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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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 Edition 4 (DSM-IV-TR) is in common use, e.g. in CG90, but was superseded by edition 5 (DSM-5) in 2013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 population[1]

"*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 response[1].

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-HT_3, 5-HT_7, 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 systems[2].

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 population[3]. The presentation of MDD is multifactorial[4] and the DSM-5 criteria[5] 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 family[6], including children[7].

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 rates[9].

For moderate-to-severe MDEs, NICE Clinical Guideline 90[10] 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 remission[11]. Other studies report comparably disappointing statistics for the effectiveness of initial therapy[12-14]. Intolerability to side-effects of antidepressant therapy is a further problem that may force patients to switch treatment[15]. 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 reasons[16].

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 problems[17]. 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 death[18]. 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 attempts[21], hospital admissions,[22] and impaired work productivity[23]. 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 included[24].

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 switch[10].

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 usage[25], 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 318[28-30]

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 ≥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-tolerated[33].

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 models[34] 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 CEAs[34-36].

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 relapse[39].

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 health[41], 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

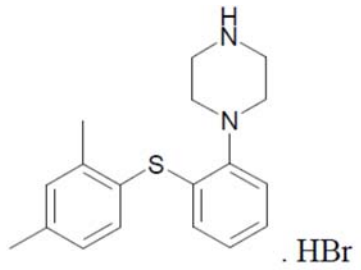
1.1 Name and therapeutic class

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



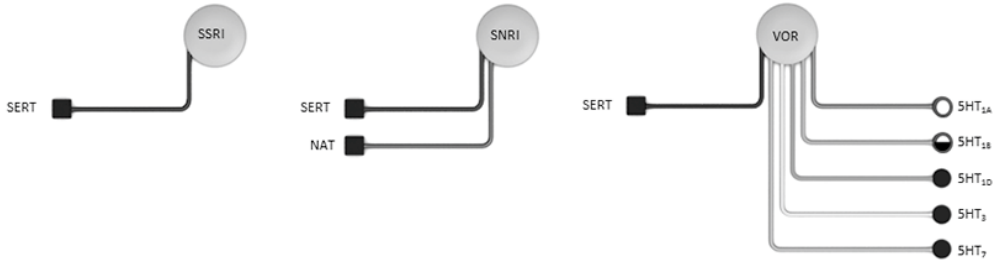
Therapeutic class: Other antidepressants (ATC-code: N06AX26)

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-HT_3, 5-HT_7, 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 systems[2]. 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 effects[2].

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 316[44].

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 states[2] 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 studies[45-49]. In recent years this decline appears to be particularly pronounced in studies conducted in the US[50], 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 failed[51]. 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 efficacy[43]. 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 MDD[52]. 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"*.

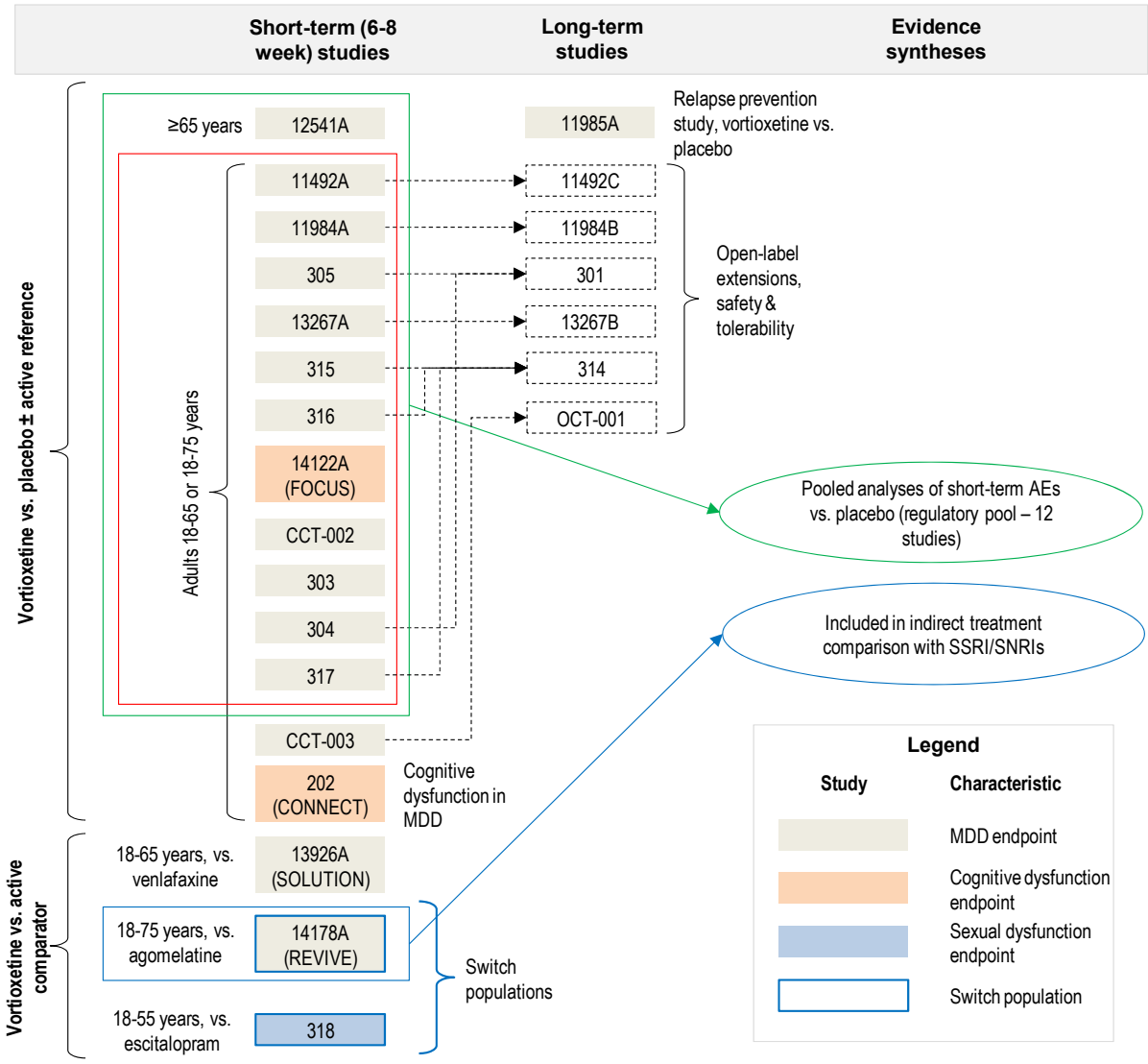
A major depressive episode (MDE) is not a disorder in itself, but rather is a clinical manifestation of major depressive disorder (MDD), as explained in section 2.1.2 below.

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 CG90[10] 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.

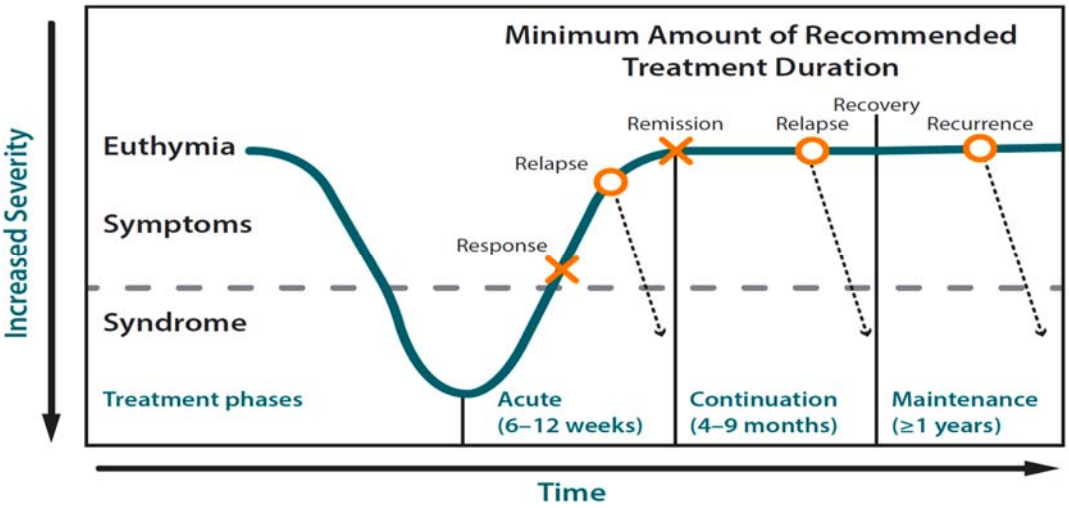
The diagnostic definitions used in NICE CG90 are based on the DSM-IV-TR[55]. Although this edition of the DSM has recently been superseded by DSM-5[54], the changes with respect to depressive disorders do not materially affect the above definitions of MDD and MDE.

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 Agam[56] 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 cause[56]. Nevertheless, severe states of depression often have no external precipitating cause. The course of MDD varies across individuals depending on a range of factors[8]. 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 rates[9]. There is consensus[57-59] 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 2001[60] and Zimovetz 2012[34])



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 baseline[61]. 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 scales[59]. 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 months[10]. 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 problem[10]. 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 switch[11], 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 later[63] and at least 10% had persistent or chronic depression[64]. 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%, respectively[65].

2.1.5 The burden of treatment failure

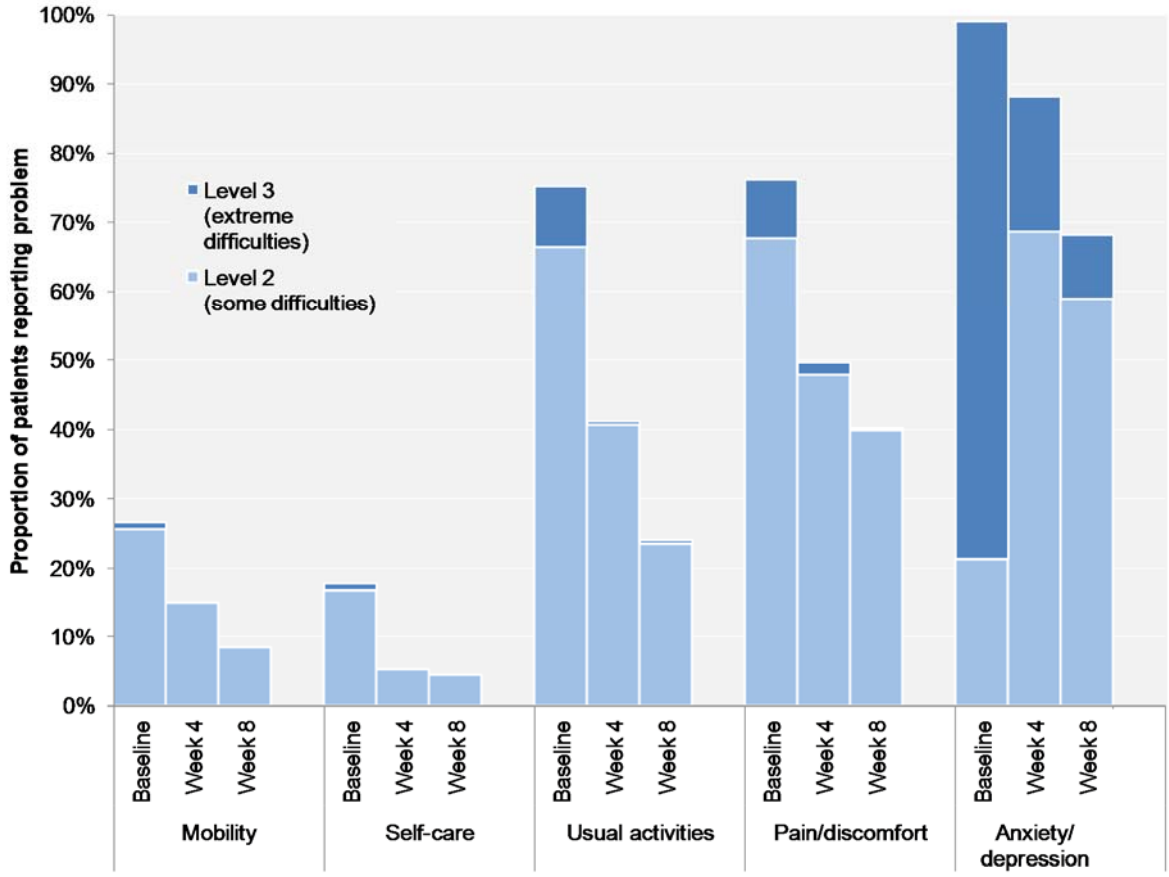
Among people with depression, those who have encountered multiple episodes or multiple lines of treatment are at greater risk of suicide attempts[21], hospital admissions[22], and impaired work productivity[23]. Such undesirable consequences of failing to achieve control early in the course of MDD underline 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 study[17] 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 study[18] 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 2004[18])



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 study[19], 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 disorders[66]. It has been proposed that comprehensive management of unipolar major depression should include psychoeducational family intervention[67]. 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 question[6], 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 studies[7]. Major depression influences parenting skills, especially in affected mothers[68], with a reduction in children's psychological wellbeing[7]. 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 problems[69]. 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 study[24], McCrone and colleagues used UK PMS year 2000 data[70] 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) survey[71], 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 study[24] 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 44,811,567[72]. 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 2008[73]. 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 studies[74] 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 colleagues[77] 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 depression[78]. A recent meta-review[79] of 20 systematic reviews and meta-analyses on mortality in mental disorders, which drew upon a meta-analysis specific to depression[80], 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 CG90[10] to define the care pathway into which vortioxetine will be introduced. Figure A5 presents an interpretation of the CG90 clinical guideline pathway[83]. 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 site[84], as shown in Figure A6.

Figure A5. Interpretation of NICE CG90 recommended management and treatment pathway (after Reid 2014[83]).

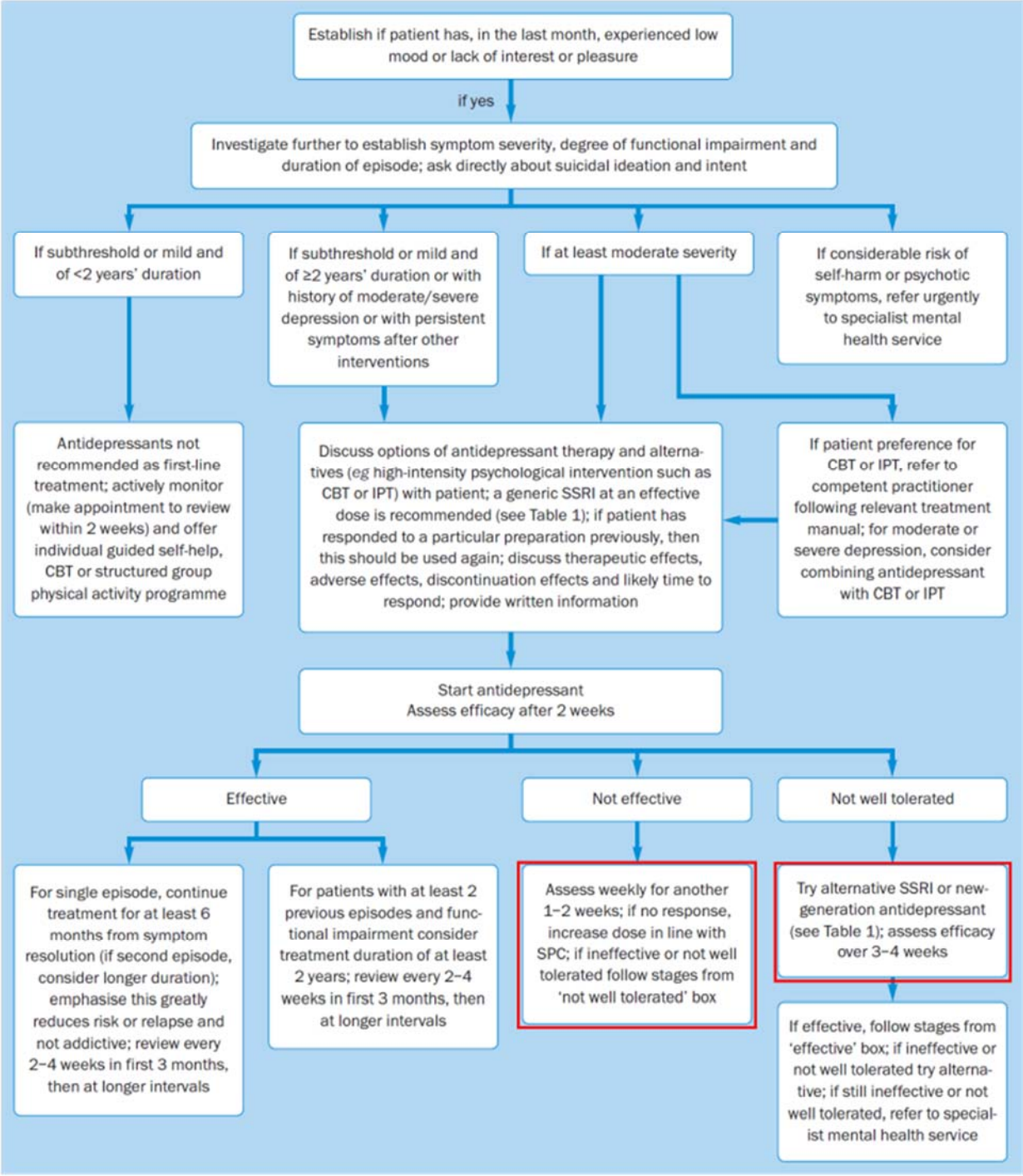
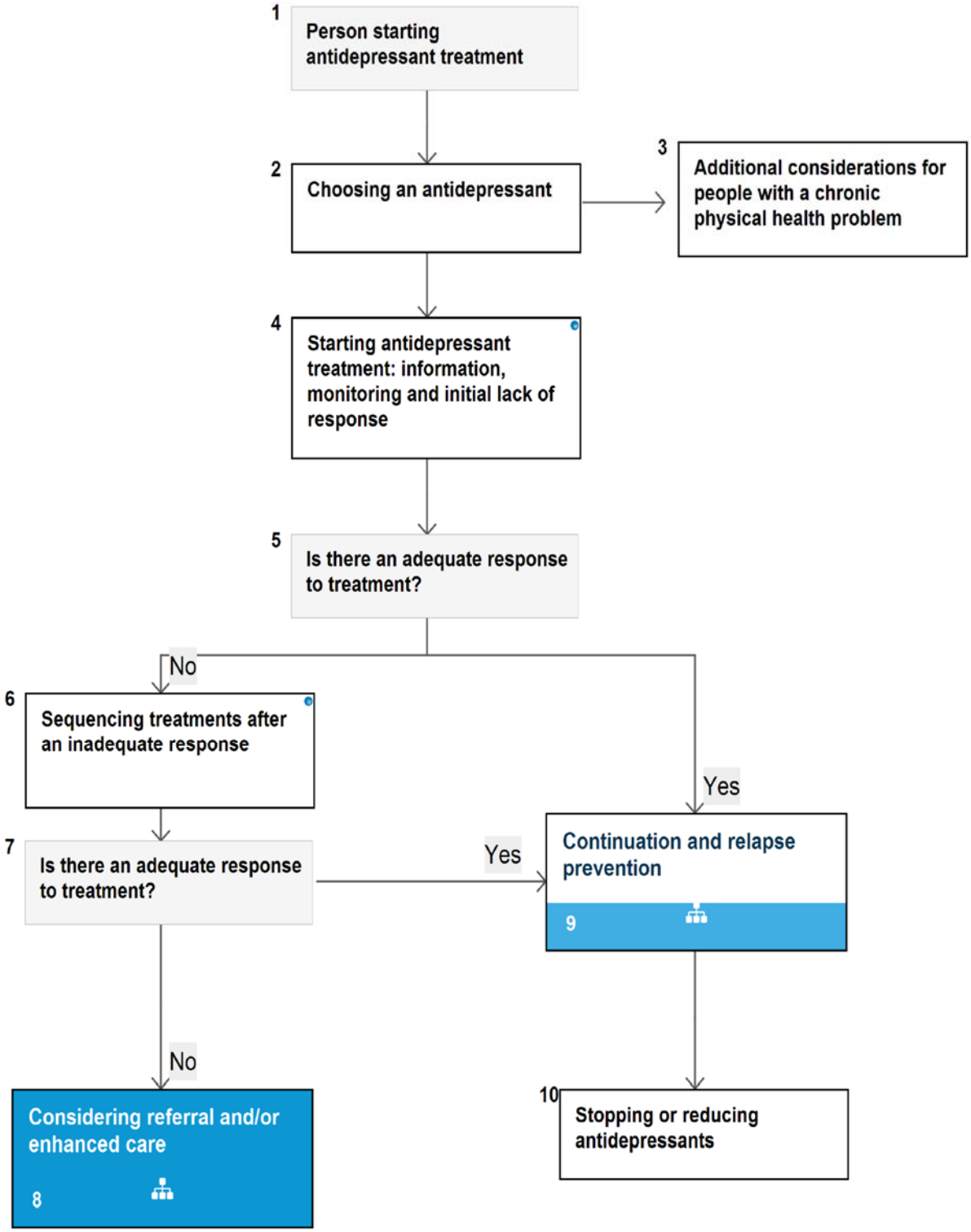


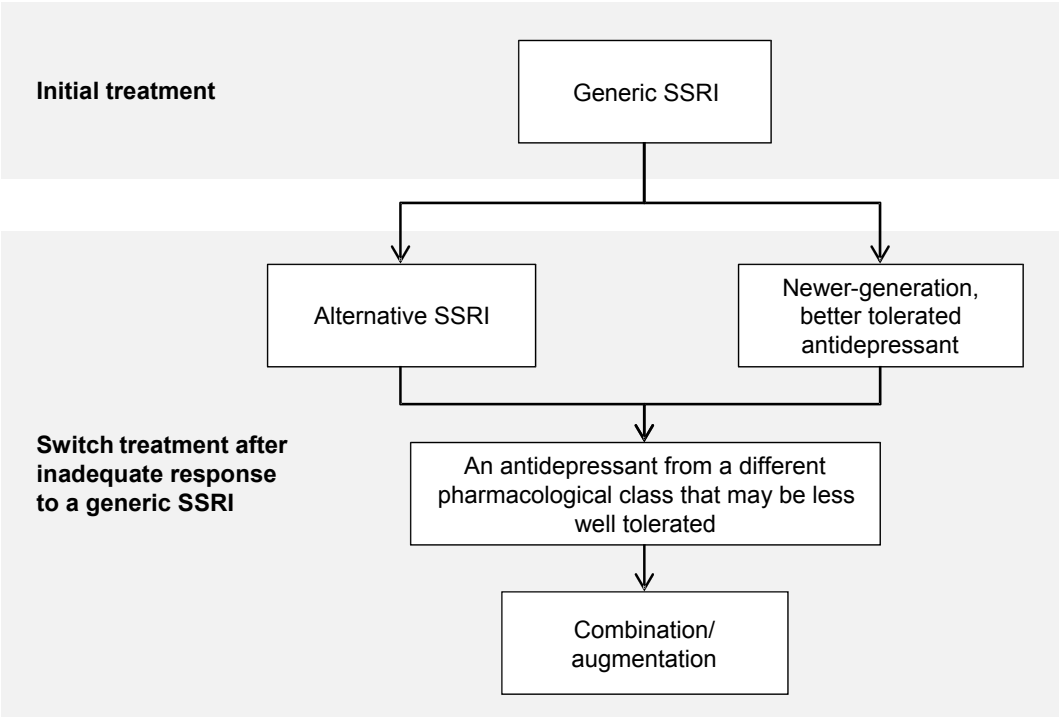
Figure A6. NICE Pathways diagram for antidepressant treatment in adults, showing the algorithm leading to sequencing treatments after an inadequate response



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 diagrammatical 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

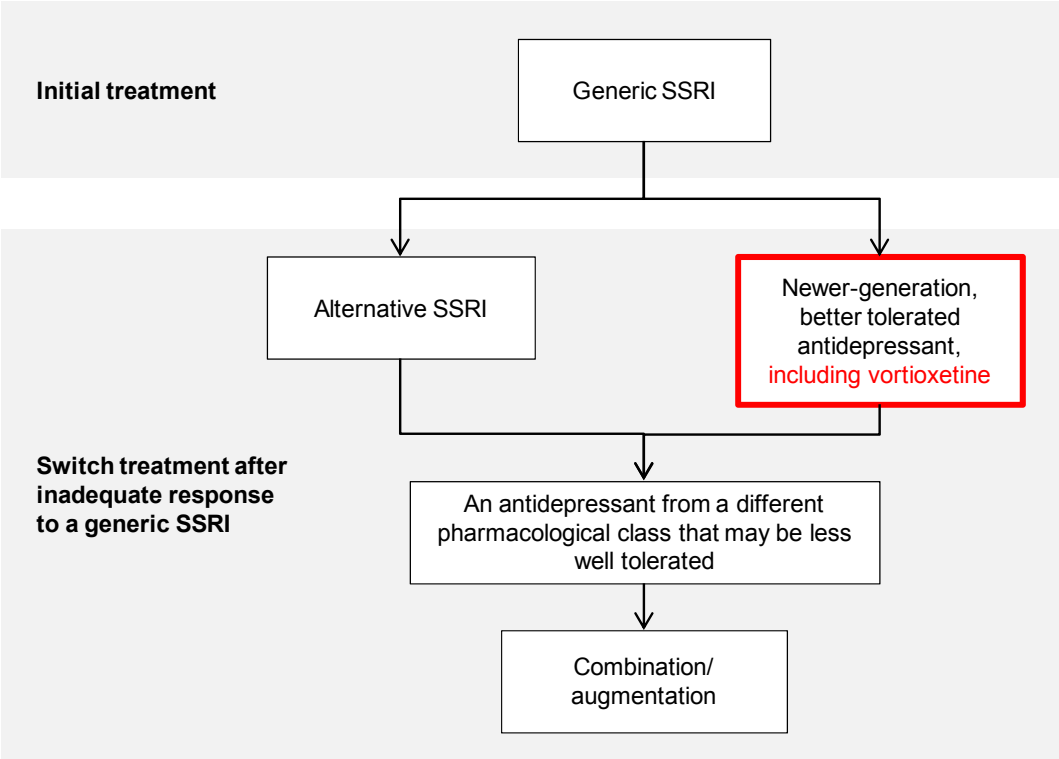
Vortioxetine has been granted a licence for the treatment of MDEs in adults. In this submission, Lundbeck is concerned with the use of vortioxetine in the following patient population, which is a subset of the licensed indication and scope of the STA:

- 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 treatment[13]. 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 thoughts[4]. 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 presentation[4]. 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 dosage[62]. In the STAR*D study[11], 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 remission[12-14].

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 admission[10].

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 treatment[15]. 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 Directory[87] (see Table A3) and the Maudsley Prescribing guideline[88] (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, Bazire[87])

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	●●	●	●	●	❍	❍	●●
Nortiptyline	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, Taylor[88])

Drug	Sedation	Hypotension	Anticholinergic effects
Selective serotonin reuptake inhibitors (SSRIs)			
Citalopram	+/-	-	-
Escitalopram	+/-	-	
Fluoxetine	-	-	-
Fluvoxamine	+	-	-
Paroxetine	+	-	+
Sertraline	-	-	-
Tricyclics			
Amitriptyline	+++	+++	+++
Clomipramine	++	+++	++
Dosulepin	+++	+++	++
Doxepin	+++	++	+++
Imipramine	++	+++	+++
Lofepramine	+	+	++
Nortiptyline	+	++	+
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 therapy[16]. In a US study[91] 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

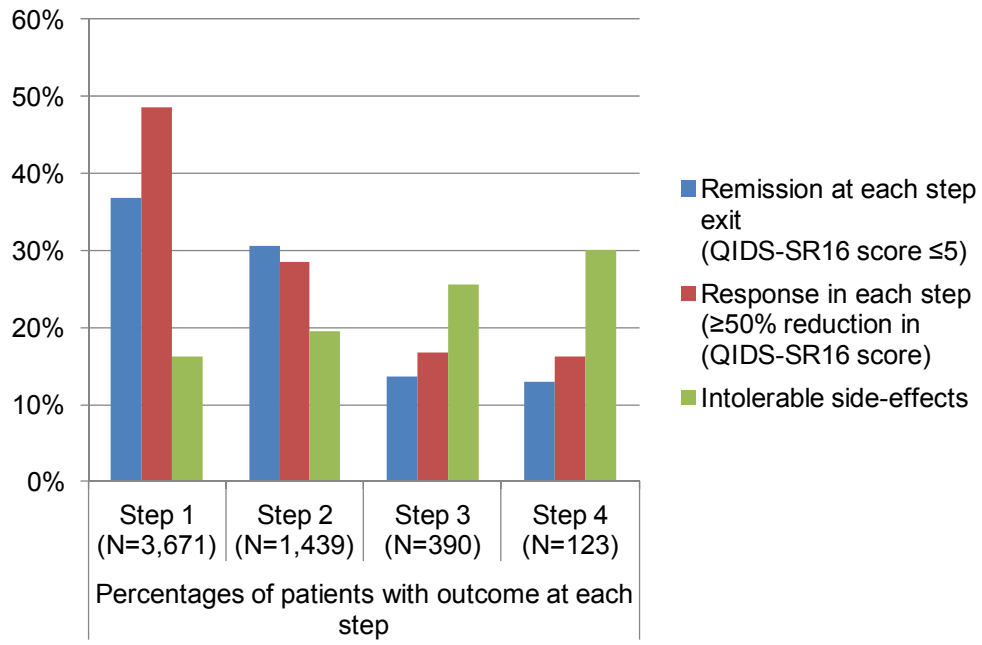
As stated in section 2.5.2 above, vortioxetine will be positioned for use in a switch population. In view of the low rates of successful initial antidepressant treatment as described in the previous section, it is unsurprising that treatment switching is frequently required. Switching is normally prompted 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 months[96]. 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 study[11], 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 phase[11]. 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 response[97].

Figure A9. Outcomes in outpatients with depression over successive steps of antidepressant treatment (after Rush 2006[11])



QIDS-SR$_{16}$: Quick Inventory for Depressive Symptomatology

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 remission[25]. 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 strategy[98]. Moreover, prescribers may find it intuitively attractive to have available an armamentarium of agents with different modes of action.

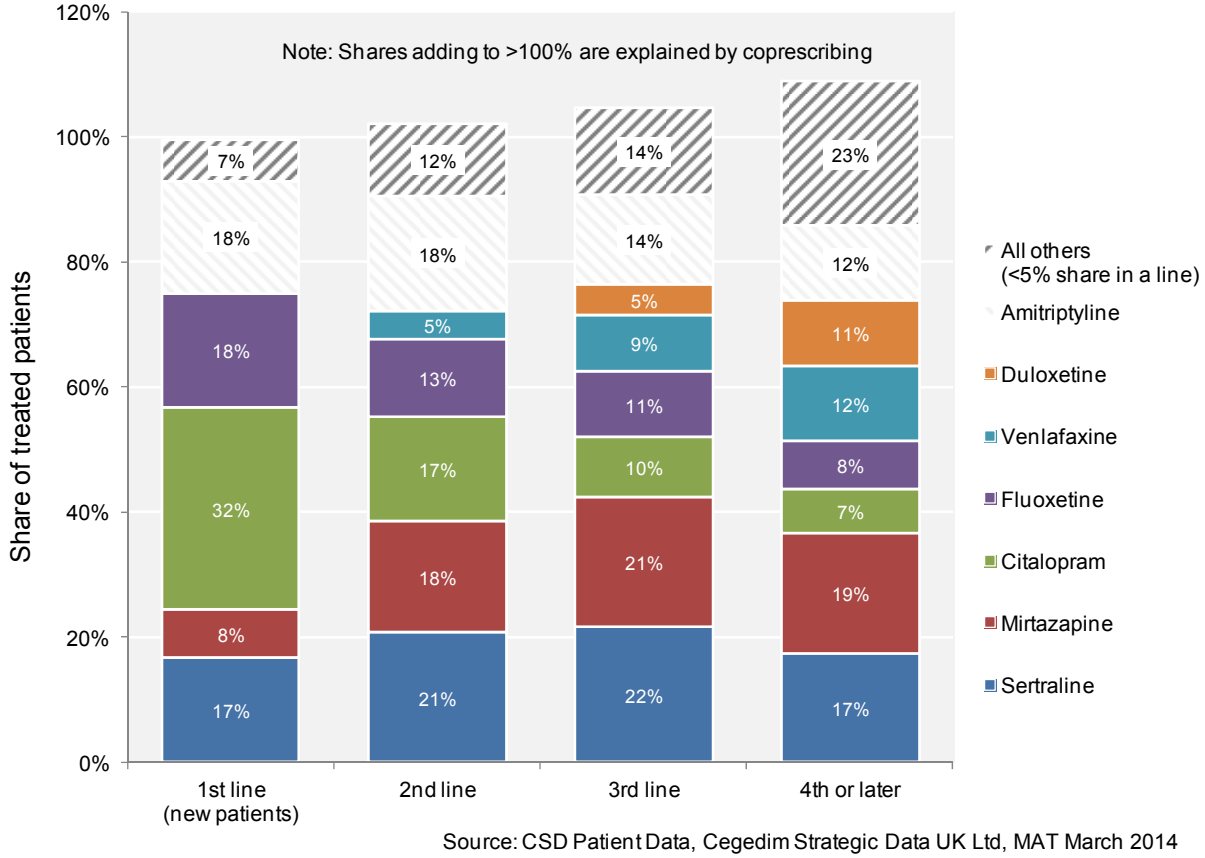
2.7 Main comparators and justification for their selection

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 A10[99]. 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 therapy[99].



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 profile[10] and its particular toxicity in overdose[100].

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 SNRIs[87]. The most recent NICE surveillance review for CG90[101] 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 TCAs[88] 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 placebo[103]. Of the randomised, placebo-controlled studies conducted in support of an antidepressant claim, approximately 50% have failed[51]. Fava states "negative double-blind, placebo-controlled trials … have become the rule more than the exception in psychiatric research[104]. Particularly high placebo response rates are seen in trials of antidepressants, ranging from 29%-48% for pooled trials of various SSRIs in MDD[105], 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 history[106]. 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 MDD[104]. 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 positive[104].

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 CG90[10] 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 Baghai[110].

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 Glasgow[114], 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 criteria[55]. The authors stated that the point prevalence was higher than that reported for the UK general population[116] 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 disabilities[117].

As a recent report by the Royal College of Psychiatrists[118] 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 trials[119].

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 function[52] 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 affected[39]. 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 episode[124].

Over recent years, the extent to which patients with MDD suffer from cognitive dysfunction has been researched. A 3-year study[125] 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 episode[125]. 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 work[126].

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 intimacy[127]. 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 cessation[2]. Poor adherence to antidepressant medication is common and patients are often seen to miss consecutive doses of treatment for several days[128]. Haddad and Anderson[129] 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 Dolan[40] 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 consider-ations, 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-analysis[25] 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 Dissemination[130]:

- 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.

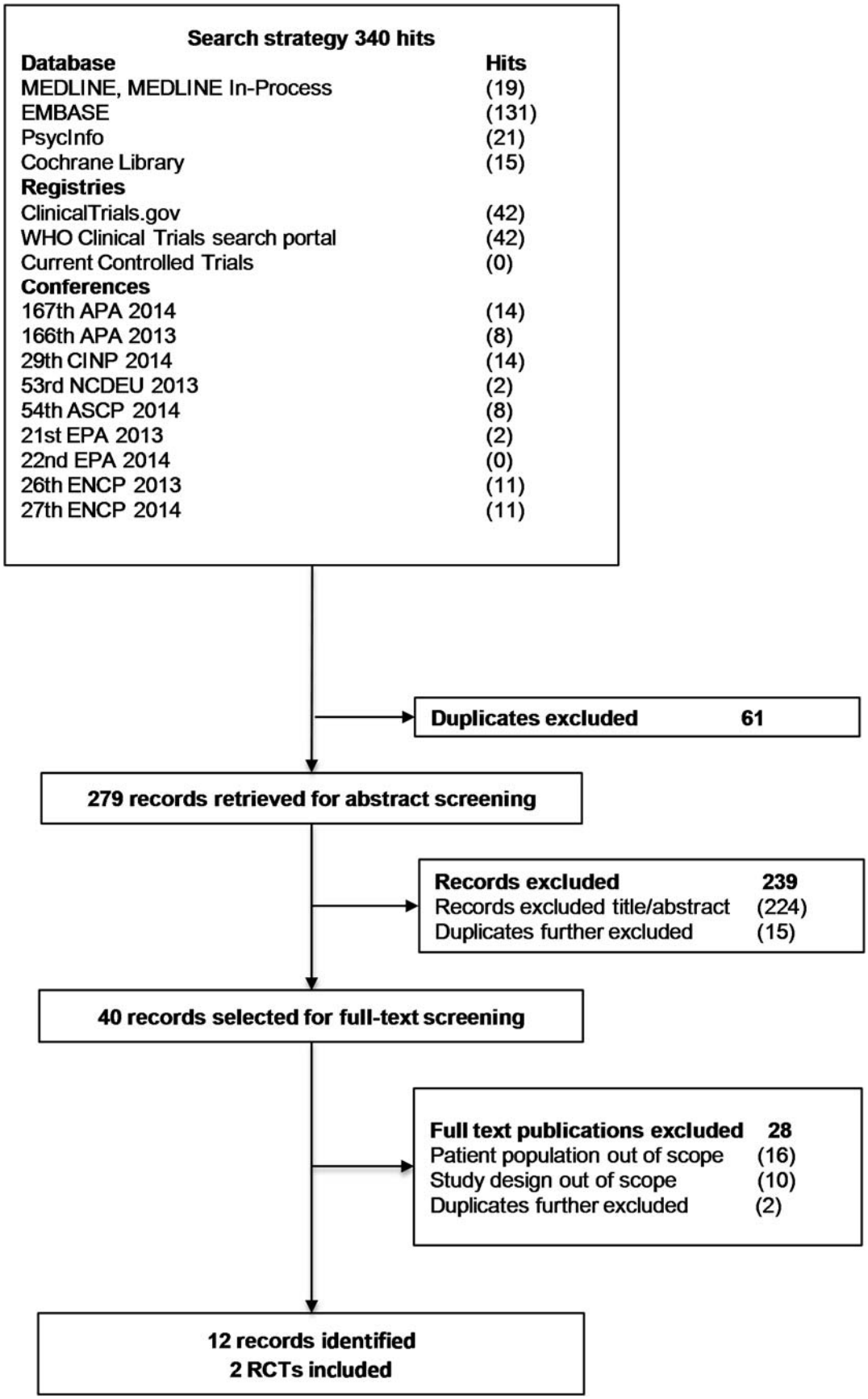
MDD: major depressive disorder; MDE: major depressive episode; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-noradrenaline reuptake inhibitor; TCA: tricyclic antidepressant; TESD: treatment-emergent sexual dysfunction; RCT: randomised controlled trial.

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 effective[164]. 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 (NCT02272517[167] and NCT02279953[168]) 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.

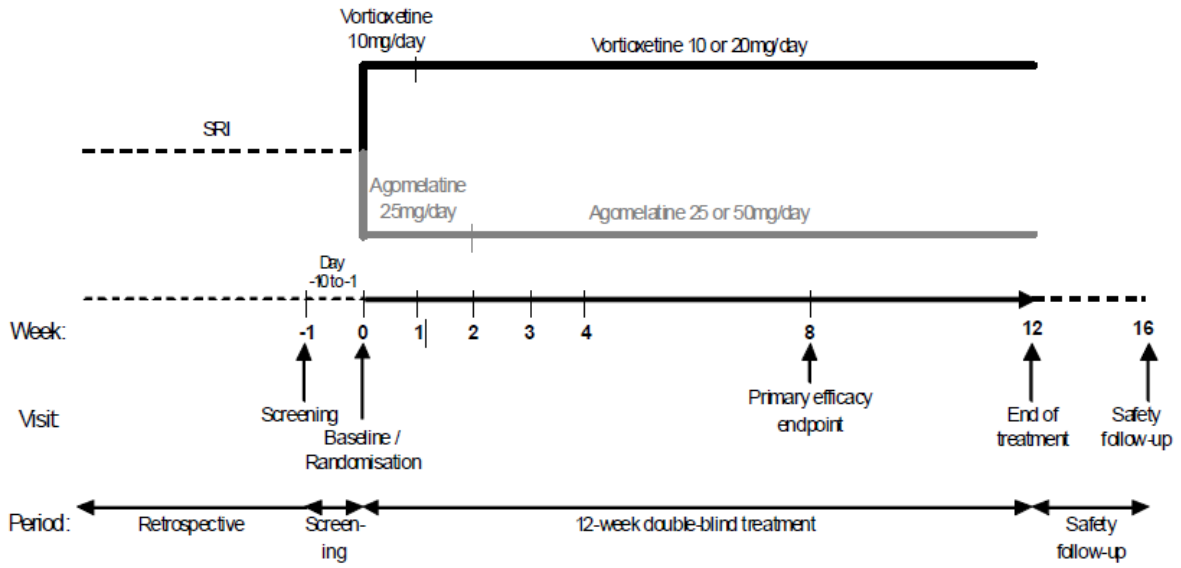
The trial scheme is shown in Figure B2. At the Baseline Visit, patients were switched from treatment with an SSRI or SNRI to treatment with vortioxetine or agomelatine. The study consisted of a Screening Period of 4 to 10 days before the Baseline Visit, followed by a 12-week double-blind treatment period 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/day[27].

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.

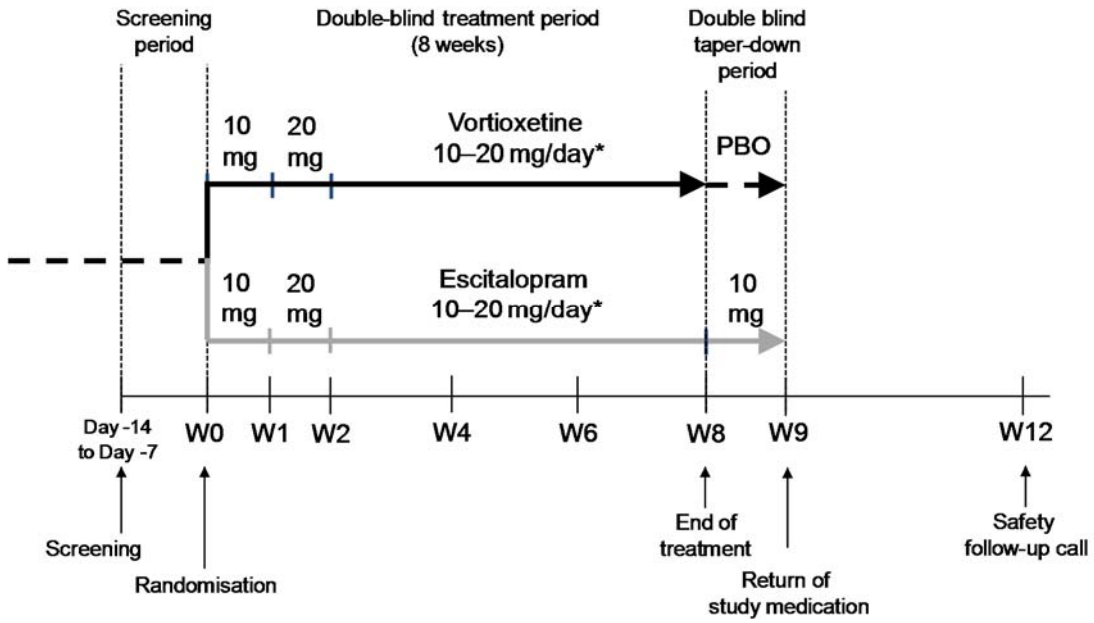
Figure B2. Design of Study 14178A (REVIVE)[27]



6.3.2.2 Study TAK318

Study TAK318[28-30] 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 TAK318[28-30]



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 2mg/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 ≥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 *Informed Consent Form*. 2. The patient has signed the *Informed Consent Form*. 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-TR™ 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 (*apparent sadness*) 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-TR™ 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-TR™ 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-TR™ criteria). 9. The patient has borderline, schizotypal, schizoid, paranoid, histrionic, antisocial personality disorders (Axis II) as comorbid or primary diagnosis (DSM-IV-TR™ criteria). 10. The patient has history of previous major depressives 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 (*suicidal thoughts*) 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/RR0.33). 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 TAK318[30]	
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 halflives 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 (×ULN). b) A total serum total bilirubin value >1.5×ULN. c) A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2×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 participants[27]

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 ± sd (median) duration of current episode (weeks)[1]	18.6 ± 10.4 (16.0)	19.2 ± 10.9 (16.0)	18.9 ± 10.6 (16.0)
Mean ± sd (median) number of previous episodes[1]	2.6 ± 2.1 (2.0)	2.4 ± 1.8 (2.0)	2.5 ± 2.0 (2.0)
Mean ± sd (median) MADRS total baseline score[2]	29.1 ± 4.4 (29.0)	28.7 ± 4.0 (28.0)	28.9 ± 4.2 (28.0)
Mean CGI-S ± sd (median) total baseline score[2]	4.4 ± 0.6 (4.0)	4.4 ± 0.6 (4.0)	4.4 ± 0.6 (4.0)
Mean ± sd (median) HAM-A total baseline score[2]	21.6 ± 6.3 (21.0)	21.4 ± 6.2 (21.0)	21.5 ± 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 participants[30]

Participant characteristic	Vortioxetine (n=255)	Escitalopram (n=222)
Age, years Mean ± sd (range)	39.3 ± 10.0 (19–55)	40.2 ± 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 ± sd	27.5 ± 4.4	27.9 ± 4.4
CSFQ-14 total score Mean ± se (range)	36.1 ± 0.39 (21–47)	36.0 ± 0.40 (21–47)
MADRS total score* Mean ± sd (range)	7.9 ± 6.3 (0–34)	8.3 ± 6.5 (0–34)
CGI-S Mean ± sd (range)	2.0 ± 0.8 (1–3)	2.0 ± 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 ≥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 ≥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 important[181].

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 ≥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 plan[182]. 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 ≥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 TAK318[30]

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

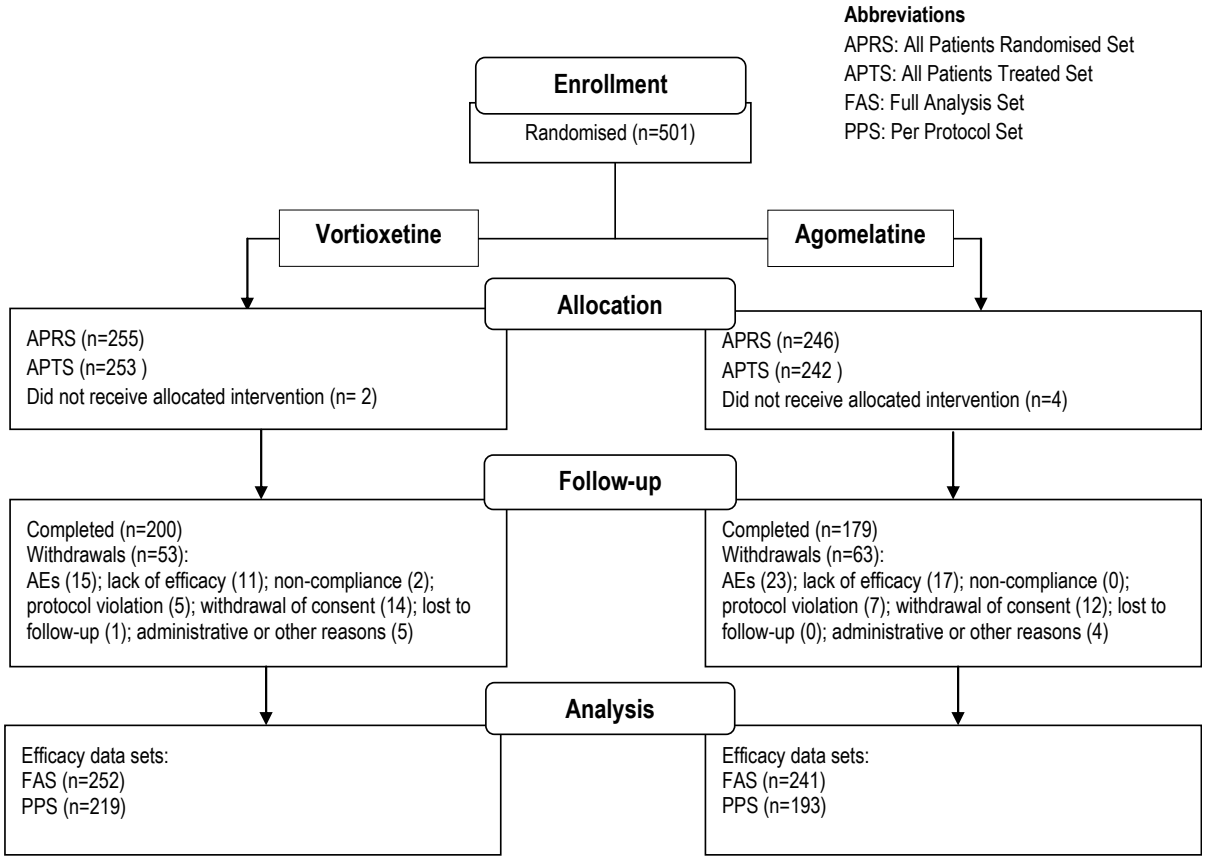
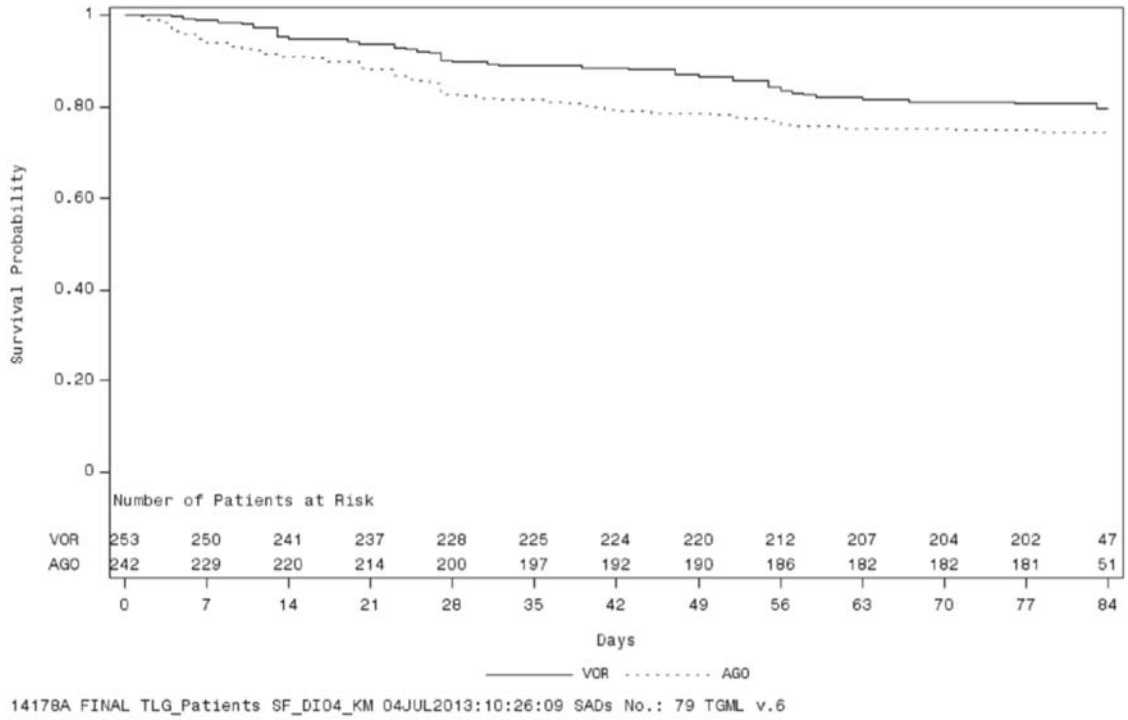


Figure B5. Study 14178A (REVIVE). Kaplan-Meier analysis of time to withdrawal (APTS)[27]



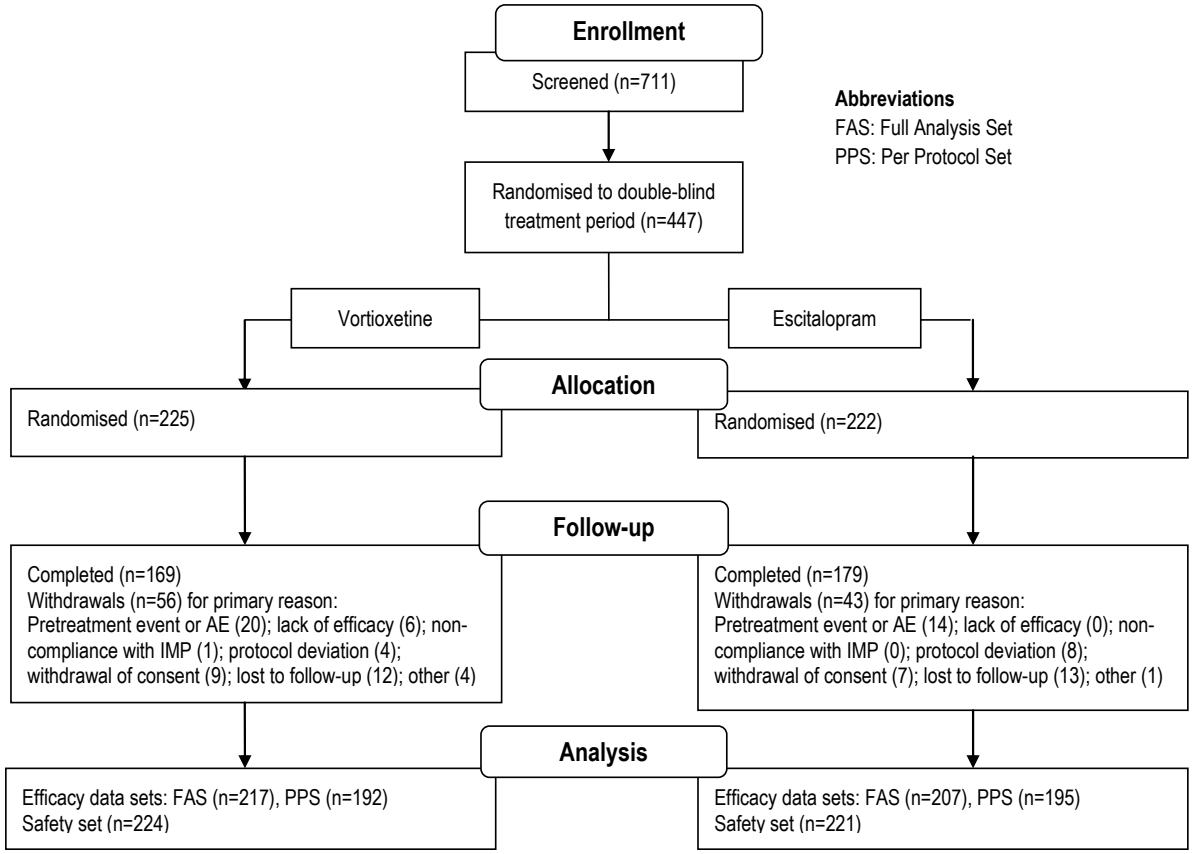
Source: CSR[27] Figure 1.

6.3.8.2 Study TAK318[30]

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 TAK318[30]. 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 *oedema peripheral* considered *probable related* 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 Pharmaco-vigilance, 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 318[30] 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): results[27]

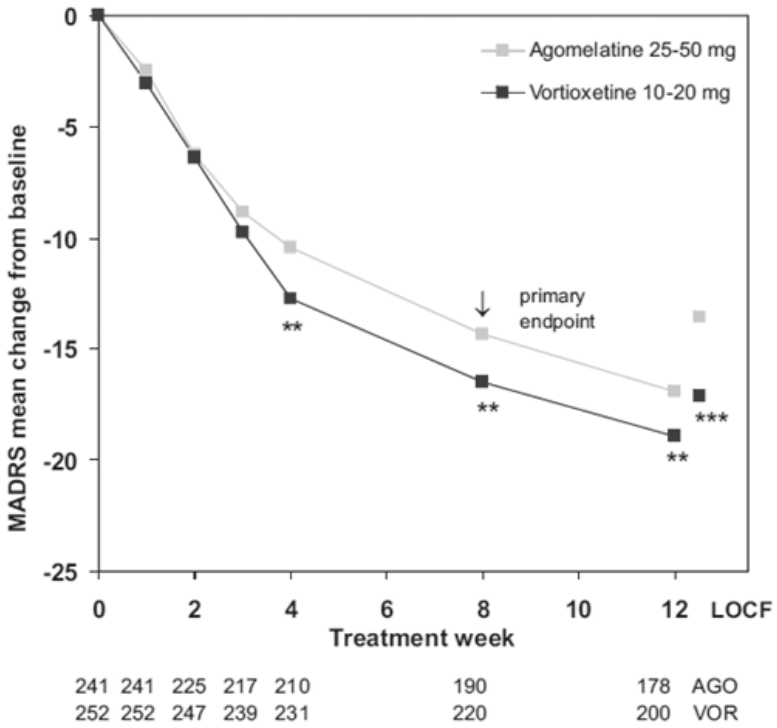
6.5.2.1 Dosage

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 12[27].



Source: CSR[27] Panel 26. ** P<0.01; *** P<0.001 versus agomelatine

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 differences[27]

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: CSR[27] 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]

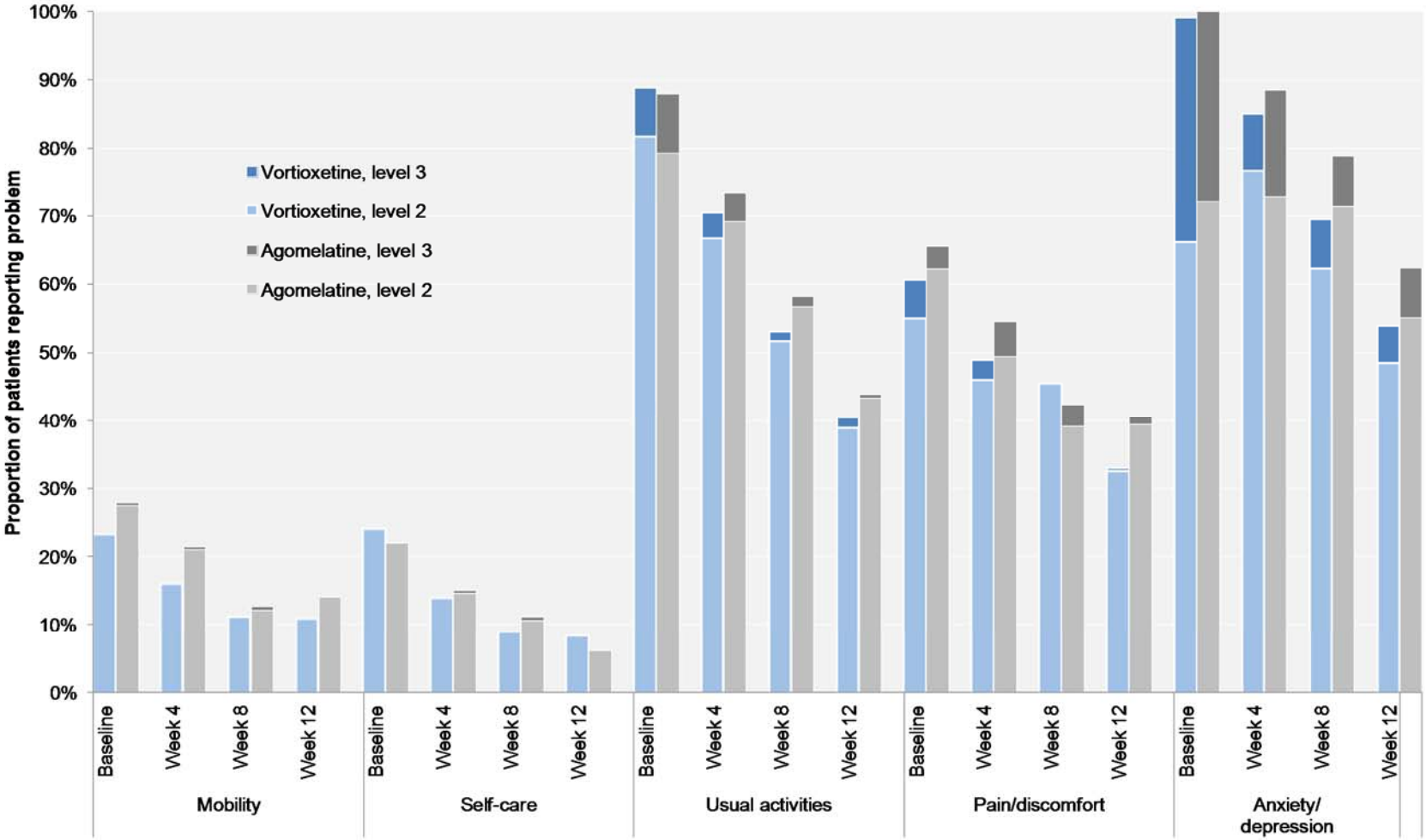
Endpoint	Week 8				Week 12			
	Vortioxetine		Agomelatine		Vortioxetine		Agomelatine	
	n	%	n	%	n	%	n	%
Response								
MADRS	155	62%**	114	47%	176	70%**	135	56%
CGI-I	186	74%***	140	58%	187	74%*	154	64%
Remission								
MADRS	102	41%**	71	30%	139	55%***	95	39%
CGI-I	104	41%*	78	32%	140	56%**	106	44%

Source: CSR[27] 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 assessments[27]. 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 problems[174]. 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 group[184]. 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 analysis[184]. 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).

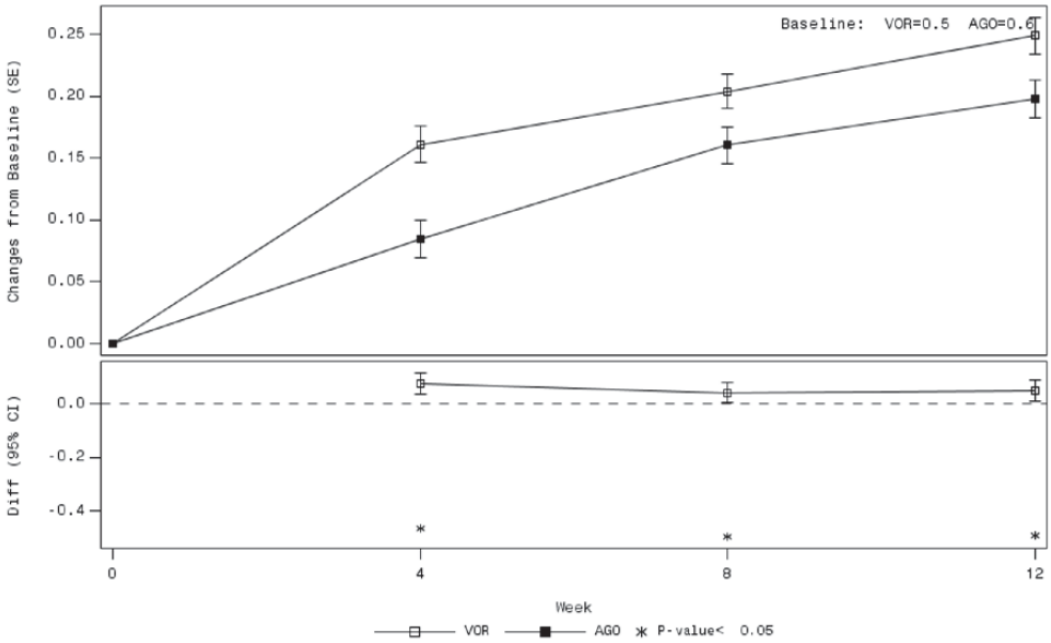
Table B15. Study 14178A (REVIVE). EQ-5D summary index scores (FAS, OC)[27]

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: CSR[27] 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: CSR[27], 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: CSR[27] 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

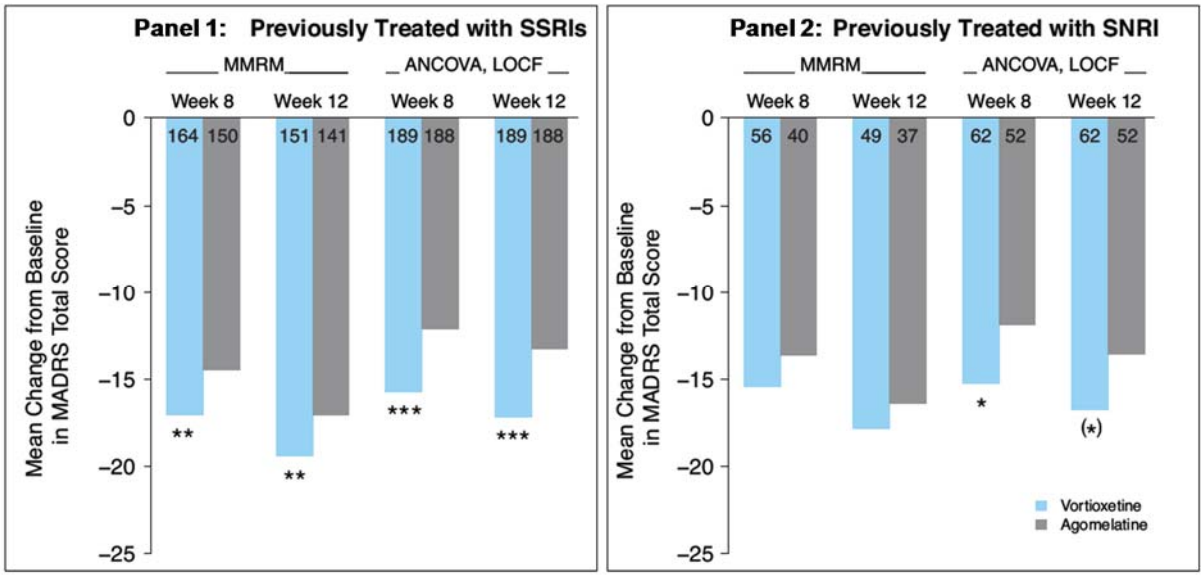
In the subgroup analyses, there was a trend towards improvement for vortioxetine vs. agomelatine across all subgroups and many reached statistical significance despite the study being powered for equivalence on the primary endpoint.

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 antidepressant[136].

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 CSR[27], 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 tolerability[27]

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 ≥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 period[27]

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 events[27]

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 endpoints[27]. 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 TAK318[30]

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

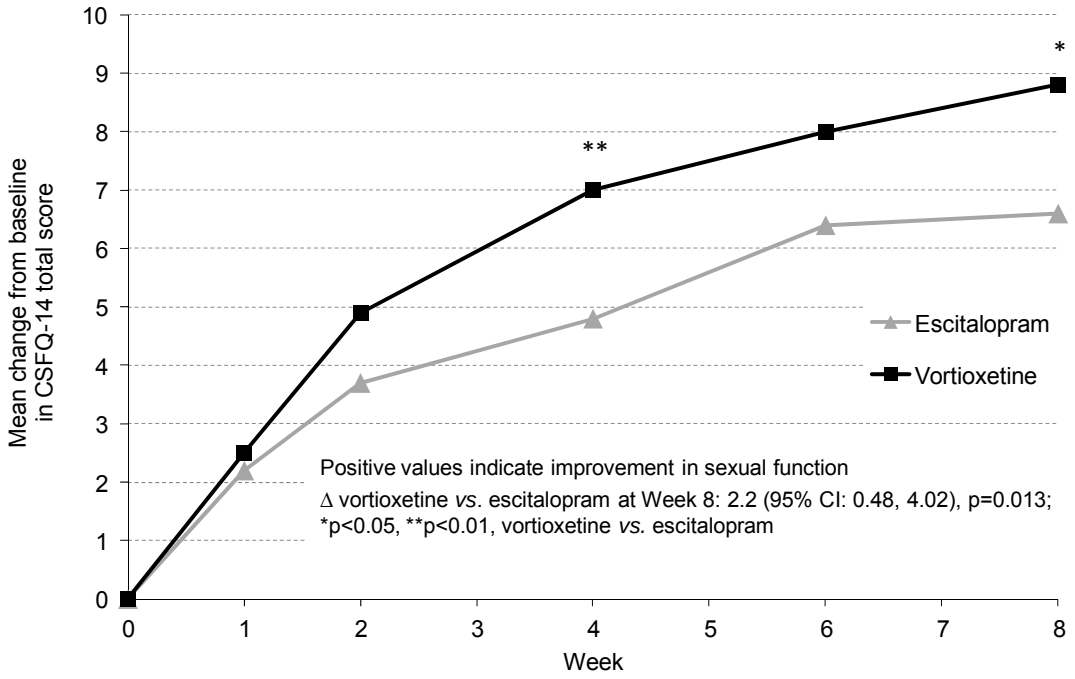
The primary endpoint was change from Baseline in the CSFQ-14 total score after 8 weeks of treatment (FAS, MMRM). Sexual functioning improved from Baseline in both groups, but to a greater extent in the vortioxetine group, with a mean difference at 8 weeks of 2.2 points between groups (p=0.013) (see Table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

Table B19. Study TAK318[30]. 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 ± se†	36.1±0.39	36.0±0.40
P value, vortioxetine *vs.* escitalopram†	0.820	
Change from Baseline at Week 8		
N	165	173
Change from Baseline LS mean ± se	8.8±0.64	6.6±0.64
P value, vortioxetine *vs.* escitalopram‡	0.013	
LS mean differences ± se from escitalopram‡	2.2±0.90	
95% CI for differences	0.48-4.02	

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

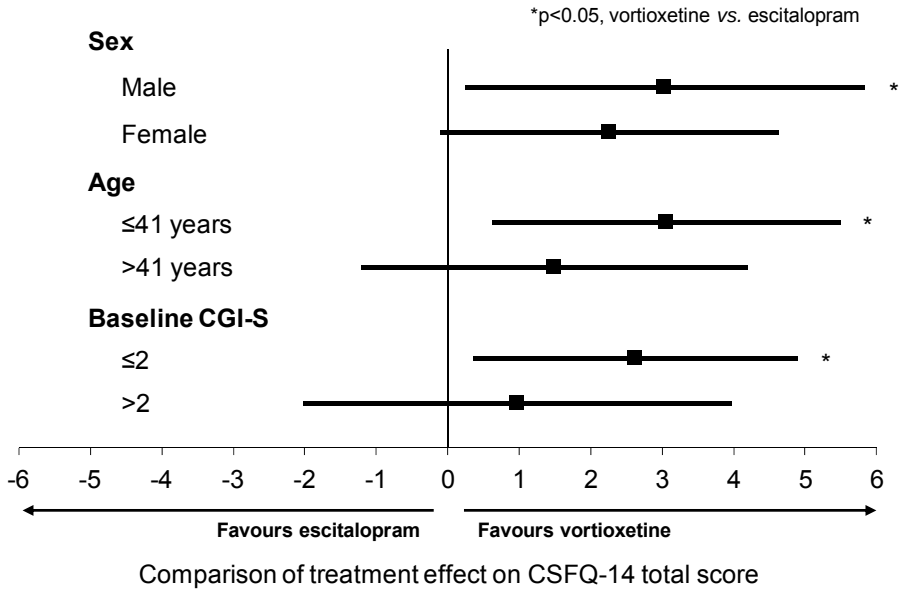
Figure B11. Study TAK318[30]. Change from baseline in CSFQ-14 total score by visit (MMRM, LS means)



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 TAK318[30]. Comparative effect of vortioxetine and escitalopram treatment in patient subgroups on CSFQ-14 total score at Week 8 (MMRM, FAS, LS means)



CSFQ-14: Changes in Sexual Functioning Questionnaire short-form; MMRM: Mixed model for repeated measures; FAS: full analysis set; LS: least-squares; CGI-S: Clinical Global Impression - Severity Scale.

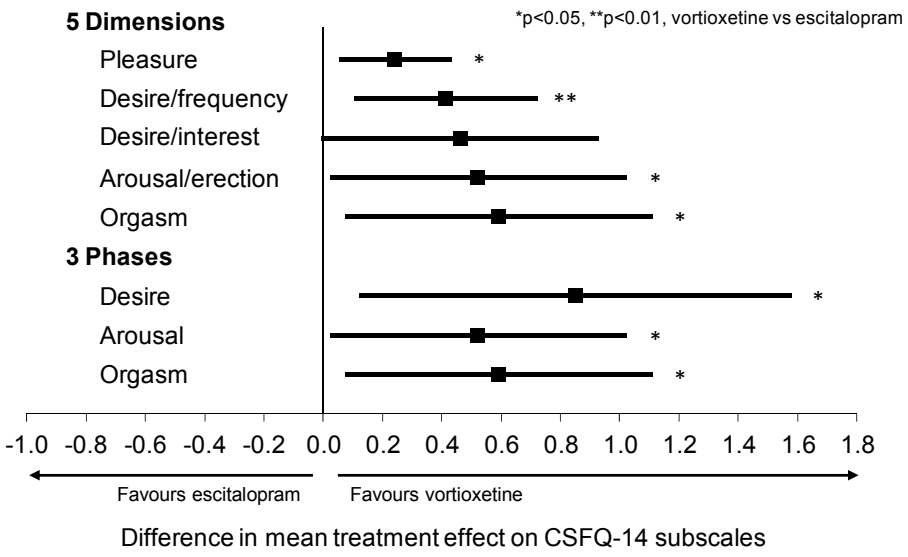
6.5.3.3 Study TAK318: secondary endpoints[30]

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 TAK318[30]. Difference between vortioxetine and escitalopram on CSFQ-14 subscales at Week 8 (MMRM, FAS, LS Means)

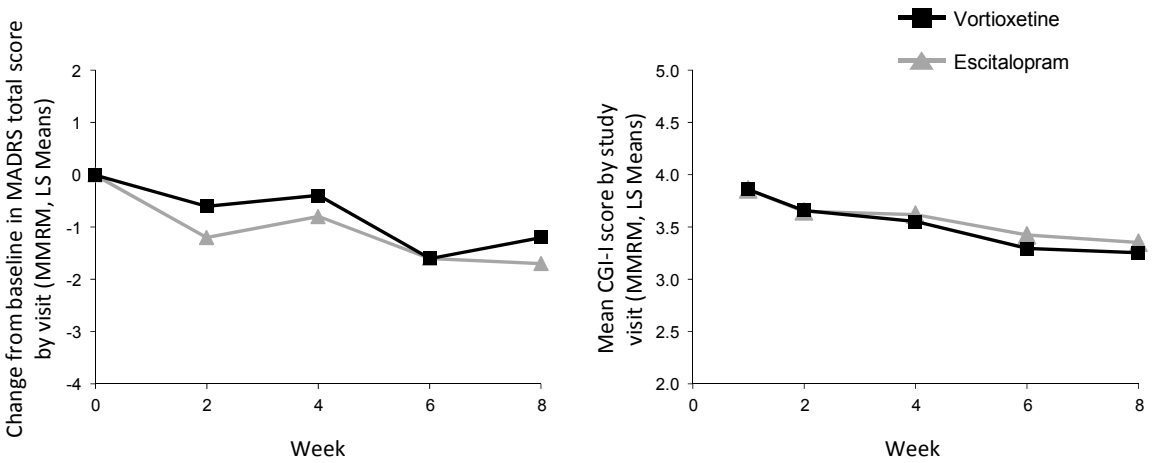


CSFQ-14: Changes in Sexual Functioning Questionnaire short-form; MMRM: Mixed model for repeated measures; FAS: full analysis set; LS: least-squares.

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; Clinical Global Impression - Improvement Scale.

6.5.3.4 Study TAK318: adverse events[30]

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 Conclusions[30]

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

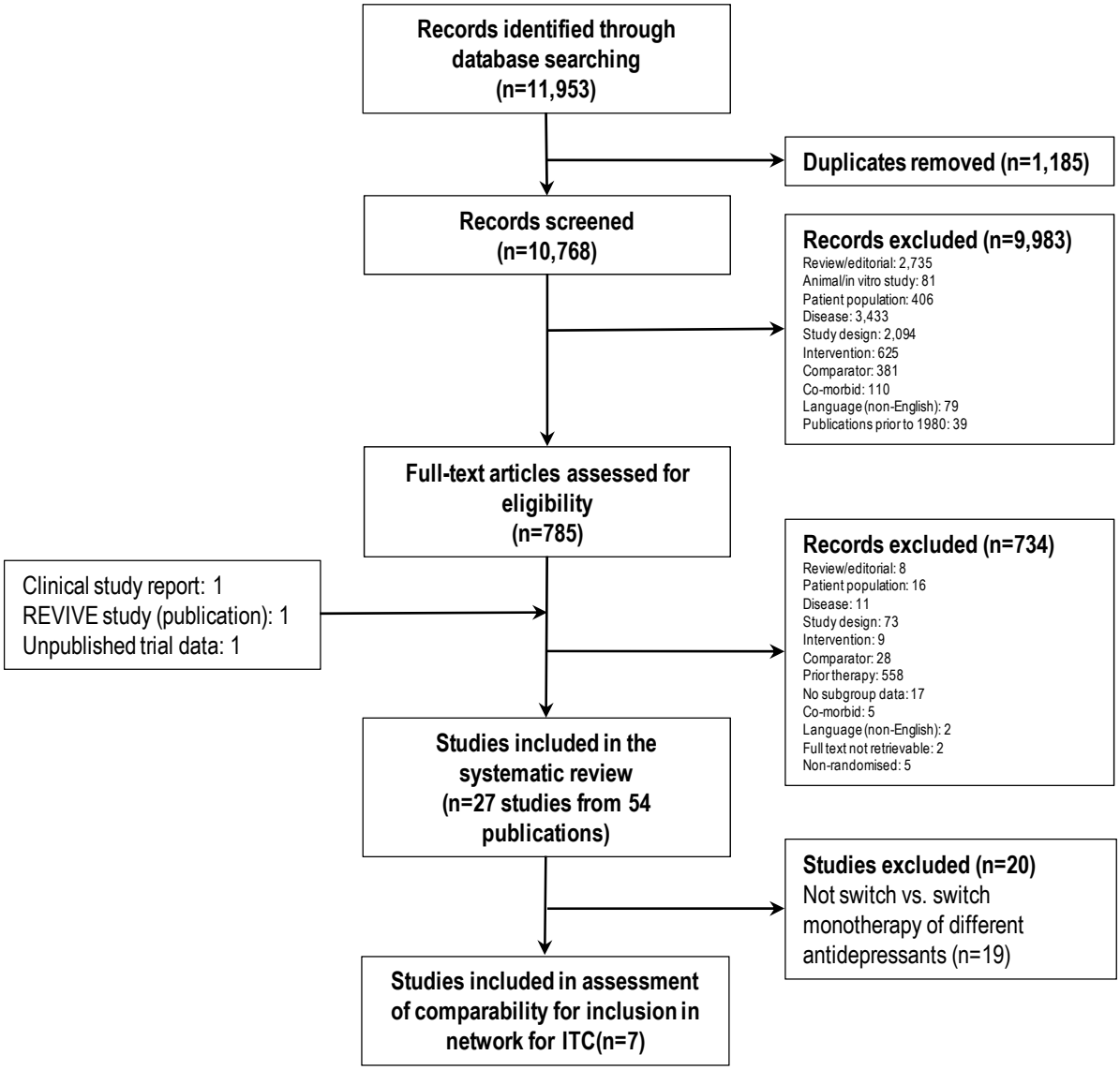
The final extraction grid is provided in the systematic review report. Data extraction was undertaken by a single reviewer with a quality check undertaken by an independent reviewer. Where more than one publication was identified as describing a single trial, the

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 report[27] 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 extraction[187]. 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 2004[188], 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 searching[189]. 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 2014[26]). 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 2007[190] and Kasper 2010[191]). 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 (AK1102356)[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]

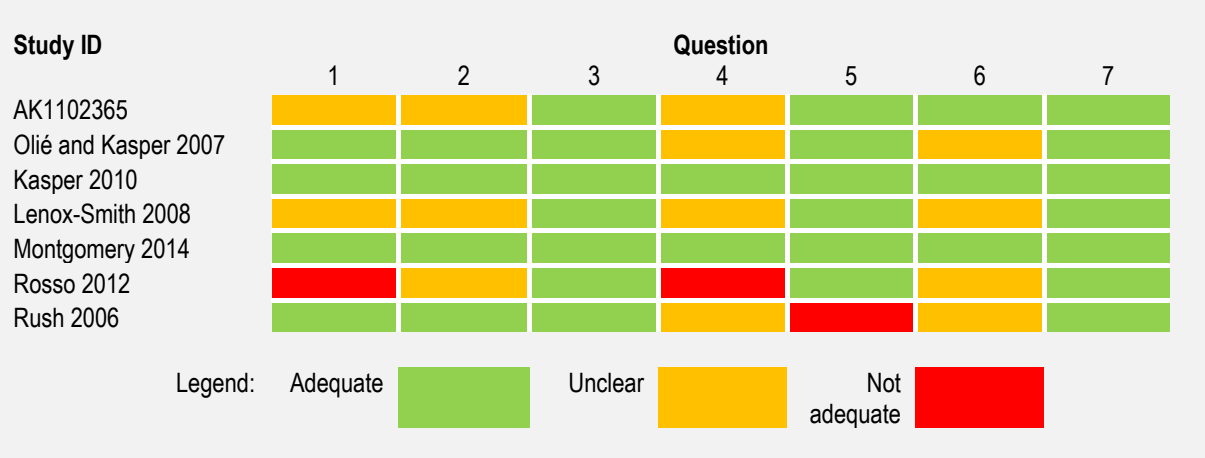
ER: Extended Release; QD: Per day; *Patients were prior treated with duloxetine 120mg QD; **Patients were prior treated with duloxetine 60mg QD Duloxetine 120mg QD; ^Data extracted from post-hoc publication (Kasper 2013) for subgroup of prior treated population

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)



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 is 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 accepted[197].

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-SR_{16}: 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-D_{21} score (all others HAM-D_{17}). 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-SR_{16}: 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 ± sd	Sex: % female	Median duration of current episode (months)	Baseline severity	Treatment duration (weeks), mean ± sd
Montgomery 2014 (REVIVE)	46±12	74.7%	3.7	CGI-S: 4.4 ± 0.6; MADRS: 28.9 ± 4.2 HAM-D_{17}: 23.3±2.) §	Vortioxetine: 10.4±3.0; Agomelatine: 9.7±3.9
Kasper 2010**	44±10	73.5%	3.1	CGI-I: 4.7 ± 0.7; HAM-D_{17}: 26.5 ± 3.0	Not reported
Olié and Kasper 2007**	44.9±10	73.0%	2.0	CGI-I: 5.0 ± 0.7; HAM-D_{17}: 27.8 ± 2.8	Not reported
Rush 2006 (STAR*D) †	42±13	58.7%	Not reported	HAM-D_{17}: 18.9 ± 7.3; QIDS SR-16: 13.2 ± 7.3	Bupropion: 8.3±5.0; Sertraline: 9.1±5.0; Venlafaxine: 9.3±5.1
Rosso 2012	47±13	67.7%	Not reported	CGI-S: 5.0 ± 0.9; HAM-D_{17}: 28.1 ± 4.7	Not reported
GSK 2009 (AK1102365)	36	45.3%	Not reported	HAM-D_{17}: 19 ± 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 be 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 be 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 ≤50%
Lenox-Smith 2008	100%	SSRI monotherapy other than citalopram	Retrospectively (medical records)	8 weeks	Patients with HAM-D_{21} ≥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-SR_{16}: 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 2012[98] 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

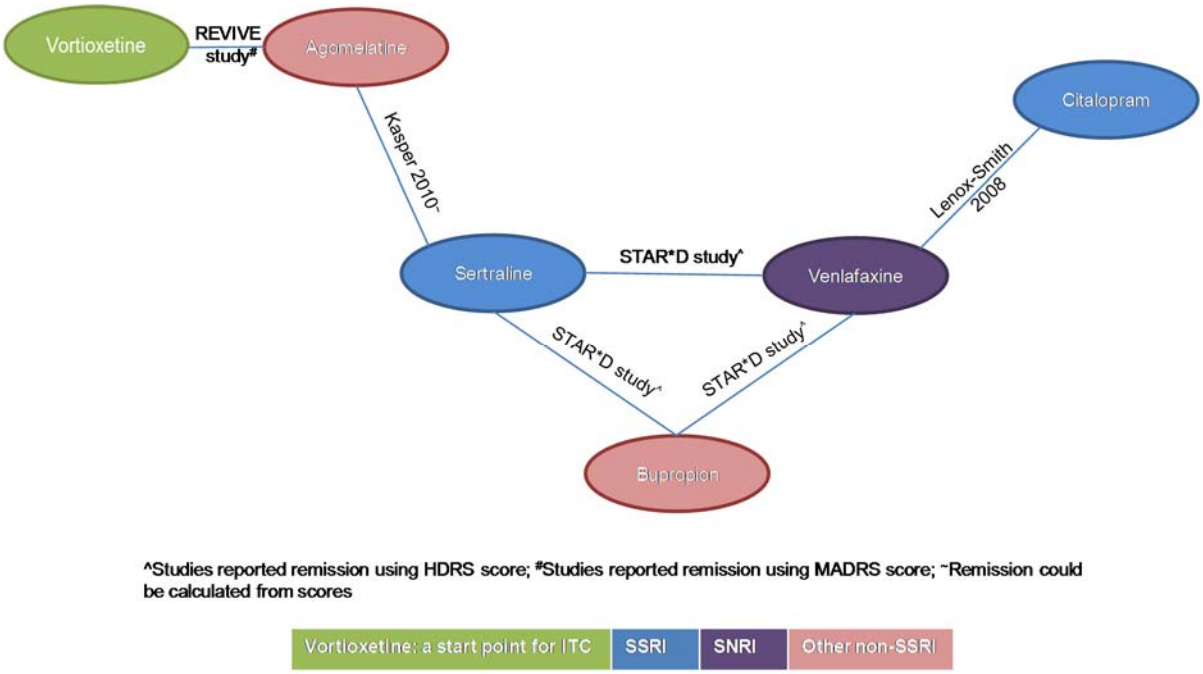
the network supporting the indirect comparison. The objective of this ITC was to provide comparative evidence for populating the cost-effectiveness model.

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 2014[26], Kasper 2010[191], Rush 2006[11] and Lenox-Smith 2008)[193], 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 buproprion) based on three studies: Montgomery 2014 (REVIVE)[26], Kasper 2010[191] 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-D_{17},[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-D_{21} of 28.7. In addition, remission rates were only available on the subgroup of patients with HAM-D_{21} 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 12[27]. 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-D_{21} in Lenox-Smith 2008 while the other two studies used HAM-D_{17} (see Table B32 below). Again, clinical opinion and the literature[201] 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 *N*	Primary endpoint	Remission definition	Endpoint assess-ment
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-D_{17}: Hamilton Depression Rating Scale 17-question version; HAM-D_{21}: 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 ± sd	46.3 ± 12.4	44.1 ± 9.8	41.8 ± 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* ± sd	NA *(21)*[1]	26.5 ± 3.0	18.9 ± 7.3	HAM-D_{21}>31
Severity at baseline *on MADRS total score* ± sd	28.9 ± 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-D_{17} and MADRS, which implies the italicised HAM-D_{17} 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-D_{21}: 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 definitions[201].

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 Bucher[202] were used to preserve the randomisation of the trials. This approach conformed to guidelines from EUnetHTA[203] and NICE[204].

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 Handbook[205].

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

$$\hat{\theta}_{AC} = \hat{\theta}_{AB} - \hat{\theta}_{CB}$$

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

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 treatmentcomparison

	Vortioxetine	Agomel-atine	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-D_{21}>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.

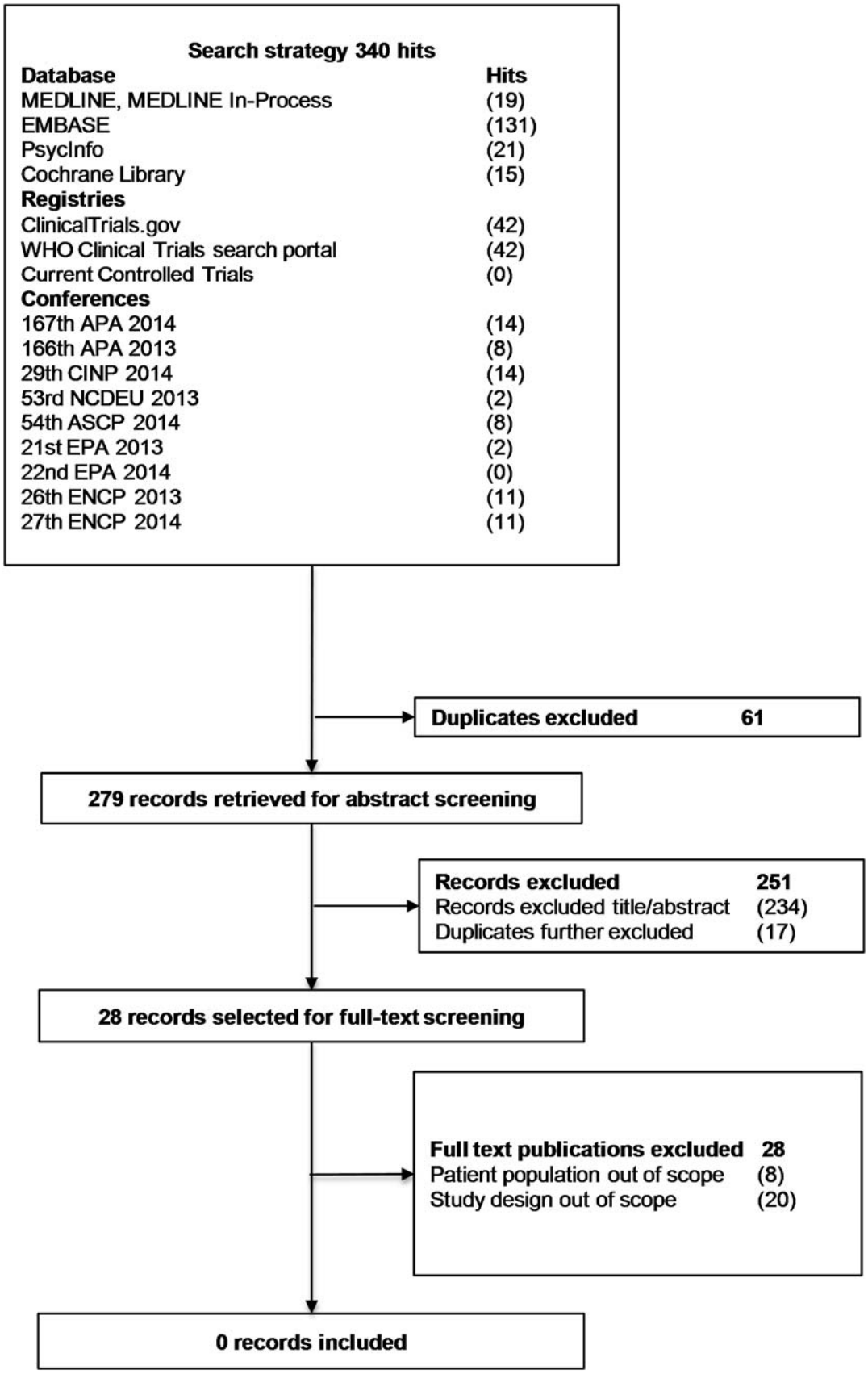
Table B40. Eligibility criteria for selection of non-RCTs

	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

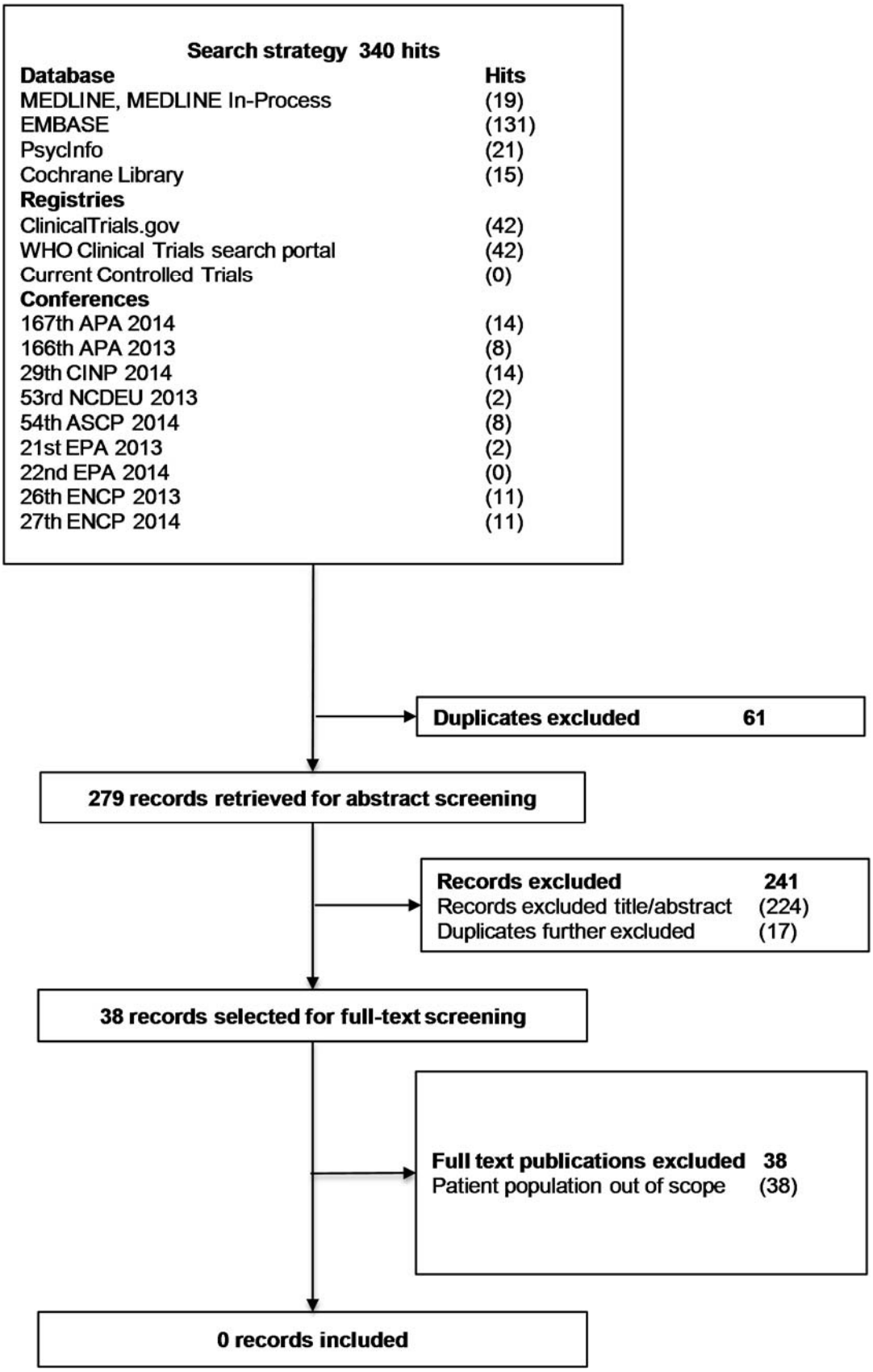
	Inclusion criteria	Exclusion criteria
Population	Adults with MDD who have experienced an inadequate response (in terms of efficacy and safety) to a previous antidepressant for the treatment of an MDE, i.e. switch patients.	Patients without MDD/experiencing an MDE. MDD patients but not specifically switch. 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

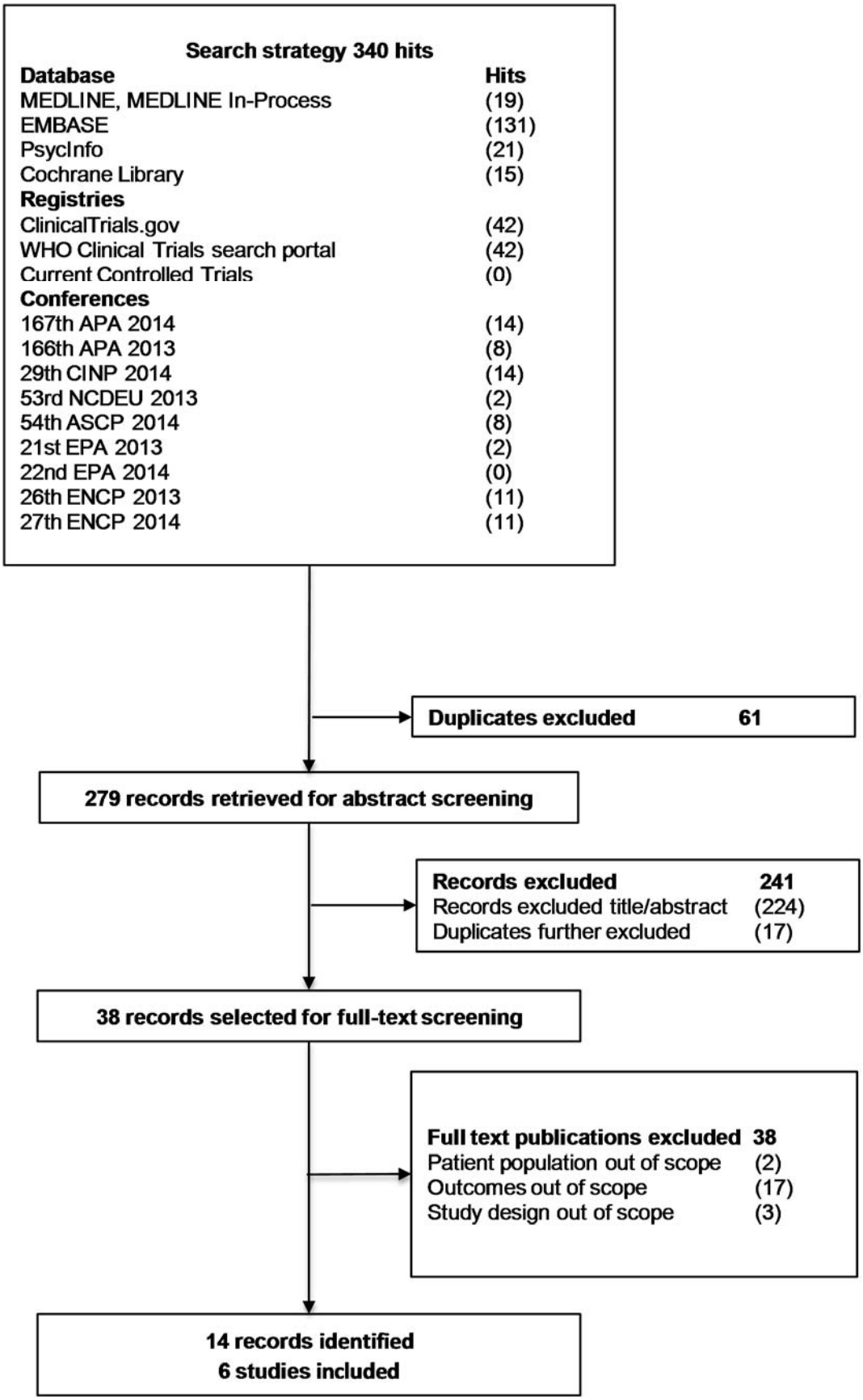


Table B43. Bibliographic details of primary safety studies in adult MDD population

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 weeks[214]. 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 ≥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 ≥5% in the open-label, long-term pool[214]

	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 analysis[214] 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 SSRIs[215] 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 response[26]. 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 MDE 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 surveillance[101].

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 monotherapy[217]. 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 class[101].

[redacted]

[redacted] 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 class[215]. 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 correlated[197]

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 and14 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 REVIVE[27], 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 though 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, TAK318[28] was concerned with a common[217] and troublesome[219] side-effect of antidepressants, treatment-emergent sexual dysfunction (TESD). TESD is experienced by 24% of patients receiving antidepressant monotherapy[217] 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 publication[26], 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 option 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

study[18] 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 Dissemination[220].

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].

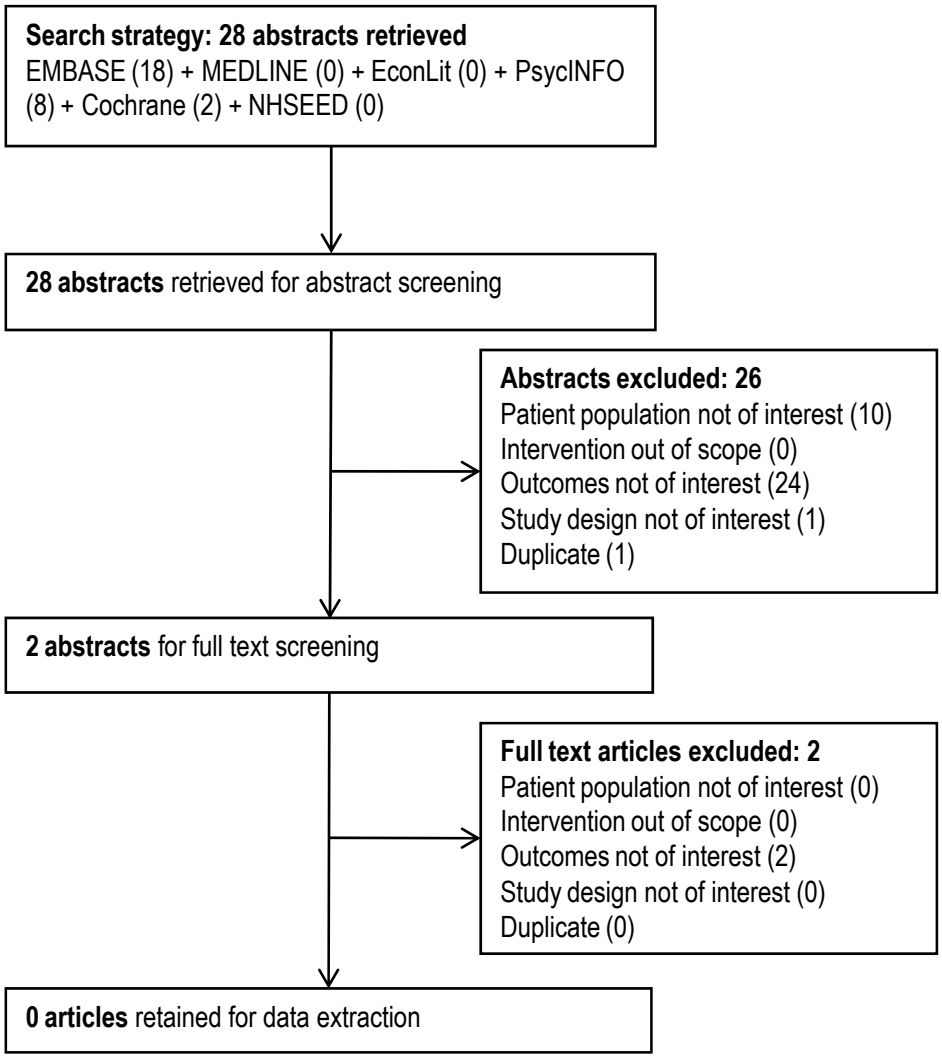
Table B45. Cost-effectiveness articles excluded following initial screening

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

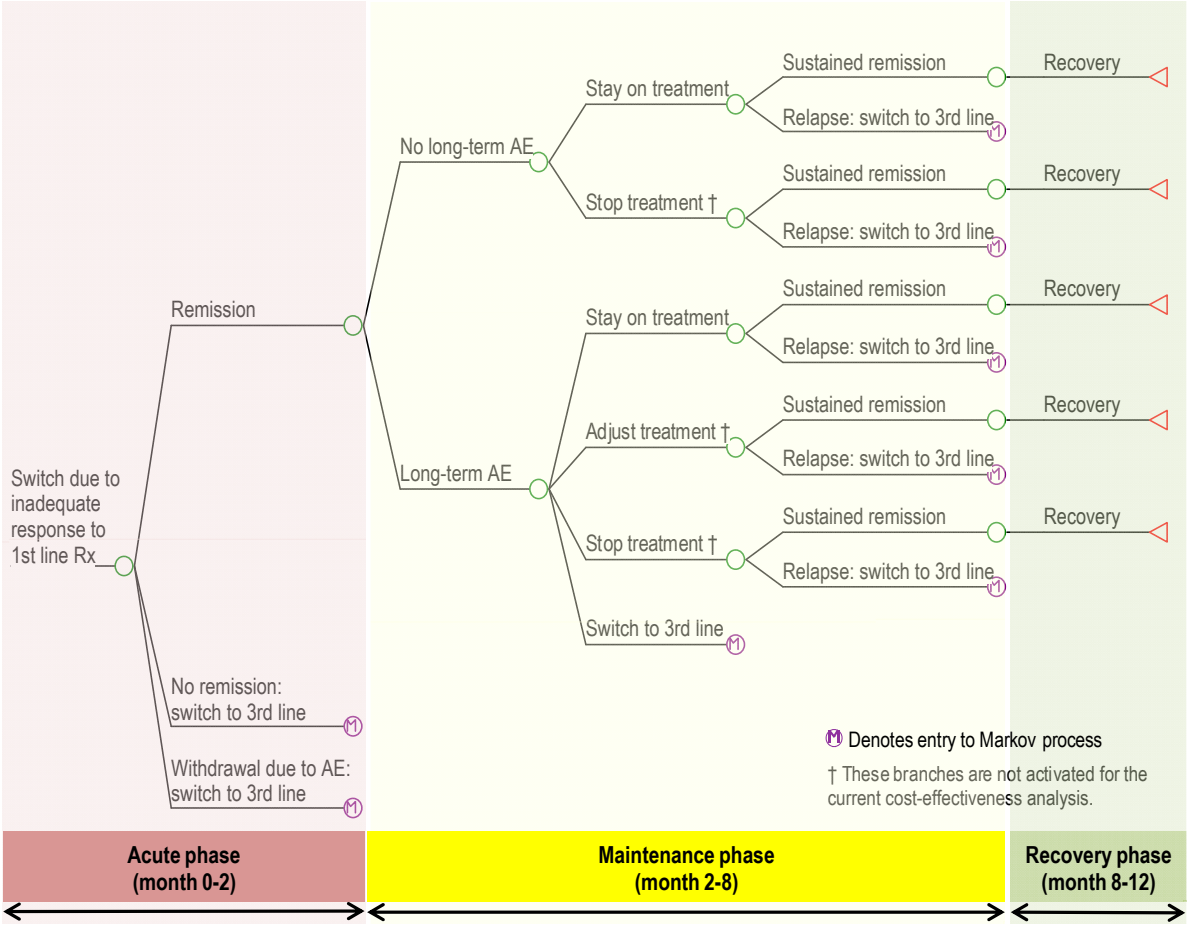
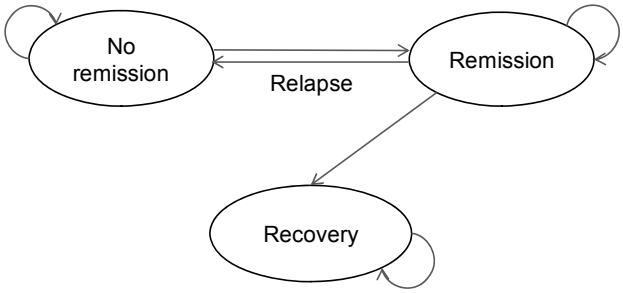


Figure B22. Markov state transition diagram for modelled events following switch to third line



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 evaluations[34-36]. In clinical trials, remission is defined by a score on the threshold of normality using a standardised instrument[186]. 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 (2nd line): Time (months) spent in				Health state at start of 3rd line treatment	After switch to 3rd line: Time (months) spent in			Total time horizon (months)
	Acute phase	*Maint-enance phase*	*Recov-ery*	Total in tree		*Acute phase*	*Mainten-ance phase*	Total in Markov model	
Remission at 8 weeks:									
Sustained remission	2	6	4	12	n/a	n/a	n/a	n/a	12
Relapse	2	3	-	5	*No remission*	2	5	7	12
Switch (long-term AEs)	2	1	-	3	*Remission*	n/a	6	9	12
No remission at 8 weeks:									
Switch (lack of efficacy)	1	NA	-	1	*No remission*	2	6	11	12
Switch (short-term AEs)	1	NA	-	1	*No remission*	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 remission[57-59]. 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 citalopram[226], 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 equivalent[5].
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 study[193] 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 2006[11]) 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 2004[227], 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 equivalent[197].

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 2010[225] and Cipriani 2012[165]). 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 state[214]. 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 2013[232], 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 2009[215] 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 2013[232], except for agomelatine, where corresponding data were taken from Goodwin 2009[231].

With respect to weight gain, a single source of data[233] 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 2013[232]. Goodwin 2009[231] 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 treatment[11], as shown in Figure A9. Hence, the model assumes the declining transition probabilities of remission observed in STAR*D[11] (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 4th line.	

Source: Rush 2006[11]

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 2006[11], 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 TESD, 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%		Distribution derived from 95% CI around risk difference between vortioxetine and each comparator	
	Difference from vortioxetine	-11.0%	Normal (95% CI: -19.4%, -2.6%,)		
	Sertraline	26.1%			
	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 3rd line	13.7%		Not included in sensitivity analysis	STAR*D
	Treatment 4th line	13.0%			
	Treatment 5th line	13.0%			Assumed equivalent to 4th line
Relapse after 6 months	Active treatment	14.2%	Beta (α: 51; β: 308)	95% CI assumes beta distribution	Limosin 2004
	Treatment 3rd line	25.0%	Beta (α: 8.74; β: 26)		STAR*D
	Treatment 4th and 5th line	42.6%	Beta (α: 6.39; β: 9)		Assumed equivalent to 4th line)

References to sources: STAR*D: Rush 2006[11], Limosin 2004[227]. 1 month is assumed equivalent to 4 weeks. CI: confidence interval.

Table B53. Model parameter inputs: withdrawal due to side-effects

Event	Treatment	Probab-ility	Distribution	Comment	Source
Discontin-uation due to side-effects at 2 months	Vortioxetine	5.9%	Beta (α: 15; β: 238)	Distribution derived from 95% CI around risk difference between vortioxetine and each comparator	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%			
	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 2010[225]; Cipriani 2012[165]. Pooled results from the sertraline[225], escitalopram[108], duloxetine[109] and citalopram[165] 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 file[238]Goodwin 2009[231], Bet 2013[232],

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 survey[240] 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 Roberts[17] 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 Sapin[18], 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 Sapin[18] 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 ound.**. 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
Depression	At study entry, i.e. switch following inadequate response to initial SSRI/SNRI	APTS	495	0.54	0.01
Remission	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
No remission	Not in remission at 8 weeks (MADRS total score >10)			0.62	0.02

Source: Lundbeck data on file[241]. 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 CG90[10], 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 Sapin[18] 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 validated[244], 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.

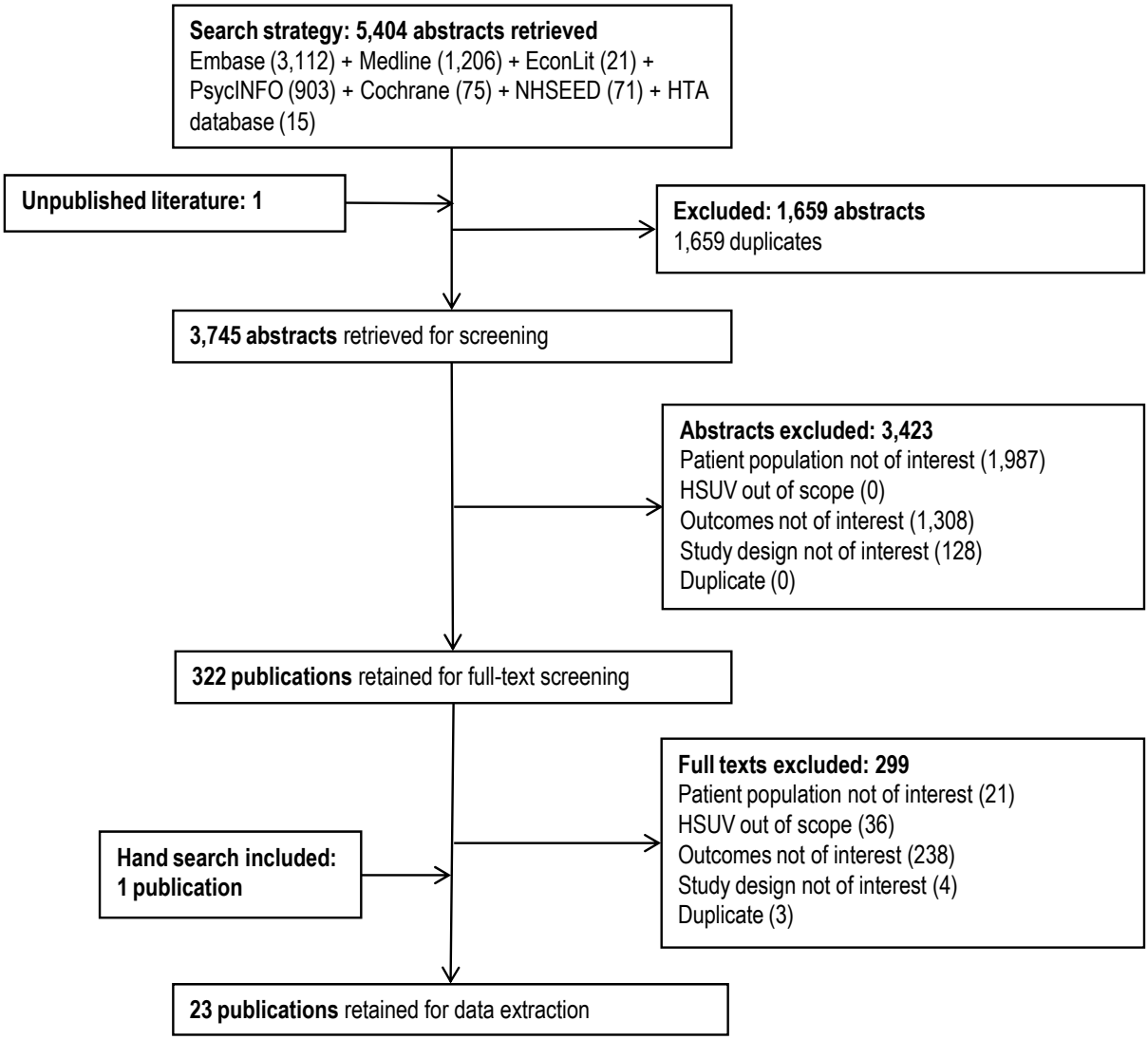
To validate the search strategy, the results were cross-checked with the HRQoL references considered relevant in NICE CG90. Seven of eight studies were retrieved[18,242,243,245-248]; the only missing study[249] concerned the consistency of computer-aided utility scoring, which reported SF-12 rather than 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 guidance[251]. 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 publication[252], 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 PERFORM[236]. 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 abstract[253] 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 study[254] 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 patients[19] and for UK patients by severity of depression, as defined by PDQ-5 score[256]. 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 models[257-261].

Soini 2011[253]

The only other publication reporting disutilities associated with TEAEs identified in the systematic review for HRQoL data was the Soini 2011 poster presentation[253]. 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	Assess-ment point	Utility value	Assess-ment point	Utility value	Assess-ment point	Utility value	Assess-ment point
Depression	0.54	Baseline	0.54	Baseline	0.33	Baseline	0.516	Baseline
Remission	0.85	8 weeks	0.82	2 months	0.85*	8 weeks	0.759	3 months
No remission	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
REVIVE[241]; 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 discontinuation[10]. 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 Sapin[18], 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 REVIVE[27] 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 REVIVE[241].

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 tariff[185]. 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 publication[237] was selected as the most appropriate source. Soini 2011[253] 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 2008[262]) 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 2004[263] 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/m^2.

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/m^2. As this value was >25kg/m^2, 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/m^2, 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			
Somnolence	0.085		Lundbeck applied Sullivan value reported for drowsiness*	
Nausea	0.065		Sullivan assumed average of GI AEs	
Insomnia	0.129		Sullivan assumed equivalent utility to anxiety	
Dry mouth	0†		No data available	
Dizziness	0†			
Sweating	0†			
Weight gain	0.032		Calculation (see below)	Dixon 2004, REVIVE CSR

Sources: REVIVE[241]; Sapin 2004[18]; Sullivan 2004[237]; Dixon 2004[263]; REVIVE CSR[27].

*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 and 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 (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)	100.0%	Uniform (α:75; β:100)	PERFORM
Remission after 8 weeks	2.15	Gamma (α:61.47; β:0.03)	100.0%	Uniform (α:75; β: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:0)	PERFORM
No remission 0-8 weeks	1.00	Gamma (α:61.47; β:0.02)	1.3%	Beta (α:2; β:152)	PERFORM
Remission after 8 weeks	0.23	Gamma (α:61.47; β:0.00)	2.9%	Beta (α:60; β:1,997)	Byford 2011
Relapse after 8 weeks	0.23	Gamma (α:61.47; β:0.00)	5.0%	Beta (α:58; β:1,109)	Byford 2011
Psychotherapy or counselling					
Remission 0-8 weeks	1.20	Gamma (α:9.00; β:0.13)	12.7%	Beta (α:9; β:62)	PERFORM
No remission 0-8 weeks	2.10	Gamma (α:1.96; β:1.07)	18.8%	Beta (α:29; β:125)	PERFORM
Remission after 8 weeks	0.0	-	0.2%	Beta (α:61; β:30609)	Byford 2011
Relapse after 8 weeks	0.0	-	0.2%	Beta (α:61; β:30609)	Byford 2011
Psychiatric ward admissions					
Remission 0-8 weeks	0.0	-	0.0%	Beta (α:0; β:0)	PERFORM
No remission 0-8 weeks	0.0	-	0.0%	Beta (α:0; β:154)	PERFORM
Remission after 8 weeks	0.22	Gamma (α:61.47; β:0.00)	5.2%	Beta (α:58; β:1,061)	Byford 2011
Relapse after 8 weeks	0.23	Gamma (α:61.47; β:0.00)	5.7%	Beta (α:58; β:958)	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)	0.5%	Beta (α:1; β:153)	PERFORM
Remission after 8 weeks	0.0	-	0.0%	Beta (α:0; β:0)	Assumed equivalent to acute phase
Relapse after 8 weeks	1.0	Gamma (α:61.47,; β:0.02)	0.51%	Beta (α:61; β:11924)	Assumed equivalent to acute phase
Accident & Emergency visits					
Remission 0-8 weeks	0.0		0.0%	Beta (α:0; β:0)	PERFORM
No remission 0-8 weeks	0.0	-	0.0%	Beta (α:0; β:154)	PERFORM
Remission after 8 weeks	0.22	Gamma (α:61.47; β:0.00)	3.1%	Beta (α:60; β:1,861)	Byford 2011
Relapse after 8 weeks	0.25	Gamma (α:61.47; β:0.00)	3.3%	Beta (α:59; β:1,741)	Byford 2011

References to sources: Byford 2011[234], 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 (α:61.47; β:0.47)	15.49%	Beta (α:52; β:2820	PERFORM
No remission 0-8 weeks	41.60	Gamma (α:61.47; β:0.68)	28.57%	Beta (α:44; β:109)	
Remission after 8 weeks	0.39	Gamma (α:61.47; β:0.01)	7.57%	Beta (α:57; β:693)	
Relapse after 8 weeks	9.50	Gamma (α:61.47; β:0.15)	22.75%	Beta (α:47; β: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 MIMS[264].

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 mainten-ance phase	Daily cost in acute phase	Daily cost in mainten-ance 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 2013[265] (£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 Byford[234]. 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 2013[265](Unit Costs of Health & Social Care 2013). Sources: Byford 2011[234], 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 Psychopharmacology[89] 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 2013[265]

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	£113.70	15.49% x 28.6 days x £113.70	£504	PERFORM; ASHE 2013 (revised) Table 1 - All Employees / Table 1.5a hourly pay - Gross	(Overall UK population)
No remission 0-8 weeks		28.57% x 41.6 days x £113.70	£1,351		
Remission after 8 weeks		7.57% x 0.39 days x £113.70	£3		Assumption
Relapse after 8 weeks		22.75% x 9.5 days x £113.70	£246		Assumption. Not used in switch

Sources: PERFORM. Data on file[236]; 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 2nd 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 an 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
	Citalopram	10.8%	9.3%	12.5%
Diarrhoea	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%

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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 guidance[204]. 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

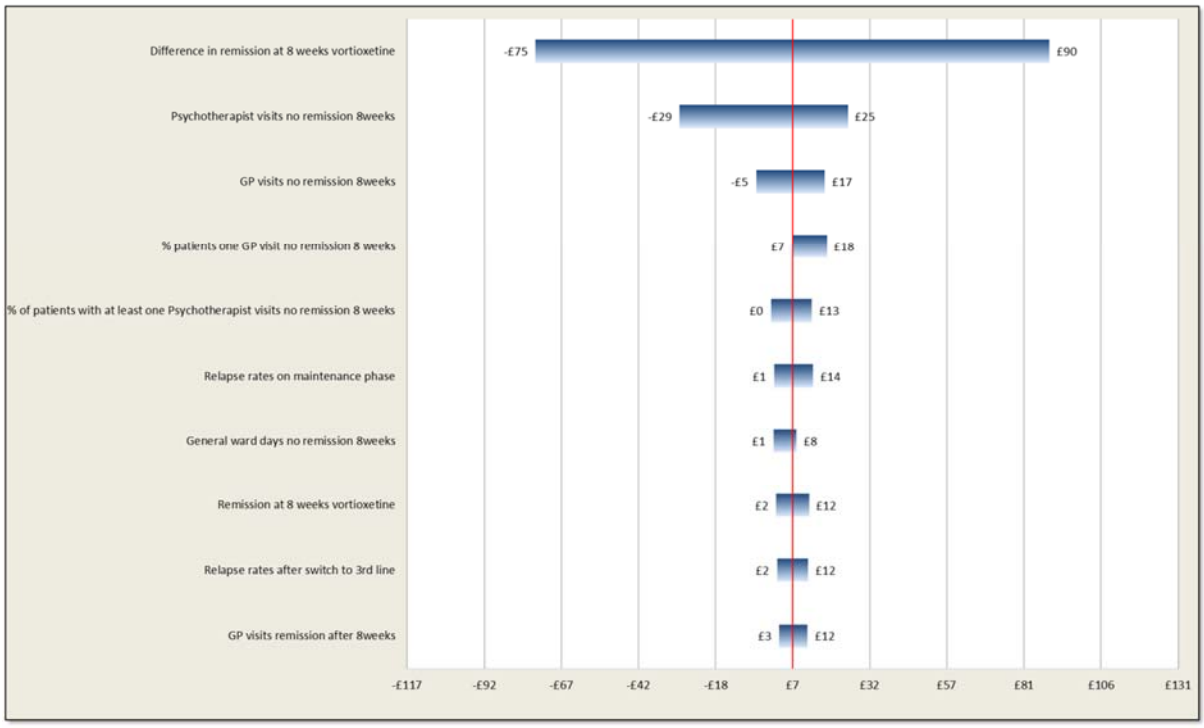


Figure B25. Sensitivity analysis of incremental QALYs: vortioxetine vs. venlafaxine

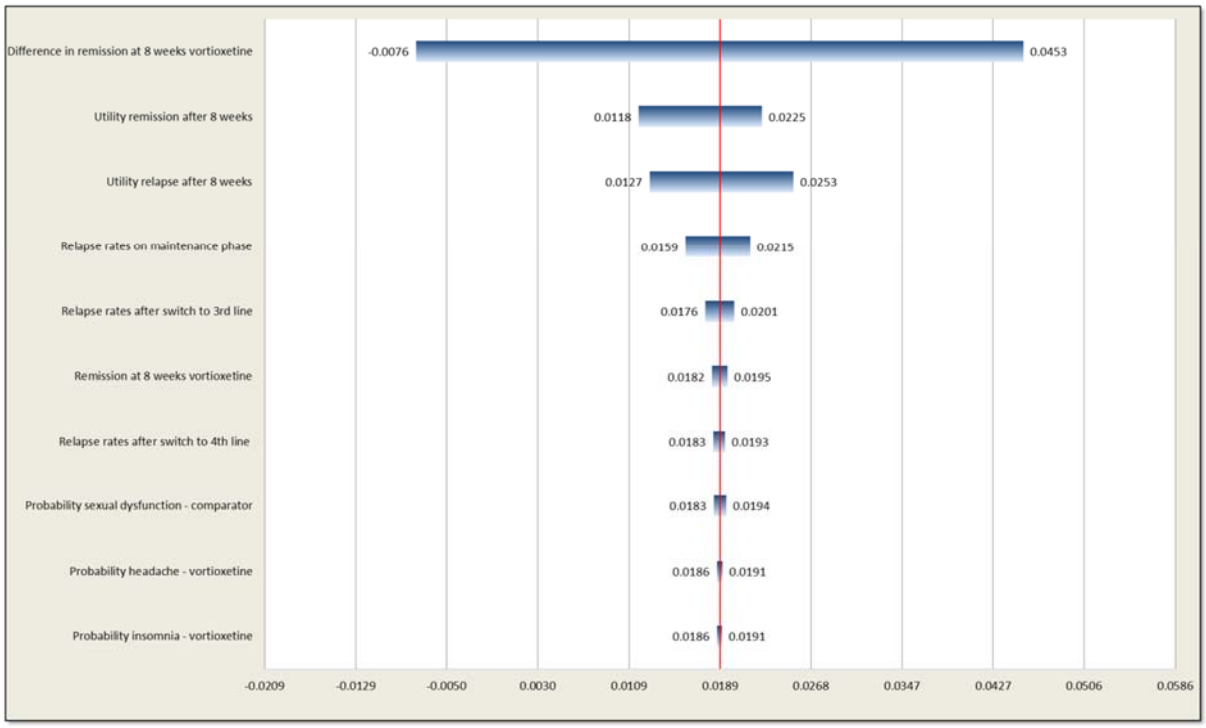


Figure B26. Sensitivity analysis of incremental costs: vortioxetine vs. citalopram

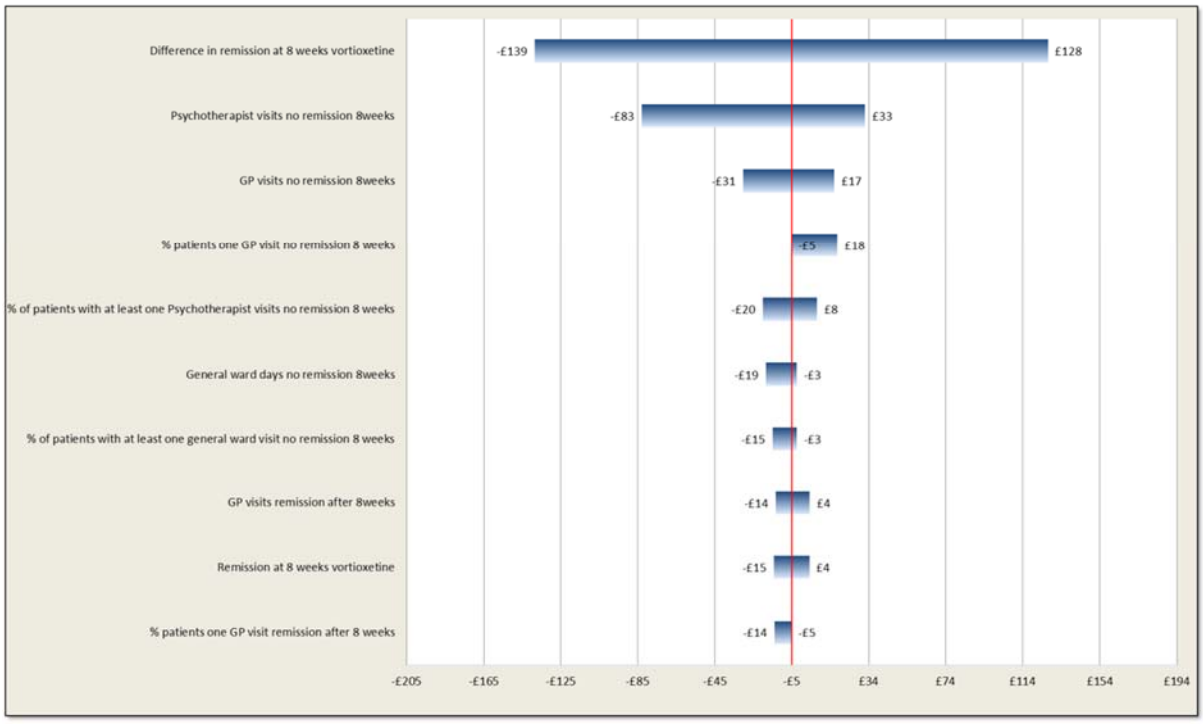


Figure B27. Sensitivity analysis of incremental QALYs: vortioxetine vs. citalopram

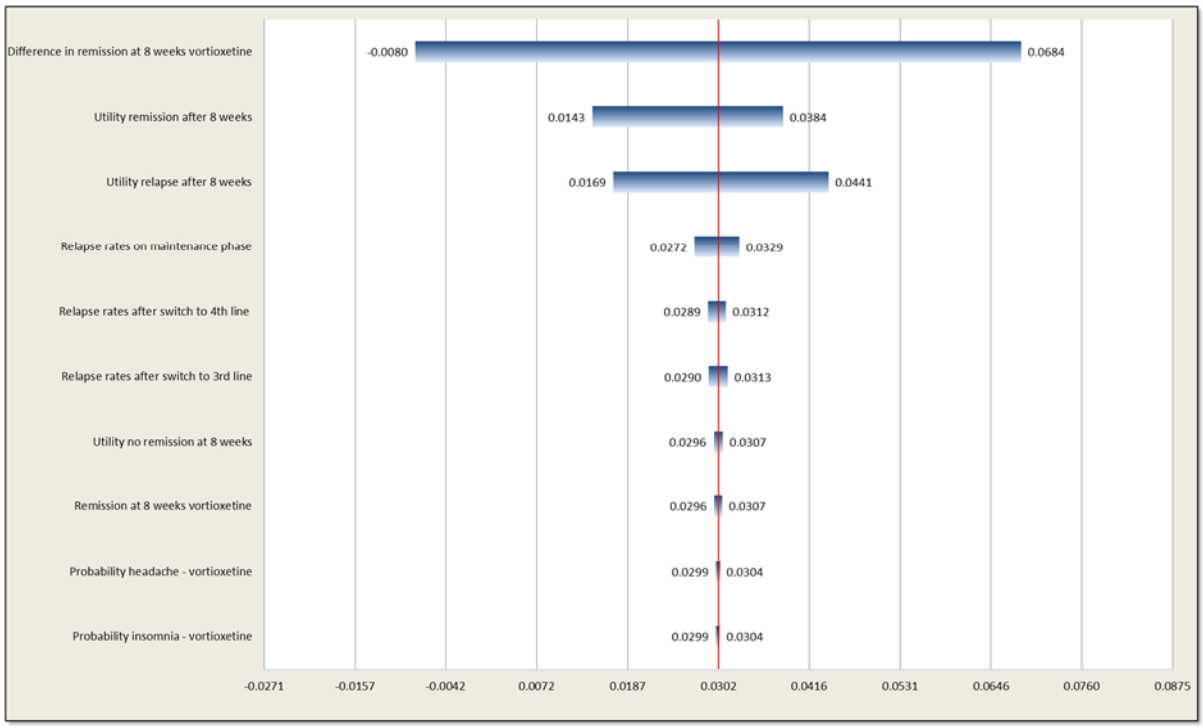


Figure B28. Sensitivity analysis of incremental costs: vortioxetine vs. sertraline

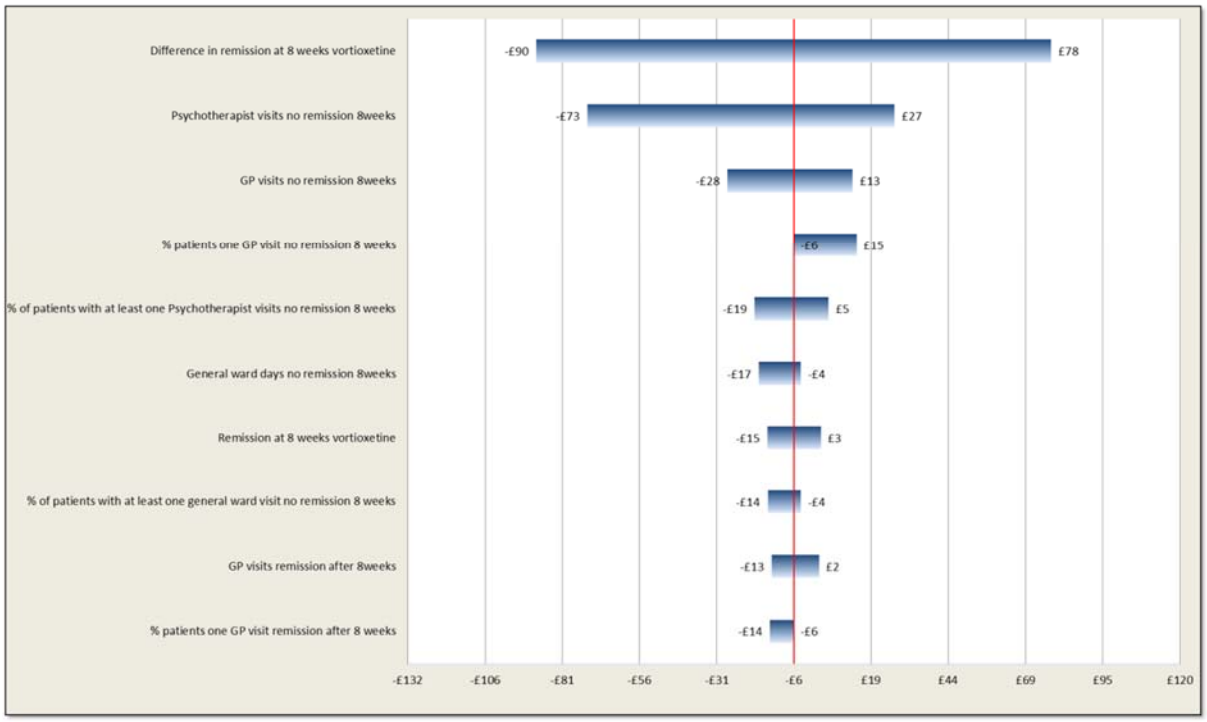


Figure B29. Sensitivity analysis of incremental QALYs: vortioxetine vs. sertraline

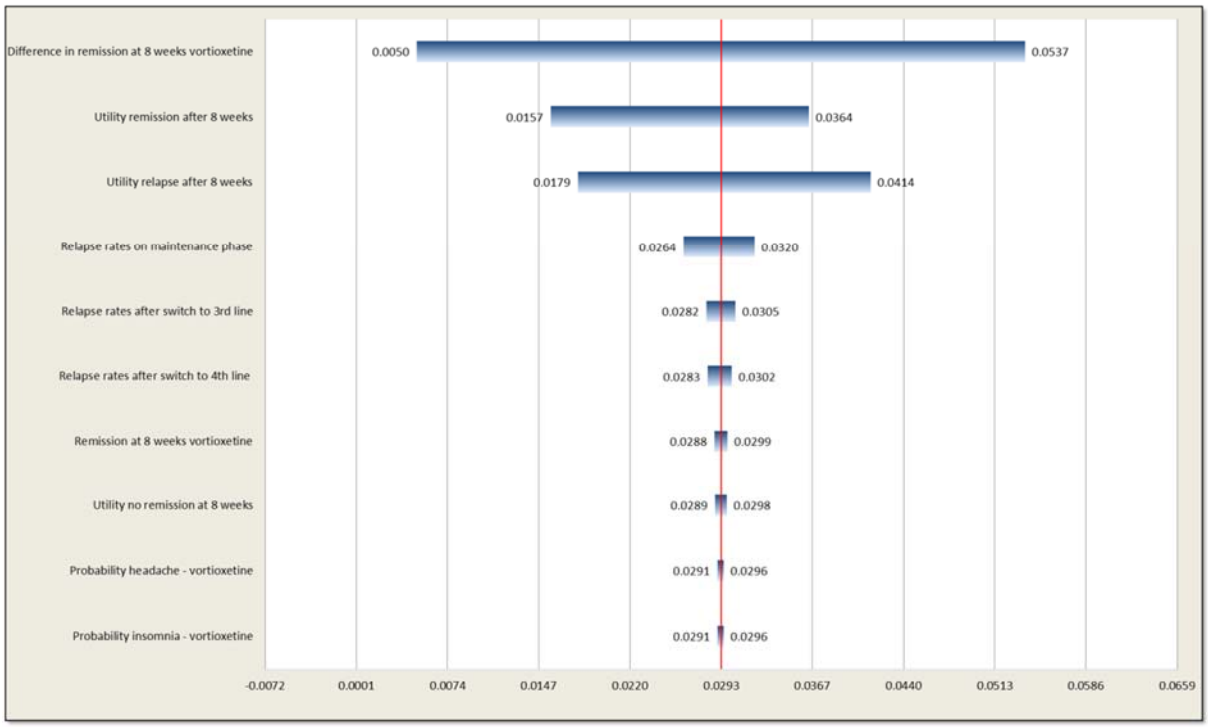


Figure B30. Sensitivity analysis of incremental costs: vortioxetine vs. agomelatine

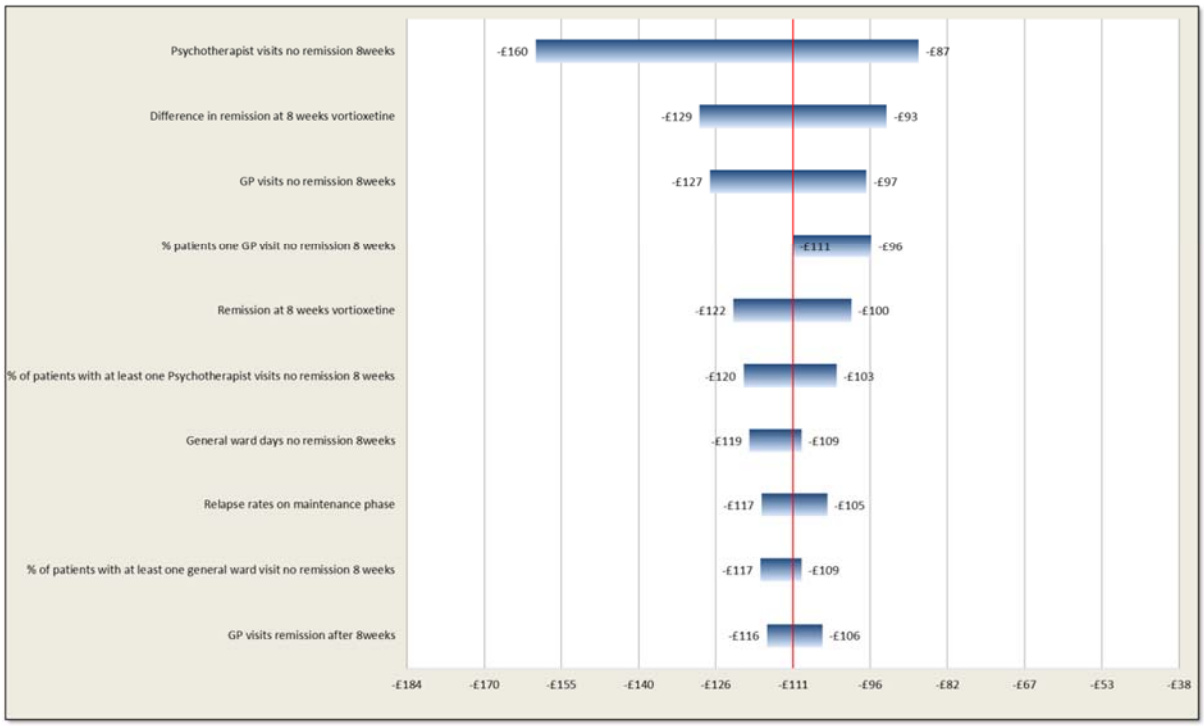
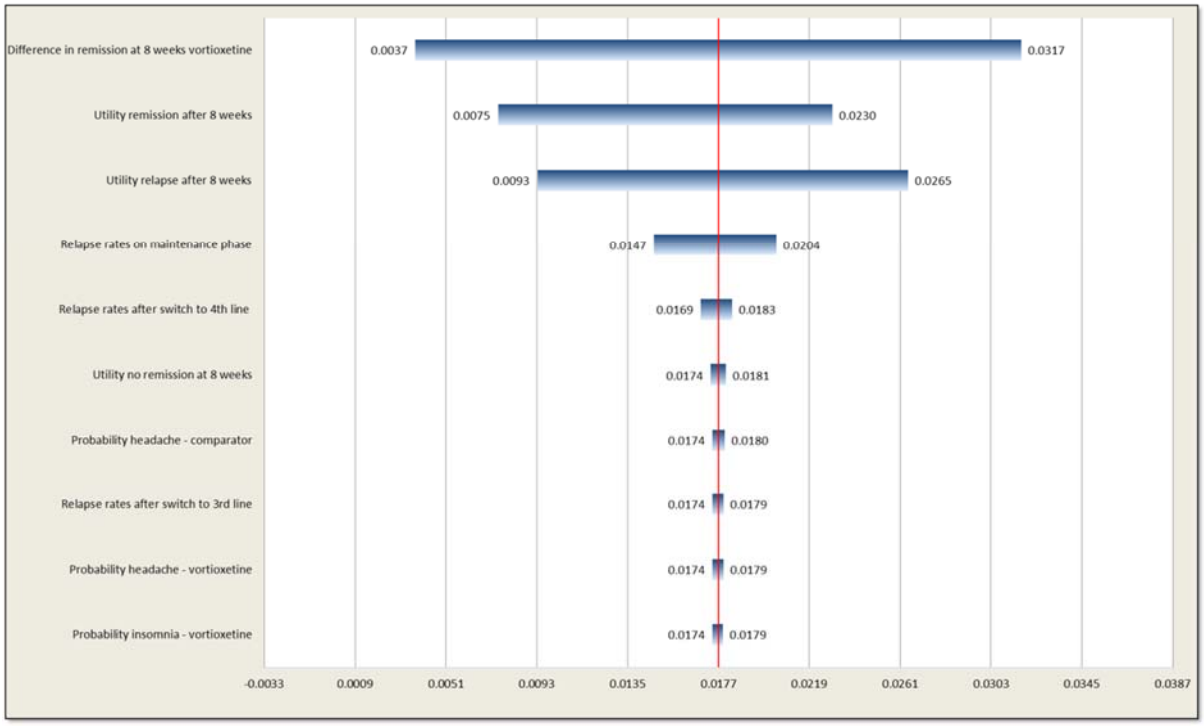


Figure B31. Sensitivity analysis of incremental QALYs: vortioxetine vs. agomelatine



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

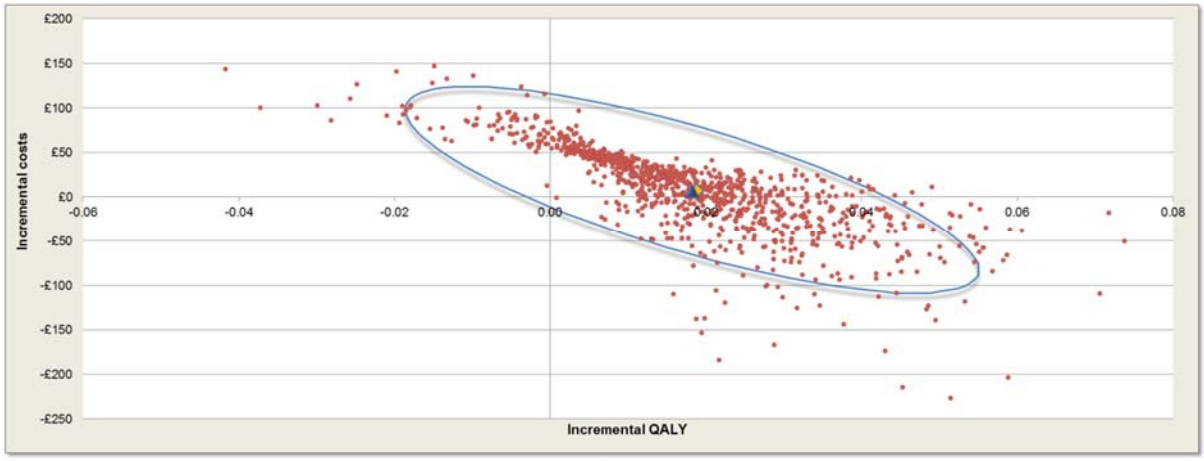


Figure B33. Cost-effectiveness acceptability curve: vortioxetine vs. venlafaxine

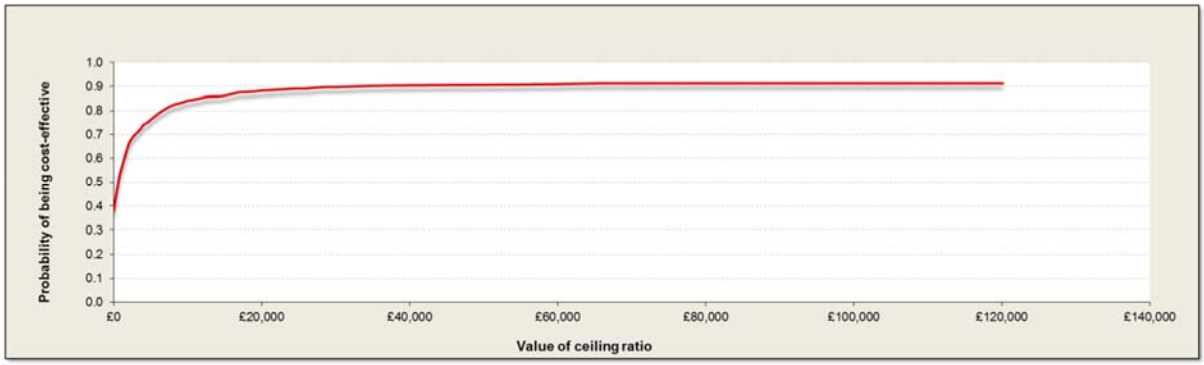


Figure B34. Scatter plot of PSA: vortioxetine vs. citalopram

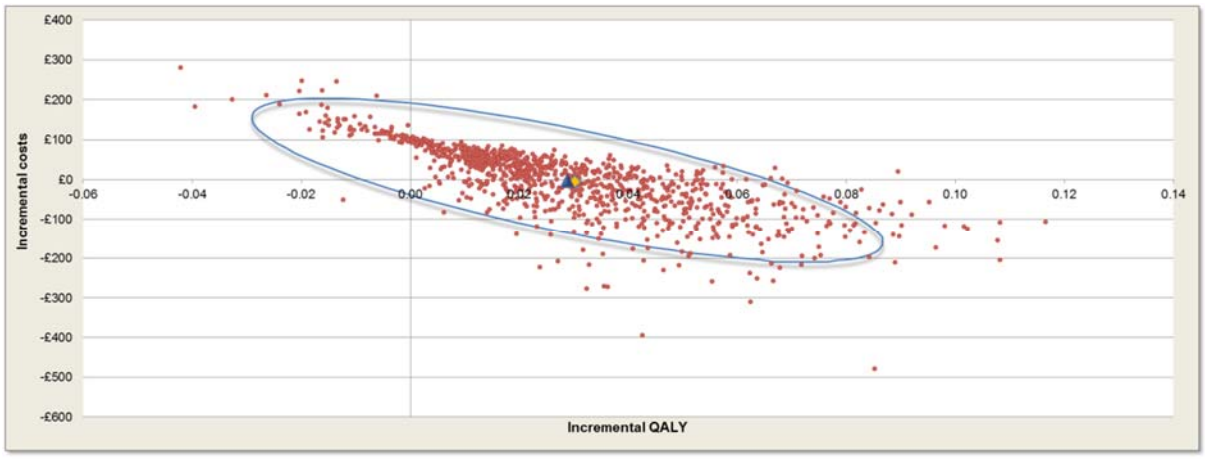


Figure B35. Cost-effectiveness acceptability curve: vortioxetine vs. citalopram

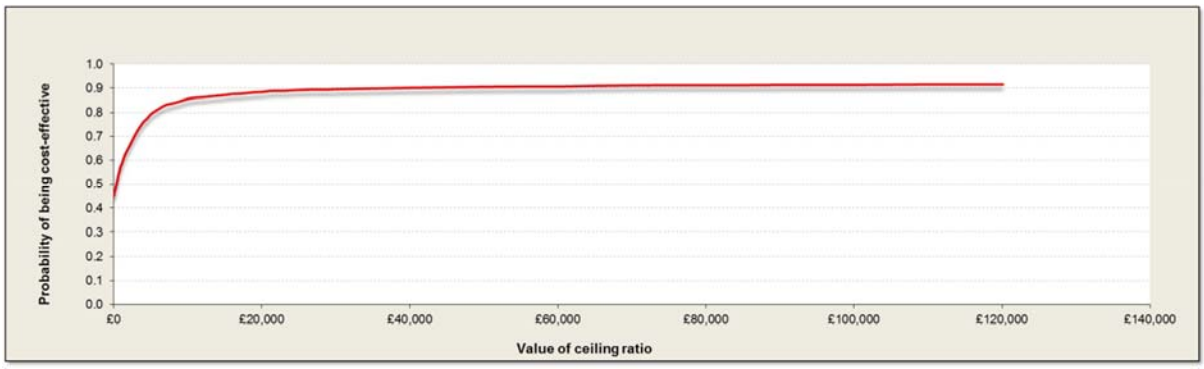


Figure B36. Scatter plot of PSA: vortioxetine vs. sertraline

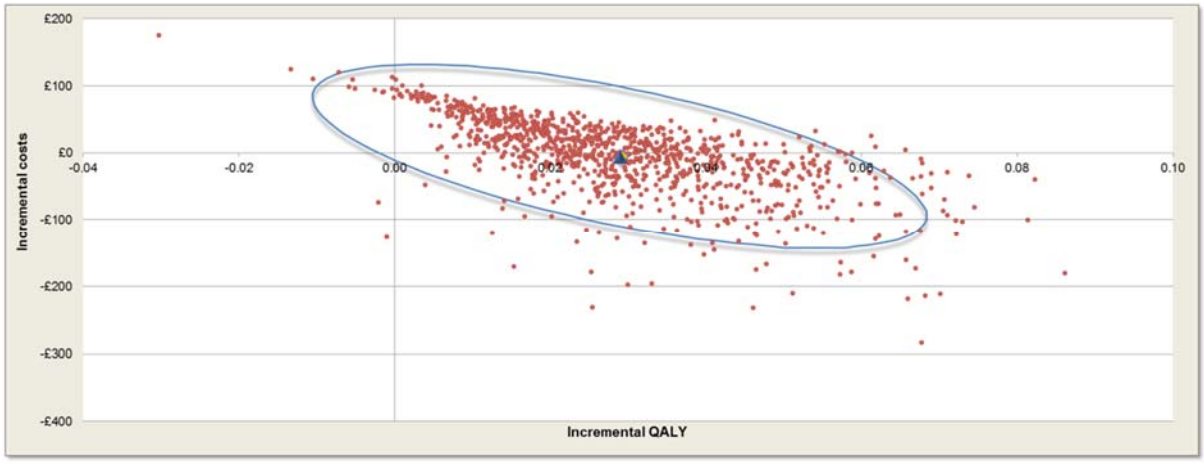


Figure B37. Cost-effectiveness acceptability curve: vortioxetine vs. sertraline

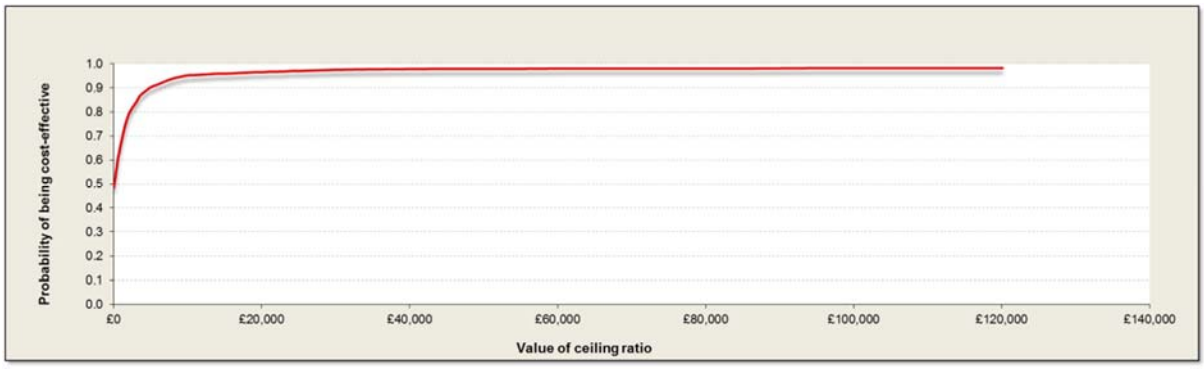


Figure B38. Scatter plot of PSA: vortioxetine vs. agomelatine

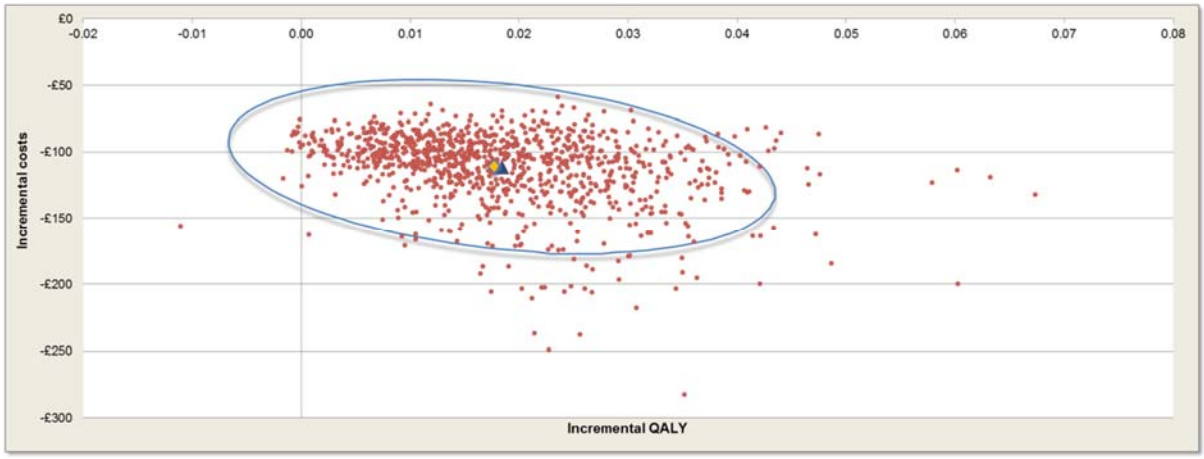


Figure B39. Cost-effectiveness acceptability curve: vortioxetine vs. agomelatine

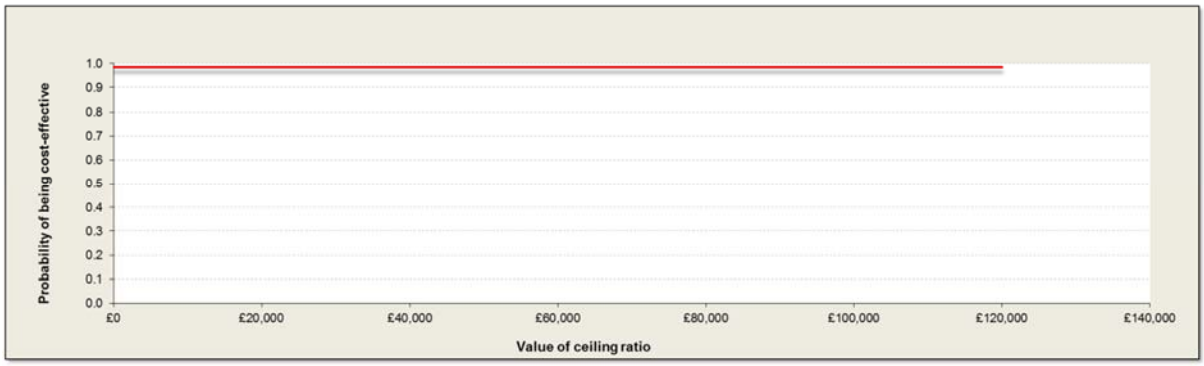
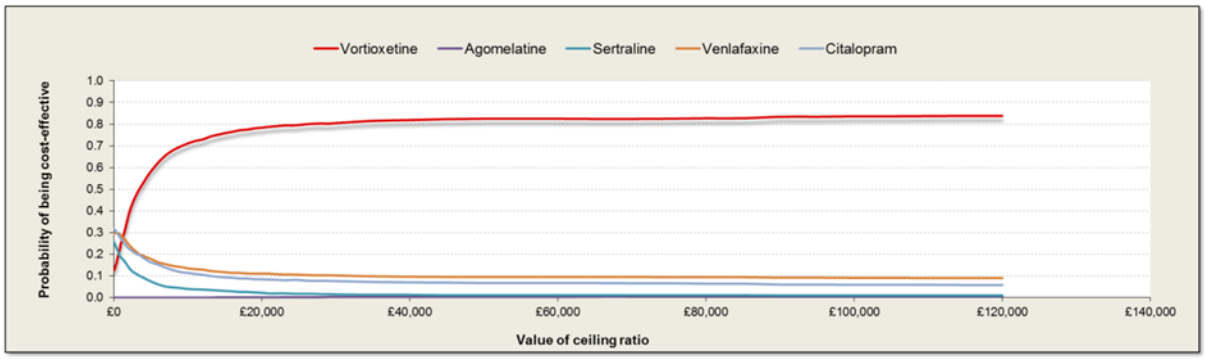


Figure B40. Multiple cost-effectiveness acceptability curves: all comparators



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 guidance[204].

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 2006[267]. 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 models[34].

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 guidelines[10] 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 analyses[270] and pharmacokinetic studies[2] 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 tariff[185] 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 Byford[234], both of which studies were conducted in the UK. As switch patients draw upon more resources than the full MDD population[20], 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 episode[227]. 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 44,811,857[72], 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 phase[10].

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.**

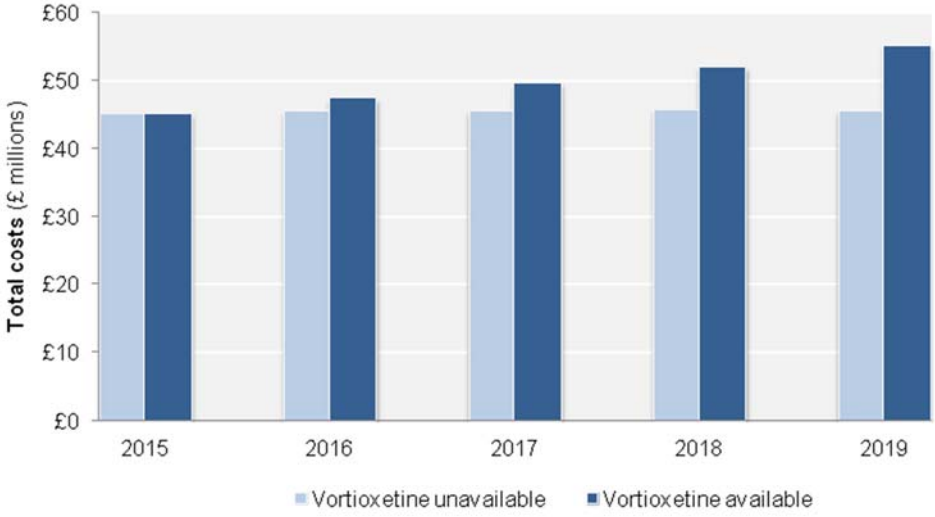
It should be noted that as the defined daily dose (DDD) is used to calculate the cost of medicine, the inherent assumption within the model is that this reflects the average dose of antidepressants prescribed and taken by patients in the UK. Expert opinion suggests that in fact the DDD does not reflect 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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