT-002, 303, 304, and 317, and 12541A
Open-label long-term pool	5	11492C, 11984B, 301, 13267B, and 314

4.5.1 Short-term pool of placebo controlled studies

The results of the review of long-term continuation studies of adverse events were reported in a separate document(23) and summarised in clarifications. A summary of incidence of TEAE during the core treatment period (from first dose to last dose in the double-blind treatment period) for vortioxetine and placebo is presented in Table 21 below. The manufacturer stated that the 15mg dose will not be available in the UK, but results for this regimen were presented here for the sake of completion.

The overall incidence of TEAEs was 64.2% in the vortioxetine group, and 57.9% in the placebo group. The Treatment-emergent adverse event (TEAE) with the highest incidence in all the active treatment groups was nausea. The incidence of nausea was 8.1% in the placebo group and 24.1% in the total vortioxetine group (relative risk 3.02; 95% CI 2.57 to 3.55). Headache, which was the TEAE with the highest incidence in the placebo group, had similar incidences in all the treatment groups (approximately 13%).

For the majority of the patients with TEAEs, the TEAEs were mild or moderate. The incidence of severe TEAEs was similar in the placebo group and in the vortioxetine total group (4.4% and 5.5%, respectively). In the vortioxetine dose groups, the incidence of severe TEAEs ranged from 4.1% in the 20mg group to 7.0% in the 5mg group.

The overall incidence of TEAE leading to withdrawal in the vortioxetine total group was higher in the vortioxetine group (6.0%) compared with placebo (4.0%), and higher in 15-20mg doses compared with 5-10mg doses (4.8% [5mg], 5.8% [10mg], 8.0% [15mg], and 7.0% [20mg]). The most common

4.5.2.1 Conclusions of the review of safety studies

No separate conclusions were provided for the review of safety studies, although the manufacturer stated that vortioxetine had a favourable safety profile in an overview of safety in relation to the decision problem (section 6.9.3).

The ERG agrees that based on the evidence presented, vortioxetine appears generally safe and tolerable in patients with MDD. The analysis of the pooled placebo controlled trials and the analysis of the pooled continuation studies included relatively large patient numbers and showed broadly comparable results. Although the incidence of adverse events was high in patients receiving vortioxetine, most AEs were mild to moderate in intensity and there was no conclusive evidence that these were dose-dependent.

However, both pooled analyses had limitations. All analyses from the pool of continuation studies were uncontrolled, and as such they are at high risk of confounding (notably due to the placebo effect). All continuation studies were one-year extensions, and nearly half of patients received vortioxetine for less than one year, which is significantly less than for patients for whom maintenance may be recommended for two years or more. Some relevant studies may have been missed, since only studies that reported safety as a primary outcome were included. Results from the pool of placebo-controlled studies showed that the rate of patients with adverse events was high for vortioxetine (64.2%) as well as for placebo (57.9%), indicating a high placebo effect, although there was a statistically significant higher risk in the incidence of some specific adverse events, particularly nausea and vomiting (approximately 3 and 3.5 times higher than placebo). These results are in line with those of the Pae 2014 review(24), which found that nausea and vomiting were some of the most common AEs reported, and had an incidence that was significantly higher in the vortioxetine than in the placebo group. They also found that nausea was the single most common AE reported as a reason for discontinuation of vortioxetine, and found that its frequency showed a trend toward a dose-response relationship. Compared with placebo, withdrawal due to adverse events was slightly higher for vortioxetine, particularly in higher treatment doses (15-20mg).

The MS and clarifications presented no evidence of adverse events when comparing vortioxetine with active comparators. The ERG concludes that the best data available are that from the two trials (REVIVE, TAK318) discussed above in Section 4.2. The indirect treatment comparisons provided by the manufacturer and in Llorca et al(22) both reported withdrawal due to adverse events, which can be considered a reasonable proxy for adverse events overall. These results are discussed in sections 4.3 and 4.6. Based on these results there is some evidence that vortioxetine has a better adverse event profile than other drugs, including venlafaxine and duloxetine. It may be less well tolerated than agomelatine, although this conflicts with results from REVIVE.

4.6 Evidence syntheses of non-switch populations

As discussed in Section 3 the ERG questions the validity of restricting the analysis to “switch” populations. The evidence to suggest that there is a difference in treatment efficacy between initial use and switch use is limited,(1, 11) and restricted to showing that where patients are switching from an SSRI due to lack of response or intolerance, a non-SSRI may be more effective than another SSRI in these switching patients.(25) There is no evidence currently available to suggest that the relative efficacy of non-SSRIs differs between initial-use and switch populations. The ERG thinks that initial-use trials should be considered as providing relevant supporting evidence, particularly for the relative efficacy of non-SSRIs, given the limited nature of the evidence in the switch population identified by the manufacturer.

The ERG therefore requested that the manufacturer provide results from trials or meta-analyses of trials comparing vortioxetine to other active treatments and/or placebo in initial use and non-switch use populations.

In response the manufacturer:

1. Provided their own meta-analyses of trials comparing vortioxetine to placebo.
2. Reported the existence of two submissions to regulatory or HTA authorities:
 - Pharmaceutical Benefits Advisory Committee (PBAC, Australia)(26)
 - Canadian Agency for Drugs and Technologies in Health (CADTH)

However, they did not provide these submissions; a redacted version of the PBAC report is in the public domain but the CADTH report has not been made public.

3. Identified four systematic reviews of vortioxetine:
 - Pae et al 2014(24)
 - Berhan and Barker 2014(27)
 - Citrome 2014(28)
 - Meeker et al 2015(29) (this review was published very recently and so was identified by the manufacturer subsequent to the MS and response to clarifications)
4. Identified one indirect treatment comparison sponsored by the manufacturer (Llorca 2015).(22)

The ERG thinks that all these analyses in non-switch populations provide relevant evidence on the efficacy of vortioxetine, and considers this evidence below.

4.6.1 Vortioxetine vs placebo

4.6.2 Vortioxetine vs active comparators

The submission to PBAC, the Pae and Meeker meta-analyses all considered trials comparing vortioxetine to an active comparator. The trials included in these analyses were generally placebo controlled trials with an active reference arm, except for one randomised trial evaluating vortioxetine and venlafaxine in a head-to-head comparison which was included in the submission to PBAC.(30) In the original submission, the manufacturer criticised the use of these active reference arms (MS, Sections 1.4.1 and 2.8.2). Active reference arms are included in trials of antidepressants to ensure that patients are responding to therapy. An active reference should be a drug of proven superiority over placebo, so it can be used to check whether the trial has successfully treated patients by confirming a difference between the active reference and placebo. Patients known to be non-responders to the active reference are excluded from this arm, so the active reference arm may include patients more likely to respond to treatment. The manufacturer therefore claimed that any comparison of vortioxetine with an active reference may be biased towards the active reference.

The ERG recognises the potential for bias because the comparison between vortioxetine and active reference is not truly randomised and there is the potential for patients to differ in likely response to treatment between arms. However, the ERG does not consider this risk of bias to be sufficiently substantial to reject such comparisons altogether. The results of these comparisons discussed in the Pae and Meeker analyses, and the PBAC submission are therefore considered below.

4.6.2.1 Pae et al.

In Pae et al. meta-analyses comparing vortioxetine to active comparator for standardised mean difference, response and remission rates were presented. The analysis did not distinguish between the different comparator treatments. Based on the references in the paper the ERG has reanalysed the data, grouping trials by the comparator included in each trial.

Figure 10 shows the results based on data from the trials in the Pae meta-analysis for standardised mean difference in depression score between arms. Figure 11 shows the results for response rate, and Figure 12 for remission rate. In all three cases vortioxetine is superior to agomelatine based on the trial of Dragheim.(31) This trial appears to be an early presentation of the results of the REVIVE trial, but this could not be confirmed because the trial was reported only as a conference presentation which the ERG could not access. There is no evidence of a difference between vortioxetine and venlafaxine, based on one trial. Vortioxetine is consistently and statistically significantly inferior to duloxetine for all three outcomes. The potential that results were biased in favour of duloxetine given the potential for bias discussed above must be considered.

Figure 10 Forest plot of standardised mean difference based on data from Pae et al.

Table 26 Indirect treatment comparison by Llorca et al.

Outcome	Results vs vortioxetine (p-value)						
	Agomelatine	Desvenlafaxine	Duloxetine	Escitalopram	Sertraline	Venlafaxine	Vilazodone
Efficacy at 2 months (SMD: <0 favours vortioxetine)	-0.156 (0.113)	0.025 (0.803)	0.090 (0.419)	-0.054 (0.695)	-0.037 (0.832)	0.124 (0.328)	-0.245 (0.111)
Withdrawal due to AE (Odds ratio: <1 favours vortioxetine)	1.769 (0.030) *	0.578 (0.035) *	0.752 (0.262)	0.671 (0.275)	0.299 (0.008) **	0.469 (0.009) **	0.640 (0.181)
Response rate (Odds ratio: >1 favours vortioxetine)	1.045 (0.815)	1.153 (0.364)	0.893 (0.514)	0.843 (0.523)	0.772 (0.575)	0.789 (0.353)	0.975 (0.934)
Remission rate (Odds ratio: >1 favours vortioxetine)	1.220 (0.470)	1.029 (0.852)	0.894 (0.526)	0.990 (0.981)	NA	0.689 (0.444)	0.983 (0.952)

* p-value 0.01 – 0.05; ** p-value <0.01

This analysis generally found no statistically significant evidence of a difference in efficacy between vortioxetine and any other treatment. Vortioxetine generally had a lower withdrawal rate than other treatments, although the results were only statistically significant for desvenlafaxine, sertraline and venlafaxine. Agomelatine had a lower withdrawal rate than vortioxetine.

This analysis was not performed in a “switch” population, however the findings of this analysis are consistent with those from the indirect treatment comparison in the switch population submitted by the manufacturer (except for agomelatine and withdrawal).

4.7 Conclusions of the clinical effectiveness section

The manufacturer’s submission focused on trials in patients who had previously received antidepressants for a current MDE but were switching treatment to vortioxetine due to lack of response or adverse events; the “switch” population. As discussed in Section 3 The ERG notes that this is a substantial restriction when compared to the original scope, which specified a general population of all adults with MDD.

The restriction to a switch population meant that only two trials comparing the efficacy vortioxetine with other antidepressants were submitted. Both trials were generally well conducted but there were a number of issues related to their design and their population which may limit the applicability of their results to UK practice. The REVIVE trial comparing vortioxetine to agomelatine found vortioxetine

had greater reduction in depression scores and lower withdrawal rates due to adverse events. It should also be noted that agomelatine is not recommended for use by NICE as no evidence for its efficacy has been submitted.

The TAK318 trial included patients who were switching due to sexual dysfunction but had responded to initial treatment. The ERG notes that this is a very narrow and specific population, so the TAK318 trial provided little information on the broader population who might take vortioxetine. It did find that vortioxetine reduced sexual dysfunction symptoms when compared to escitalopram. However it is not clear whether this finding is specific to vortioxetine, or whether any non-SSRI would have a similar beneficial effect.

The restriction to switch populations meant that the indirect treatment comparison in the submission included only four trials in its main analysis. The ERG has considerable concerns over the validity of the network analysis because of the high apparent diversity in the populations across trials, including very different patients and severities of depression. For one trial (Kasper) the analysis used a subset of patients who had been treated in the past year. This is not the same as patients who were switching treatment, so the ERG does not think this trial should have been included; without it, there is no connected network, rendering the analysis invalid. As such the ERG does not think the results of the indirect treatment comparison are valid, but notes that the analysis found no convincing evidence of difference between vortioxetine and other treatments in terms of remission rate (except for agomelatine). There was some evidence that vortioxetine may have lower withdrawal rates, but the high apparent heterogeneity across trials means the validity of this finding is questionable.

The manufacturers did not identify any trials reporting safety data in the switch population other than data reported in REVIVE and TAK318. The manufacturers therefore expanded the review of safety data to non-switch populations. This review identified 12 short-term placebo controlled trials and five longer-term open label extension trials of vortioxetine. In the placebo controlled trials severe adverse event rates and adverse events leading to withdrawal were more common on vortioxetine than placebo. However, based on the evidence presented, vortioxetine appears generally safe and tolerable in patients with MDD. Both the analysis of placebo controlled trials and the analysis of continuation studies included relatively large patient numbers and showed broadly comparable results. Although the incidence of adverse events was high in patients receiving vortioxetine, most AEs were mild to moderate in intensity and there was no conclusive evidence that these were dose-dependent. The manufacturer did not present any safety comparisons of vortioxetine with any active comparators in the broad MDD population, so the safety profile of vortioxetine compared to other antidepressants is uncertain.

Importantly, too, costs are assumed to be different in the acute phase compared to the remainder of the 12 months.

5.3.9.2 Acquisition costs

The acquisition costs for antidepressants are based upon the cheapest way of achieving the required daily dose, which in the acute phase is given by the WHO DDD (defined daily dose). In the case of agomelatine, an additional cost is factored in, which is the cost of carrying out a liver function test. In the acute phase, it is assumed that three liver function tests will be administered for each patient.

Table 39 Acute phase drug acquisition costs

Treatment	Assumed pack	Pack price	Dose in acute phase	Additional cost	Daily cost in acute phase
Vortioxetine	28 x 10mg Brintellix	£27.72	10mg	n/a	£0.99
Agomelatine	28 x 25mg Valdoxan	£30.00	25mg	3 x liver function test	£1.46
Sertraline	28 x 50mg	£1.75	50mg	n/a	£0.06
Venlafaxine	28 x 150mg VenlaBlue XR	£9.95	100mg	n/a	£0.24
Citalopram	28 x 20mg	£1.10	20mg	n/a	£0.04

Pack prices are taken from MIMS December 2014. Because doses are routinely adjusted upwards following initial treatment, the decision model allows for a higher dosage in the maintenance phase compared to that assumed in the acute phase. The manufacturer makes this assumption through observed increases in dosage for each comparator from the respective trials included in the indirect treatment comparison. In reality doses may be up-titrated at various points, for example after 2-4 weeks, but in the model the dose is raised after 8 weeks only. The results of dose titration for acquisition costs are illustrated in the table below.

Table 40 Post-acute phase drug acquisition costs

Treatment	Assumed pack	Pack price	Dose in maintenance phase	Additional cost	Daily cost in acute phase
Vortioxetine	28 x 20mg Brintellix	£27.72	20mg	n/a	£0.99
Agomelatine	28 x 25mg Valdoxan	£30.00	42.93mg	2 x liver function test per 8 weeks	£2.10
Sertraline	28 x 50mg	£2.15	135.5mg	n/a	£0.10
Venlafaxine	28 x 150mg VenlaBlue XR	£9.95	192.3mg	n/a	£0.46
Citalopram	28 x 40mg	£1.28	51mg	n/a	£0.06

8 Overall conclusions

8.1 Clinical effectiveness

The manufacturer restricted consideration of vortioxetine to patients who were switching from an initial antidepressant because the initial therapy was ineffective or not tolerated. This “switch” population is considerably narrower than the broad population specified in the scope

The restriction to a switch population meant that only two trials directly comparing the efficacy vortioxetine with other antidepressants were included in the MS. The REVIVE trial comparing vortioxetine to agomelatine found vortioxetine had greater reduction in depression scores and lower withdrawal rates due to adverse events. The trial was designed as a non-inferiority trial, and was not designed to detect superiority of vortioxetine. It should also be noted that agomelatine is not approved for use in the UK as no evidence for its efficacy has been submitted to NICE. The TAK318 trial included patients who were switching due to sexual dysfunction but had responded to initial treatment. The trial found that vortioxetine reduced sexual dysfunction symptoms when compared to escitalopram. The ERG notes that this is a very narrow and specific population, so the TAK318 trial provided little information on the broader population who might take vortioxetine.

The ERG has considerable concerns over the validity of the network analysis because of the high apparent diversity in the populations across trials, with very different included patients and severities of depression. The ERG does not think the results of the indirect treatment comparison are valid, but notes that the analysis found no convincing evidence of a difference between vortioxetine and other treatments in terms of remission rate (except for agomelatine). There was some evidence that vortioxetine may have lower withdrawal rates, but the high apparent heterogeneity across trials means the validity of this finding is questionable.

Based on the safety evidence presented, vortioxetine appears generally safe and tolerable in patients with MDD. Most adverse events were mild to moderate in intensity and there was no conclusive evidence that these were dose-dependent. The submission did not present any safety comparisons of vortioxetine with any active comparators, so the safety profile of vortioxetine compared to other antidepressants is uncertain.

Given the limited nature of the data in the switch population the ERG considers that data in non-switching and initial-use populations should be considered. Although such data are not in the switch population it is relevant to the broader population of all patients with MDD specified in the NICE scope. The manufacturer justified excluding trials of non-switching populations by claiming that treatment efficacy in a switch population may be different from in initial use. The ERG considers that the evidence submitted to justify this claim was limited. The ERG therefore concludes that this

restriction was inappropriate and evidence on non-switch populations is relevant when examining the efficacy and safety of vortioxetine.

Direct evidence comparing vortioxetine to other active treatments in non-switching populations was primarily available from placebo controlled trials with active reference arms. The EMA and the manufacturer have criticised the use of active references because they are not true randomised comparisons and patients known to be non-responsive to the reference are excluded, possibly biasing results in favour of the active reference. While the ERG accepts the potential for such bias it does not consider this potential bias to be substantial enough to exclude these trials. The ERG reanalysed results from these trials and found no evidence of any difference in efficacy between vortioxetine and venlafaxine, based on two trials. There was evidence that vortioxetine was inferior to duloxetine in terms of reducing depression scores, response and remission. While there is a possibility of bias in favour of duloxetine in these analyses it is not clear whether any bias would be sufficient to completely explain this inferiority.

An indirect treatment comparison in non-switch populations found no evidence of any difference in efficacy between vortioxetine and other treatments, but there was some evidence to suggest that vortioxetine had a lower withdrawal rate due to adverse events than some treatments, including sertraline and venlafaxine. While this is an indirect analysis, and not conducted in a switch population, the number of trials included in this analysis suggests that this may represent the most reliable evidence for comparing vortioxetine to other treatments.

The ERG concludes, based on the totality of the evidence, that vortioxetine is likely to be of similar efficacy to other antidepressants, but may be superior to agomelatine and inferior to duloxetine. Vortioxetine appears to have a lower withdrawal rate due to adverse events than other treatments, and so may have a better overall safety profile, however data on adverse events with vortioxetine, particularly when compared to other antidepressants, are too limited to draw any firm conclusions on the safety of vortioxetine.

8.2 Cost effectiveness

The MS presents cost-effectiveness evidence for vortioxetine as a second line option for MDE ("switch population"), a restriction to its licensed indication and the scope of the NICE appraisal. The ERG considers that the appropriate population and potential position of vortioxetine within current pathways should have been more formally considered by the manufacturer.

The MS establishes cost-effectiveness assuming the use of vortioxetine in primary care. The MS presents a decision model that evaluates the progression of a single MDE. The model is based on

treatment. No evidence was presented to suggest that the relative efficacy of non-SSRIs may vary between initial and switch use, and no evidence was specific to vortioxetine.

This restriction also meant that only two trials comparing vortioxetine to other antidepressants were presented. One compared vortioxetine to a drug not recommended for use by NICE, and the other was focused only on patients with SSRI treatment-emergent sexual dysfunction. Therefore neither appeared representative of most UK patients likely to be switching antidepressant treatments.

The restriction meant that only four trials were used in the main indirect treatment comparison. These trials were very diverse in both the populations included and in their results. The ERG concludes that, as a result, this analysis did not present reliable evidence on the relative efficacy of vortioxetine compared to other antidepressants.

In terms of cost-effectiveness, the ERG expressed several concerns about the structure of the manufacturer's decision model; in particular the fact that the manufacturer has not attempted to formally consider response in the model, and the fact that the appropriate positioning of vortioxetine within the current treatment pathways has not been fully explored. The manufacturer has assumed that the most appropriate position of vortioxetine is as a second-line treatment (i.e. 1st switch therapy).

The ERG also expressed several uncertainties about the evidence used in the manufacturer's model, the most important being the restricted evidence on relative effectiveness used, the use of STAR*D [ref] to inform prognosis after failure to achieve remission with the initial switch treatment and the use of separate sources of HRQoL data.

Additional exploratory analyses regarding the key areas of structural uncertainty were not deemed feasible within the timelines available to the ERG. Hence the ERG's exploratory analyses focus primarily on those uncertainties surrounding key effectiveness inputs and the outcomes after failure of therapy, and showed these were crucial to cost effectiveness results.

8.3.3 Areas of uncertainty

The relative efficacy of vortioxetine when compared to other antidepressants remains uncertain because of the different sources of evidence considered: trials in the switch population, placebo controlled trials not in the switch population, and trials with active reference arms. All these sources of evidence have problems. There are limited data in the switch population; placebo-controlled trials may not represent the population most likely to receive vortioxetine (i.e. a switch population); active reference arms may be biased in favour of the active reference. Given the different nature of these sources of evidence, and some conflicting results between them, the clinical efficacy of vortioxetine relative to active comparators remains unclear.