Vortioxetine for the treatment of major depressive disorder [ID583]

NICE Single Technology Appraisal

Response to consultation on Appraisal Consultation Document

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2. Document format

This Appraisal Consultation Document (ACD) response document is presented as two sections:

- Response to the request for further information and analyses by the Committee, including discussion, summary and results (Section 3)
- Specific comments from Lundbeck on the content of the Appraisal Consultation Document. (Section 4)

3. Response to the request for additional analyses by the Committee

3.1. Executive summary

3.1.1. Executive summary

In response to the Appraisal Consultation Document (ACD) Lundbeck presents revised analyses specified to meet the requests from the Committee.

Decision problem

The Committee requested analyses to inform the recommendation of vortioxetine for use in 3rd line and onwards. Therefore the response to address the decision problem focusses on the cost-effectiveness of vortioxetine in patients with a major depressive episode (MDE) who have experienced an inadequate response (either due to lack of efficacy or intolerability) to 2 or more previous antidepressants.

Comparators

Comparators relevant to a positioning at 3rd line and onwards were identified based on CG90, treatment usage in clinical practice, clinical opinion and the availability of evidence. These are listed below:

- Agomelatine
- Citalopram
- Duloxetine
- Escitalopram
- Sertraline
- Venlafaxine

As in the main submission the availability of data restricted the possible comparisons. Ideally, a comparison vs. mirtazapine would have been undertaken. However, as acknowledged at the last Appraisal Committee meeting by Prof Grunze, it is not suitable for all patients due to its distinct tolerability profile (particularly the association with weight gain and sedation). Therefore, based on expert clinical advice, Lundbeck does not believe the lack of comparative data to be a major limitation in addressing the decision problem.

Combination (combining two or more antidepressants, usually of a different class) or augmentation (typically adding in an antipsychotic to existing treatment) therapy was also suggested by clinicians to be relevant at this stage in treatment. However, Lundbeck also does not view the lack of data for

this to be a major limitation to the evidence addressing the decision problem as the proportion of patients receiving combination or augmentation therapy in the UK is small (7.6% and 3.4% the population respectively for overall strategies, less for each specific combination, (CPRD analysis, Lamy et al. (2015)), and these treatment strategies are associated with a greater side-effect burden and range of interactions with other treatments when compared to antidepressant monotherapy.

Data sources considered in the cost-effectiveness modelling

There are limitations associated with each of the data sets presented in the ACD (switch network, Llorca (2014), Pae, par/equivalent efficacy assumption) to populate the cost effectiveness model, as well as with the SOLUTION study which is an additional data set presented within this response document.

Therefore, Lundbeck proposes that the most appropriate assumption to be equivalent/par efficacy to populate the efficacy inputs in the base-case. This approach is in agreement with the information in the ACD regarding the committee's view on vortioxetine's relative efficacy:

"The Committee concluded that no convincing evidence existed to show that vortioxetine was any more or less effective than other antidepressants", pg 40.

This also aligns to the conclusions drawn within CG90 (NICE 2009) which states:

"Antidepressants have largely equal efficacy", pg 411.

Specifying treatment pathways in depression

In MDD, more so than in other disease areas, a strict treatment pathway is unlikely to provide the optimal treatment strategy for this large and highly heterogeneous patient population. When choosing appropriate treatments, clinicians account for individual treatment and patient profiles, including factors such as a patient's previous treatment experience and preferences. This approach is supported by both guidelines and expert clinical opinion. The explicit matching of treatment to patient is especially apparent and important at 3rd line treatment an onwards, where patients are often treated by clinicians with expertise in mental health/depression, such as GPs with a special interest or psychiatrists. These subtleties are not necessarily captured in clinical trial data and in addition, the relevant comparators will change according to specific patient's history/pathway. Both of these factors make modelling these specific aspects of the clinical decision making process challenging.

However, many of these aspects merit consideration, and the favourable safety and tolerability profile of vortioxetine are likely to translate into clinical and economic benefits for patients who have switched treatment due to adverse events or who have contraindications to other antidepressants, such as hypertension or QTc prolongation.

Cost-effectiveness model

As in the original Manufacturer's submission, the revised economic evaluation is model-based and incorporates a decision tree with a Markov component. The clinical starting point is a cohort of adult

patients who are switching to a new treatment following inadequate response in terms of efficacy and/or tolerability to two previous antidepressants. The analytic time horizon has been extended to 24 months to meet the requests of the Committee. In addition, based on the feedback and requested analyses from the Committee, the decision tree now assesses patients based on 4 initial acute-phase health states: remission, response (but not in remission), no response and short-term adverse events leading to discontinuation. The model structure was adapted from that reported by Trivedi et al. (2004), a review of national and local clinical guidelines, feedback via questionnaires from UK clinicians, and finally validated through an advisory board with Prof Allan Young, Prof Cornelius Katona, Prof Guy Goodwin and Dr Hamish McAllister Williams. The expert advisors believed the revised structure was a more accurate reflection of clinical practice for patients receiving 3rd line treatment and onwards.

Cost-effectiveness results

The key features of the base-case model included the assumption of up to 6 months maintenance treatment with initiation and maintenance treatment being undertaken in the primary care setting. The cost-effectiveness results are presented in Table 1.

Table 1: Base-case cost-effectiveness results (2015 £)

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI	Pairwise PSA – Pr(vortioxetine being CE)	
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)	k = £20k	k = £30k
BASE-CASE: PAR EFFICACY									
Citalopram	£1,341.88	1.414	£4,589.85	Ref	Ref	Ref	NA	63%	65%
Escitalopram	£1,347.28	1.414	£3,956.04	£5.40	-0.001	Dominated	NA	62%	65%
Sertraline	£1,357.42	1.412	£2,746.00	£10.13	-0.002	Dominated	NA	65%	67%
Vortioxetine	£1,399.00	1.427	NA	£41.58	0.015	£2,746.00	Ref	NA	NA
Venlafaxine	£1,399.52	1.410	Dominant	£0.52	-0.017	Dominated	Dominated	65%	67%
Duloxetine	£1,548.77	1.411	Dominant	£149.25	0.002	Dominated	Dominated	72%	72%
Agomelatine	£1,567.40	1.428	£243,078.85*	£18.63	0.016	£243,078.85	£243,078.85	52%	52%

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * 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.

In pair-wise analyses, vortioxetine was shown to be cost-effective treatment option vs. all comparators when a threshold of £20-30k was considered. The ICER vs. agomelatine represents a willingness to accept rather than willingness to pay however, in this scenario, the treatments are almost identical in health gain (0.001 QALY difference) but vortioxetine is approximately £170 cheaper. Pair-wise probabilistic sensitivity analyses indicated vortioxetine was the most likely treatment to be cost-effective at a cost per QALY threshold of £20k and £30k.

In scenario analyses, including increasing the length of maintenance treatment to up to 22 months (in addition to a minimum of 2 months in the acute phase) and changing the setting of care, the cost-effectiveness conclusions remain unchanged.

In addition to the base-case data source of par efficacy, inputs from SOLUTION, the Switch network, Llorca (2014) and Pae (2014) were modelled. In the main, the results supported the cost-effectiveness conclusions from the par efficacy data set. However, there was inconsistency in cost-effectiveness conclusions between SOLUTION, Llorca (2014) and Pae (2014) for certain comparisons. This was the case in both pair wise analyses of vortioxetine vs. the comparators and also for comparators vs. each other. These significant differences are primarily driven by the limitations associated with the methodology of some of the data sources.

Conclusions

Vortioxetine is an antidepressant with a new and unique mechanism of action. It has been shown to be as efficacious, and generally better tolerated, than other antidepressants. This has been observed consistently in the full MDD population through both direct head-to-head and indirect evidence. Furthermore, as far as Lundbeck is aware REVIVE is the only head-to-head study which has demonstrated statistically significant differences between two active treatments on the primary endpoint in patients who had previously experienced a lack of efficacy with prior SSRI or SNRI therapy (non-TRD population)."

Vortioxetine is a clinically logical and cost-effective treatment option at 3rd line and onwards for patients with MDD in England and Wales.

3.2. Overview of request from Committee & Lundbeck's approach to addressing these requests

As a quick reference guide Table 2 details Lundbeck's response to the specific requests made by the Committee.

Table 2: Overview of Lundbeck's approach to addressing the Committee's requests

Committee's request as detailed in the ACD	Lundbeck's approach to address request
CE analysis of vortioxetine compared with relevant treatment options third line and beyond for MDD	As detailed in Section 3.5, a cost-effectiveness analysis accounting for all of the aspects of treatment, and benefits of vortioxetine is challenging. However, as in the original model, the analyses will be conducted by considering a specific treatment line. As the focus is now on a positioning of 3rd line and onwards in the treatment pathway, patients will be assumed to have experienced inadequate response (due to efficacy or tolerability) to two previous treatments (e.g 2 SSRIs or an SSRI and an SNRI) before entering the decision tree. To better reflect the expected population outcomes at 3rd line, parameters have been updated as detailed in Section 3.6.3. Efficacy inputs have been adjusted to the appropriate lines based on the proportional reductions in absolute rates observed in STAR*D in line with the approach taken by the ERG and preferred by the Committee. In addition, due to the revised positioning the comparators have been reviewed based on UK prescribing data, expert clinical opinion, a CPRD analysis and CG90 (Section 3.3.1.)
Incorporating the broader evidence base for antidepressants (including at first line)	Considering the limitations of the evidence available for populating a cost-effectiveness model of treatments at 3rd line, and the Committee's, ERG's and CG90's recognition that in terms of efficacy, antidepressants are similar, Lundbeck proposes that the analysis of equivalent efficacy should be considered the base-case (see Section 3.4). In addition to the base-case data source, the cost-effectiveness results based on the switch network, Llorca (2014), SOLUTION (Wang 2015) and Pae (2014) are also presented in Section 3.4.
Define treatment success, and decisions to switch, by response and remission	The model structure has been updated to include both response and remission as clinically relevant outcomes through the inclusion of an additional branch in the decision tree (see Figure 2 – a schematic of the decision tree model structure). The revised structure was inspired by the Trivedi (2004) publication, a thorough review of switching recommendations in guidelines (both national and local) and clinicians' responses to a clinical questionnaire who were surveyed in July 2015. In addition, the final model structure was validated as being representative through a clinical advisory board with UK depression experts, Dr Hamish McAllister-Williams, Prof Allan Young, Prof Guy Goodwin and Prof Cornelius Katona in July 2015.
Use the time point in which	Treatment switches associated with lack of efficacy are now assumed to occur at 8

patients change to another treatment from the trials, for the time point in the model	weeks or after, in line with the clinical data available and the UK clinical advice received. Withdrawals due to adverse events continue to be assumed to occur at 4 weeks (extracted from 8 week trial data) based on clinical advice and data from REVIVE supporting an earlier switch due to AEs compared with a switch due to efficacy.
Consider that patients may receive treatment for 2 years	Two scenarios are presented for the length of maintenance treatment: up to 6 months (Analyses sets 1,3, 4 and 6) and up to 22 months (Analyses sets 2 and 4) (See Table 10 and Table 11 for a summary of analyses).
Include a risk of relapse at all stages of depression	The risk of relapse was previously included in all health states within a depressive episode (i.e. all but recovery). The probability of recurrence has now been included as a risk in the recovery phase of the model in some analyses (Analyses sets 1 and 4; See Table 10 and Table 11 for a summary of analyses).
Use utility values from REVIVE	Utility values from REVIVE have been applied in line with the ERGs analyses. For the revised model structure utility values for the 3 response subgroups (remission, response and no response) have been applied.
Include a 24 month time horizon	The model time horizon has been extended to 24 months.
Present pairwise and incremental analyses for probabilistic CE analyses	Pairwise probabilistic analyses are presented for the base-case. Due to time constraints incremental probabilistic analyses are not available.
Disaggregated results for each of the pairwise comparisons	The incremental costs and QALYs for each of the pairwise comparisons are reported.

CE, Cost effectiveness; CPRD, Clinical Practice Research Datalink; ERG, Evidence Review Group; MDD, Major Depressive Disorder; QALYs, Quality Adjusted Life Years.

3.3. Decision problem

In line with the Committee's requests Lundbeck are presenting analyses to support the 3rd line and onwards place in therapy of vortioxetine.

Therefore the decision problem focusses on the cost-effectiveness of vortioxetine in patients with a major depressive episode (MDE) who have experienced an inadequate response (either due to efficacy or intolerability) to 2 or more previous antidepressants.

3.3.1. Comparators

Due to the revision of the decision problem to focus on the use of vortioxetine at 3rd line and onwards it is relevant to consider the treatment options specified in the clinical guidelines, treatment usage in clinical practice and UK clinical opinion at this place within the pathway, to identify the appropriate comparators.

CG90 states explicitly that at 3rd line *"an antidepressant from an alternative class"* should be tried. For the vast majority of patients in the UK requiring 3rd line treatment, this rules out the use of another SSRI (as an SSRI is recommended to be used 1st line and potentially second line) and for some, it also rules out SNRIs as duloxetine or venlafaxine may have been used 2nd line.

Therefore based on prescribing data (see Figure 1), and applying the above criteria, the list of most relevant comparators at 3rd line becomes:

- Mirtazapine
- Venlafaxine (for those who have not yet received an SNRI for the treatment of their MDE)
- Duloxetine (for those who have not yet received an SNRI for the treatment of their MDE)
- Others e.g. agomelatine

It is at this stage in the pathway where lesser-used antidepressants from a different class, such as agomelatine, become relevant additions to the available treatment options.

As stated in Lundbeck's original submission, no comparative data are currently available for mirtazapine. Although it is widely used as a treatment at 3rd line and onwards, 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 (Taylor, 2012) 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 or safe option for patients who depend on alertness by clinicians due to the impact on psychomotor speed (Wingen et al. 2005), e.g. people in occupations requiring mental concentration or stamina, professional drivers and carers.

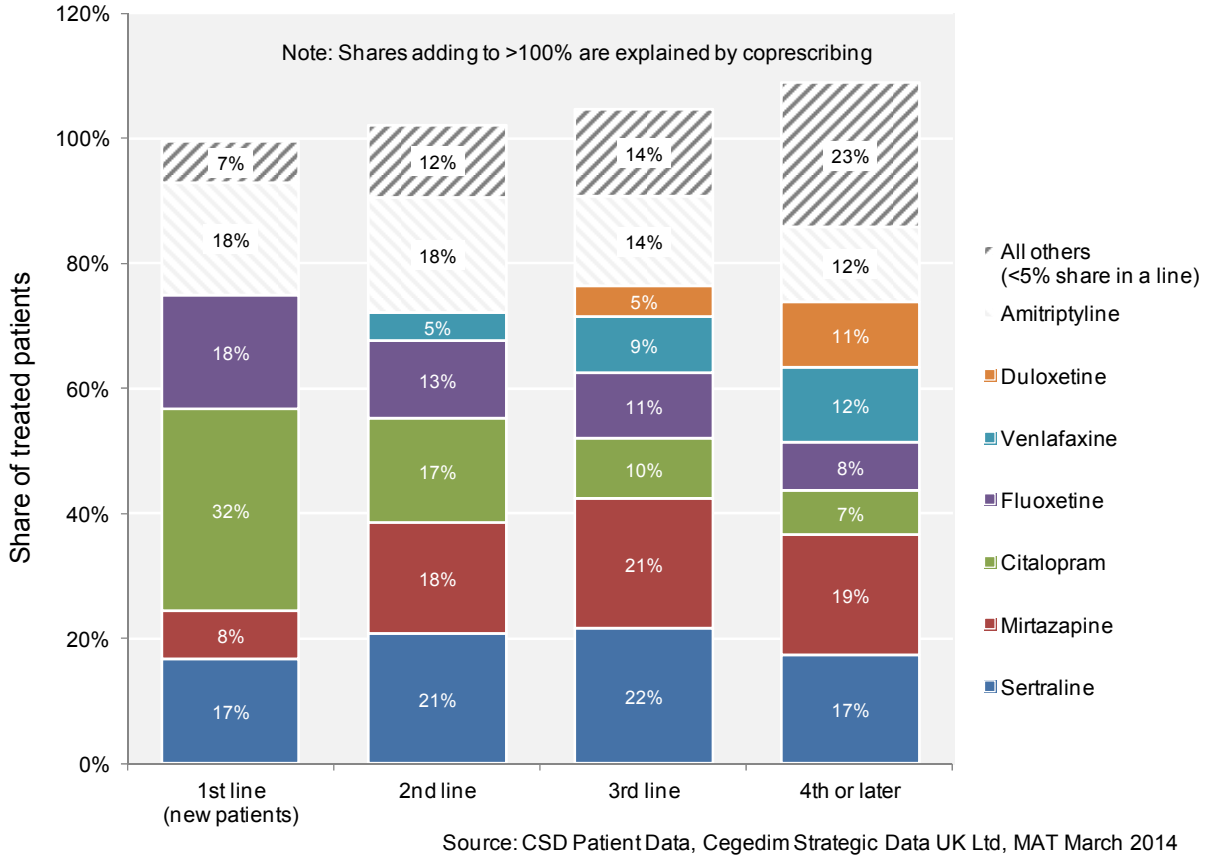
In addition, no data have been identified to allow a comparison of vortioxetine to combination or augmentation therapy. Therefore, the analyses presented do not include comparisons between vortioxetine and treatment combinations (with 2 or more antidepressants) or augmentation (an antidepressant with an antipsychotic).

In a recent CPRD analysis (Lamy, 2015), in the 3rd line treatment setting combination and augmentation strategies made up only a small proportion of treatment approaches employed (8.4% and 3.9% respectively). Given that there are many possible combination or augmentation treatment regimens the actual market share of each of these is substantially lower than the overall strategies detailed above (see Appendix 6.1) for the breakdown of market shares by combination strategies from the CPRD analysis).

The increased side effects associated with combination and augmentation treatment (NICE 2009), along with the well-recognised polypharmacy issues associated with antipsychotics (NICE 2009, Lam et al. 2009, Werder 2003) are likely to contribute to lower adherence and treatment length and increased risk of relapse. Mainly for these reasons, clinical opinion suggests that these options are used in patients with multiple previous episodes that have been more difficult to treat.

For these reasons, though augmentation and combination treatment were raised as valid treatment strategies at 3rd line through the questionnaire responses described in Section 6.6.4, and they are also mentioned as a strategy to be considered in NICE CG90, Lundbeck do not believe the lack of comparison between the vortioxetine and these alternative strategies is a major limitation or gap in the evidence base provided to inform the decision making process.

Figure 1: Pharmacological treatments prescribed for patients ever diagnosed with depression, by line of therapy.



Source: CSD Patient Data, Cegedim Strategic Data UK Ltd, MAT March 2014

3.3.2. Proposed place of vortioxetine within the clinical pathway

Lundbeck propose that vortioxetine is positioned after inadequate response due to efficacy and/or tolerability to two or more previous antidepressants. This is in line with the requests from the Committee with regards to the reassessment of cost-effectiveness within this position. It is also reflective of independent recommendations from the Maudsley group within their recently published guideline (Taylor 2015).

3.4. Discussion of clinical data sources for consideration

There are no data available for vortioxetine 3rd line and onwards and a review for other comparators has not been undertaken due to time constraints. Therefore two questions were asked:

1. Which clinical data source is the most appropriate to populate the efficacy and withdrawal due to adverse event rates in the cost-effectiveness model?

2. How will the clinical data be adjusted to 3rd line?

3.4.1. Q1. Which clinical data source is most appropriate?

Lundbeck understands the reasons expressed by the ERG and NICE for the incorporation of the broader evidence base to inform the decision making process. As highlighted in the appraisal process, several sources can be considered to inform the relative efficacy of vortioxetine vs other antidepressants. Lundbeck revisited these sources to establish the most appropriate for the base-case of further cost-effectiveness analyses. Key considerations included the applicability of the data to the 3rd line and onwards population, and possibility to derive robust comparative estimates of the efficacy inputs required to populate the model (i.e. response and remission). The strengths and limitations of each of the sources are detailed below to support the choice of the proposed evidence base-case.

3.4.1.1. Justification of equivalent/par efficacy as the base-case

Considering each of the available data sources, and the important methodological variations between these sources which affect the assessment of the relative efficacy of vortioxetine, Lundbeck proposes that the most appropriate assumption to be equivalent/par efficacy to populate the efficacy inputs. This approach is in agreement with the statement in the ACD regarding the committee's view on vortioxetine's relative efficacy:

> "The Committee concluded that no convincing evidence existed to show that vortioxetine was any more or less effective than other antidepressants", pg 40.

In addition, it aligns to the conclusions drawn within CG90 (NICE 2009) which states:

> "Antidepressants have largely equal efficacy", pg 411.

Within this section, the overarching issue associated with non-constant relative efficacies shall be discussed. Further, this section discusses the variations and considerations associated with the Switch network, Llorca (2014), Pae (2014) and SOLUTION given the objective of populating the current cost-effectiveness model.

3.4.1.2. Relative efficacies

As in the original submission, Lundbeck still believes there to be a difference in relative efficacy across treatment lines. In order to better understand this, a systematic literature review looking at before and after switch due to lack of efficacy was undertaken. When this evidence is considered in its totality there seems to be a general trend towards there being a difference in relative efficacies before and after switch for all antidepressants (see Appendix 6.2).

This evidence, the implicit beliefs supporting the recommendations in CG90 and clinicians' feedback (both externally to Lundbeck but also at the 1st Appraisal Committee meeting) lead to the conclusion that a switch to a different class may improve outcomes. Therefore the following would hold:

- 1st line: within England and Wales a generic SSRI would usually be chosen in line with the guidelines.
- 2nd line: the guideline suggests switch to an alternative SSRI or a newer generation, better-tolerated antidepressant.
- 3rd line: CG90 recommends switching to an antidepressant of a different class. This is supported by the clinical expert at the 1st Appraisal Committee meeting who, as detailed in the ACD (pg. 38), noted that the relative effectiveness of antidepressants compared with one another may also change at each subsequent line of treatment; Prof Heinz Grunze stated (though this is not reflected in the ACD) that a switch between class may often lead to a greater efficacy rate than a switch within class. Therefore, at this point in the pathway, if a patient had received 2 previous SSRIs, then the following are examples of treatment options that may be considered: an SNRI, mirtazapine (if sedation is necessary and weight gain is not an issue) or agomelatine. If they have received, for example, an SSRI and an SNRI, it would therefore not be recommended that they have an additional SSRI or SNRI, limiting their treatment options.

Based on the CG90 recommendations, the clinical recognition that the relative efficacies of antidepressants may differ based on pre-treatment, with support from the systematic literature review findings in Appendix 6.2, there is potential uncertainty around all data sources when applying these to a 3rd line setting as none were undertaken in this population; in particular the majority of patients included in the analyses by Llorca (2014), Pae (2014) and SOLUTION (Wang et al. 2015) were predominantly treatment naïve.

3.4.1.3. Switch network

Lundbeck acknowledge the limitations regarding the switch network as raised by the ERG. It was highlighted that the network included heterogeneous patient populations at baseline including severity, limited evidence within the switch network leading to single trials supporting the comparisons, and differing assessment time point for outcomes.

However, there is no evidence of the effectiveness of vortioxetine used for the treatment of MDEs at 3rd line and onwards, andm through literature searches, Lundbeck has not been able to identify reviews of other products at this place in therapy. Based on external expert opinion, the switch network provides a better matched population to those at third line, compared to the other data sets in the overall MDD population, in which most patients are treatment naive.

3.4.1.4. Llorca (2014)

There are factors which limit the applicability of the evidence from this publication when considering the use to populate the cost-effectiveness model which have not yet been considered by the ERG or Committee.

Llorca (2014) presents results from a meta-regression based on the full MDD patient population (the vast majority being treatment naïve). As detailed in Section 3.4.1.2, this may limit the applicability of

the Llorca population to the 3rd line, who have already failed on two previous treatments, such as two SSRIs or an SSRI and SNRI.

In addition, the objective of the Llorca analysis was to estimate relative efficacy and tolerability of vortioxetine in major depressive disorder based on:

- standardised mean difference in change from baseline to 2 months for efficacy corresponding to the primary endpoint (MADRS or HAM-D) in each of the selected studies (primary analysis) and;
- rate of withdrawals due to adverse events for tolerability

The inclusion of studies in the systematic review undertaken, and therefore in the network, were based on the assessment of the outcomes above being possible. The assessment of response and remission at 2 months was only undertaken as sensitivity analyses. Due to this, as it is clearly stated in the original publication, *"a high number of studies included in the primary analyses have missing data for response and remission".* Consequently, the analyses have been conducted on a sub-sample of studies, affecting the number of patients in each analysis, and also the ability to provide results for some comparators (e.g. sertraline). As stated in the manuscript, and what is of huge importance, is that the missing outcome data for response and remission was mainly seen in *"failed studies (defined as studies with no statistical difference from placebo for the primary outcome)".* This therefore adds substantial reporting bias to the results and is highly likely to have an impact on the relative efficacy estimates as data were fully reported for all vortioxetine studies regardless of study outcome.

In addition, the ERG (ERG report) and Committee (ACD) felt there to be substantial heterogeneity in the patient population included in the switch network, with one of the reasons cited being the differences in baseline severity of patients (HAM-D scores between 21 and 31). With this in mind, the Llorca manuscript includes patients with baseline HAM-D scores ranging from 18-33.

For these reasons, Lundbeck considers the Llorca analyses to be inappropriate for providing adequate response and remission rates for the purposes of populating the current cost-effectiveness model in the 3rd line setting to address the decision problem.

3.4.1.5. Pae (2014)

As stated in the response to the Clarification Questions, the company believes the analysis undertaken by Pae is fundamentally flawed as it includes active reference arms as if they were active comparators. For reasons well explained in the Manufacturer's submission (Sections 1.4.1 and 2.8.2), the EMA (2013) has stated the comparison of efficacy between active reference and vortioxetine is invalid and the results cannot be considered reliable.

3.4.1.6. SOLUTION

SOLUTION was undertaken in the full MDD population; however it provides a direct comparison of vortioxetine to venlafaxine XR and therefore is of some relevance to the decision problem (a full summary of the study is provided in Appendix 6.3 in line with the requirements in the submission template).

SOLUTION is one of only three head-to-head randomised controlled trials (REVIVE and TAK318 being the only others). When considering the hierarchy of evidence, RCTs (and meta-analyses of) are the gold-standard method, ranking above the evidence from indirect treatment comparisons (NMHRC 2009). To assess the generalisability of the study to patients in England and Wales, the study was presented at an advisory board with key UK clinical experts, Dr Hamish McAllister Williams, Prof Guy Goodwin, Prof Cornelius Katona and Prof Allan Young (full report from the meeting along with biographies of the experts can be found in Appendix 6.4). This advisory board focussed only on the generalisability of SOLUTION and also the revised structure of the decision tree.

This group of UK experts believed that despite the study population being 100% East Asian the results were generalisable to MDD patients in England and Wales for the following reasons. Vortioxetine is extensively metabolised in the liver, primarily through oxidation catalysed by CYP2D6 and to a minor extent CYP3A4/5 and CYP2C9 (Brintellix SmPC, June 2015). In vitro and in vivo studies indicate that venlafaxine is biotransformed to its major active metabolite, ODV, by CYP2D6. In vitro and in vivo studies indicate that venlafaxine is metabolised to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4 (Effexor SmPC January 2015). Sistonen et al (2007) suggests that there is considerable variation of CYP2D6 within populations, but not between populations. Bradford (2002) found that Asians have a higher prevalence of a reduced function CYP2D6 allele, however since both vortioxetine and venlafaxine are primarily metabolised via CYP2D6 this should affect both venlafaxine and vortioxetine groups equally. Similarly any geographic variation in the CYP3A4 gene, which plays a minor role in the metabolism of both vortioxetine and venlafaxine, should affect both groups equally. A study in Asians and Caucasians (Mizutani et al 2003) found that in both populations, the poor metaboliser frequencies of the CYP3A4 and CYP2C9 were low. Thus geographic location per se, should affect the metabolism of vortioxetine and venlafaxine equally and the relative efficacy should be comparable in studies carried out in European and East Asian populations.

Though SOLUTION provides a robust indication of the relative efficacy of vortioxetine and venlafaxine XR, it is limited only to this comparison.

3.4.2. Q.2. How will the clinical data be adjusted to 3rd line?

Given that the ERG, the Committee, clinical opinion and Lundbeck agree there to be an absolute fall in efficacy at subsequent treatment lines, an adjustment was applied to ensure efficacy reflected that of a 3rd line and onwards positioning.

In line with the ERG's approach and the Committee's preference as stated in the ACD (page 47), the vortioxetine efficacy rates from REVIVE were adjusted to 3rd line based on the proportional reduction in efficacy between 2nd and 3rd line treatment observed in STAR*D (Rush, 2006). The odds ratios from each of the above considered data sets were then applied to provide comparative efficacy rates to other antidepressants (See Table 4 and Table 5).

3.5. Specifying treatment pathways in depression

A strict treatment pathway is unlikely to provide the optimal treatment strategy for a large proportion of patients with MDD. Firstly, treatments have diverse individual profiles, including differences in specific tolerability aspects, contraindications and cautions. In addition, patients are also highly individual, for example with regards to their preferences and previous treatment response for current and previous episodes (in terms of efficacy and tolerability). Therefore many treatments are not suitable for many patients.

Faced with this heterogeneity on both levels (treatments and patients), a clinician has to match the treatment to the individual; an approach supported by both guidelines (NICE 2010, Bauer et al. 2013, Anderson et al. 2008) and expert clinical opinion. In the majority of cases, patients who receive a 3rd line or later treatment are seen by a clinician with expertise in mental health such as a GP with a special interest in depression and previous experience in harder to treat patients or a psychiatrist.

It is challenging to account for the factors associated with patients and treatments, and the consequential clinical judgements based on these in a cost-effectiveness analysis. Firstly, these subtleties are not necessarily captured in clinical trial data. In addition, the relevant comparators will change according to specific patient's history/pathway.

3.5.1. Safety and tolerability of vortioxetine – consideration outside of the economic modelling

3.5.1.1. Safety and tolerability

Clinical opinion has supported that, for patients who have been unable to tolerate previous treatments, an antidepressant with a more favourable tolerability profile should be switched to.

It has been recognised by the ERG (ACD pg. 22) and Committee, that though the data are limited, "vortioxetine may have a better safety profile than other antidepressants" (ACD pg. 41.). This is supported by the unadjusted rates of adverse events associated with each of the comparators applied within the model.

Although the favourable tolerability of vortioxetine has been reflected in the model to some extent, not all implications could be included. For example, the impact on decreased compliance to treatment, and the impact on premature cessation of treatment on clinical outcomes such as recurrence, have not been considered. In addition, the lack of discontinuation symptoms associated with vortioxetine compared to all other antidepressants apart from agomelatine (Taylor 2015) have not been included in terms of either their impact on HRQoL or decrease in follow-up consultations where close monitoring of down-titration is necessary.

In addition, a patient's profile, previous treatment history including previous side-effects, and a patient's preference, determines the choice of suitable treatment options. Consequently, at later treatment lines the number of appropriate comparators will lessen. Therefore modelling this explicitly proves challenging without increasing uncertainty in the results as a vast number of additional assumptions would be required to support this.

3.5.1.2. Particular safety considerations: Contraindications and cautions with other antidepressants

Patient safety when choosing any treatment should be a primary consideration. There are cautions and contraindications associated with certain treatments relating to QTc prolongation and blood pressure (Table 3 includes details from product specific SmPCs). For the patients these refer to, some treatments will not be valid options anywhere in the pathway, therefore stipulating them before the use of vortioxetine or as relevant comparators to vortioxetine at 3rd line and onwards is inappropriate.

QTc Prolongation

Although congenital long QT syndrome is fairly rare (roughly 1 in 2500 live births, (Orphanet.com 2008), the list of products known to prolong QT intervals are fairly extensive and includes commonly used treatments (see Table 30 included in Appendix 6.5).

In clinical practice, the co-medication contraindications and cautions linked to QTc prolongation stipulated for the most commonly used SSRIs and SNRIs in the NHS limit the treatment options for those patients affected. Additional pharmacological treatments which are not associated with QTc prolongation, such as vortioxetine are therefore important treatment options.

Hypertension and blood pressure

Table 3 shows there are cautions and contraindications associated with hypertension and blood pressure for the SNRIs. For patients with hypertension who have failed on previous SSRI therapy, vortioxetine could provide a viable, well-tolerated and safe treatment alternative.

In addition to the contraindication associated with the SNRIs in patients with uncontrolled hypertension additional blood pressure monitoring is required for both duloxetine and venlafaxine. The cost of this is not factored in to any economic modelling Lundbeck have currently presented.

Table 3: Antidepressant contraindications and cautions: QTc prolongation, hypertension and blood pressure

Antidepressant	QTc prolongation	Hypertension and blood pressure
Vortioxetine	None	None
Citalopram	Contraindicated in patients with known QT prolongation Contraindicated with products known to prolong QT interval	None
Duloxetine	None	Initiation should not occur in patient with uncontrolled hypertension. Caution in patients with hypertension and/or other cardiac disease. BP monitoring recommended.
Escitalopram	Contraindicated in patients with known QT prolongation Contraindicated with products known to prolong QT interval	None
Fluoxetine	Should be used with caution in patients with congenital long QT syndrome, a family history of QT prolongation or other clinical conditions that predispose to arrhythmias (e.g. hypokalemia and hypomagnesemia, bradycardia, acute myocardial infarction or uncompensated heart failure). If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.	None
Sertraline	Should be used with caution in patients with risk factors for QTc prolongation.	None
Venlafaxine	All patients should be carefully screened for high blood pressure and preexisting hypertension should be controlled before initation of treatment. Blood pressure should be reviewed periodically, after initiation of treatment and after dose increases. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure, e.g., those with impaired cardiac function. The balance of risk and benefits should be considered before prescribing venlafaxine to patients at high risk of serious cardiac arrhythmia or QTc prolongation.	Initiation should not occur in patients with uncontrolled hypertension. Caution in patients with hypertension and/or other cardiac disease. BP monitoring recommended.

Source: Individual product SmPCs.

3.5.1.3. Conclusions

As stated above, the specification of a strict treatment pathway within MDD is unlikely to provide one single and optimal treatment strategy for the majority of patients. The heterogeneity at the patient and treatment level limits the appropriate treatment options considered appropriate. Therefore, a greater array of pharmacological options, especially those which are different in terms of tolerability profile, provide valuable alternatives, particularly within later lines of treatment.

For the reasons provided within this section, certain aspects of vortioxetine's favourable safety and tolerability profile cannot be explicitly modelled. However, these benefits are expected to translate into clinical and economic benefits.

3.6. Revised model structure and parameterisation

3.6.1. Revised model structure

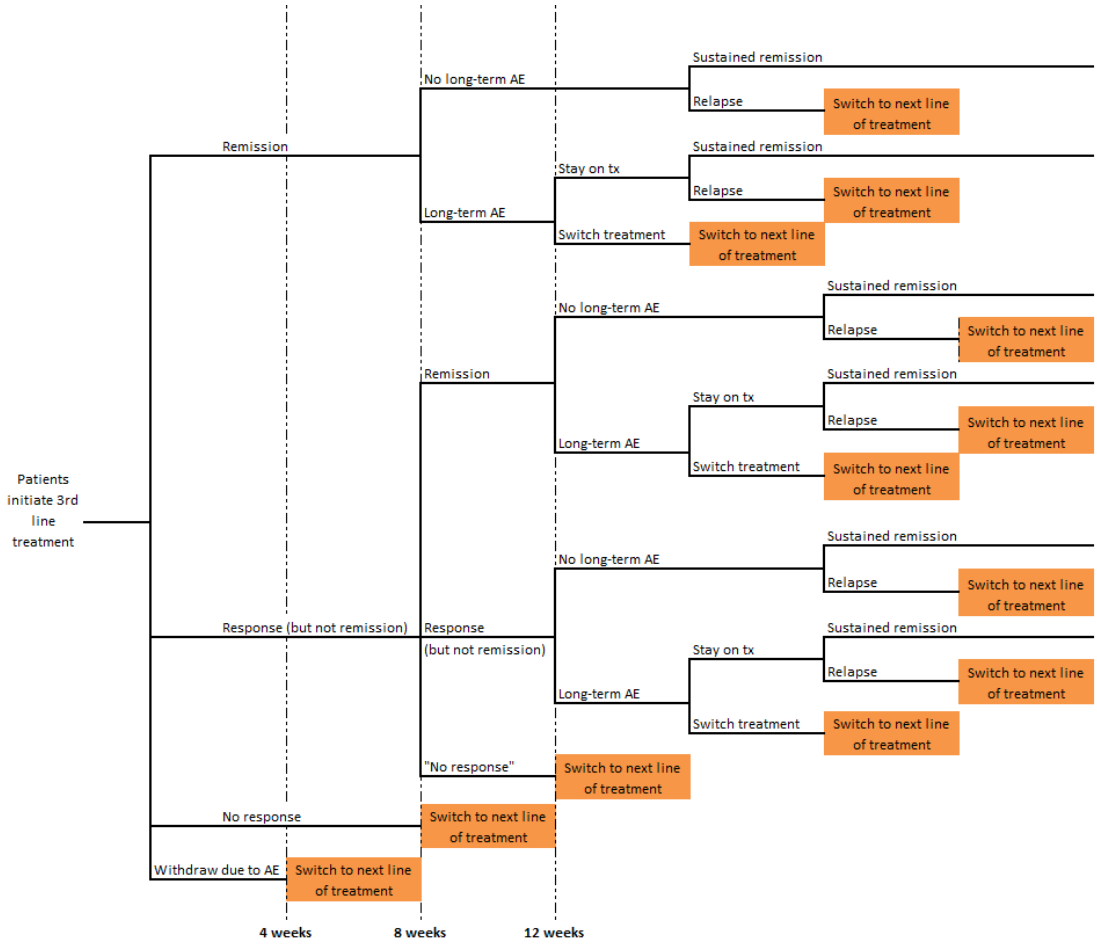
Lundbeck have updated the model structure to include both response and remission as efficacy endpoints to respond the Committee's requests. Figure 2 and Figure 3 provide an overview of this revised structure.

The structure of the decision tree has been adapted from the model presented in the Trivedi et al. publication (2004). In addition, to further inform and validate the model structure, a comprehensive review of both national and local guidelines, along with current clinical practice through both questionnaires and an advisory board have been undertaken (Section 3.6.2 provides further detail).

The main structural change is that a patient is now able to take one of three efficacy pathways at 8 weeks post treatment initiation: **remission, response but no remission (*herein known as response*), or no response**; or the patient could **discontinue due to adverse events**. In addition, in line with the Committee's requests the time horizon has been extended to 24 months. Discounting of both costs and QALYs has been applied in the second year.

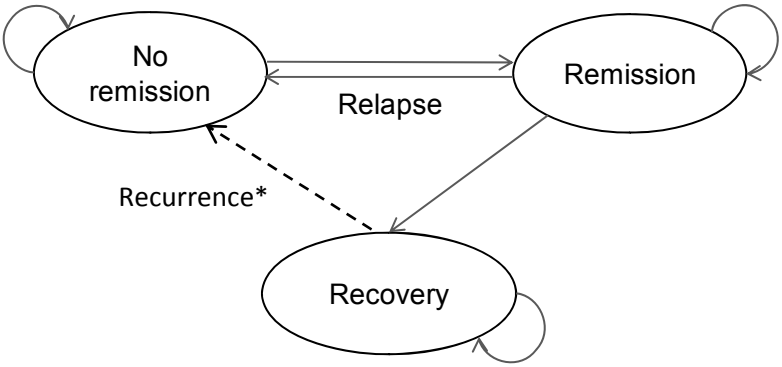
The clinical support and rationale for the changes from the original model structure are provided explicitly in Section 3.6.2.

FIGURE 2: REVISED DECISION TREE STRUCTURE



n.b. Patients in sustained remission can enter the recovery phase. In this phase a patient's depression can recur in some analyses. Should this occur patients would then start 4th line tx. Abbreviations: AE: Adverse event, tx: treatment.

FIGURE 3: MARKOV STRUCTURE - SUBSEQUENT TREATMENT LINES (4+)



*Applicable for specific analyses only

3.6.1.1. Decision tree

3.6.1.2. Pathway for patients achieving remission at 8 weeks

Patients in remission are assumed to continue in remission entering the maintenance phase which lasts up to either 6 or 22 months depending on the analyses. This assumption is a simplification of reality but is generally supported by clinical expert opinion (see Appendix 6.4) and evidence available from the period between 8 and 12 weeks in REVIVE. Up to 22 months is specified as the longest period a patients could be in the maintenance phase as the soonest a patient is able to reach remission is 8 weeks. Of patients who achieved remission at week 8, only 7% of these were no longer in remission at week 12: 3% had moved into the response health state and 4% had experienced an early relapse, moving to the non-response health state. Based on these data, Lundbeck is confident that the cost-effectiveness estimates will not be materially affected by the simplification of the remission arm at week 8.

As stated above, within the decision tree, patients who achieve remission at 8 weeks continue into the maintenance phase. Once a patient has entered the maintenance phase they are subject to a risk of relapse (treatment independent) and a treatment specific risk of long-term adverse events which may lead to treatment withdrawal (25% probability of withdrawal if a long-term event is experienced, informed by clinical opinion as in the original model). In both of these cases the patient will stop treatment and move on to a 4th line therapy. In the analyses that look at a 6 month maintenance phase (Analyses sets 1, 3 and 4) rather than treatment with a single antidepressant for up to 22months in the maintenance phase (Analyses sets 2 and 5)) patients can then enter the recovery phase where they may be subject to a risk of recurrence. Should this occur they will then re-enter the Markov model at the next line of treatment in the no-remission health state.

3.6.1.3. Pathway for patients in response at 8 weeks

The revised model structure allows patients to continue on treatment after achieving response at week 8. In this case a patient will be reassessed at week 12; these patients may subsequently achieve remission, continue in response or return back to depression. In line with the advice received from the NICE team, ERG and Committee, the week 12 conditional probabilities have been informed by analysing this population within REVIVE, providing non-treatment specific estimates for these transitions between week 8 and week 12 (See Table 6).

If a patient has achieved remission or is in response at week 12 they will enter the maintenance phase of the model in their respective health states. In this phase these patients will continue on treatment where they will be at risk of long-term adverse events which may lead to treatment discontinuation (25% probability of treatment switch) or relapse. Patients who discontinue for either of these reasons will switch treatments, and will hence enter the Markov model. Patients who complete the maintenance phase in remission or response will enter the recovery phase where they may be subject to a risk of recurrence (Analyses set 1).

If at 12 weeks the patient has moved from response to no response they are switched to another line of therapy entering the Markov portion of the model at this point.

3.6.1.4. Pathway for patients in no response at 8 weeks

If patients have not achieved response or remission (and have not discontinued due to AEs) at week 8 they are assumed to be switched to the next line of therapy, entering the Markov section of the model at week 8.

3.6.1.5. Pathway for patient withdrawing due to short-term adverse events (STAE)

As in the original model, withdrawal due to STAEs occurs at week 4 in the model. These patients then enter the Markov portion of the model.

The rate of withdrawals due to STAEs is independent of the rates of individual STAEs.

3.6.1.6. Markov model

Patients that switch to fourth and subsequent lines of treatment, whether in the acute phase or the maintenance phase following remission or response, enter the recursive Markov part of the model. Here, in a given cycle patients may either remain in no-remission or achieve remission. Patients discontinuing treatment due to long-term adverse events after reaching remission or response at week 12 are assumed, as in the initial model, to start in the remission health state of the Markov model. In the following cycles, patients who have achieved remission may sustain remission for up to 6 or 22 months dependent on the maintenance phase length scenario applied after achieving remission, or if a patient relapses. Once patients have sustained remission for the maintenance period, they then move to recovery where they will no longer receive treatment. In some analyses, they are at risk of recurrence of their depression within the recovery phase (Analyses sets 1 and 4). After recurrence, patients are assumed to switch to the next line of treatment.

3.6.2. Justification and validation of structure and sensitivity analyses to UK clinical practice

The Committee was mainly concerned with how the efficacy outcomes were included in the model. Firstly, regarding the time point at which a switch of treatment occurred in case of lack of efficacy, and secondly, whether all clinically relevant efficacy outcomes were included (i.e. response and remission). Therefore, these were the focus of Lundbeck's review of further information regarding clinical practice from the following sources to inform and validate the model structure:

- National and local clinical guidelines (Section 6.6.2 and 6.6.3) (Appendix 6.6)
- A questionnaire on the treatment and management of depression focussing mainly of clinical triggers for switching antidepressants (Appendix 6.6.4 and 6.7)
- An advisory board with 4 leading UK clinical experts (Dr Hamish McAllister Williams, Prof Allan Young, Prof Guy Goodwin and Prof Cornelius Katona) (full report can be found in Appendix 6.4)
- Additional analyses of individual patient level data from REVIVE where appropriate

Based on this, the four distinct pathways (i.e. remitters, responders, non-responders and patients who withdraw due to STAEs) were included with the model. In addition, these sources provided further information on the timing of switching decisions, length of maintenance treatment and also treatment setting.

3.6.2.1. Remitters

There was unanimous agreement between sources that remitters would be continued on treatment. As the clinical data available for this was available at week 8 this assumption remained as in the original model.

3.6.2.2. Responders (but not remitters)

The revised model structure now assumes that patients in response at week 8 are continued on treatment until week 12, at which point they are assessed and categorised in the following health states: remission, response (but not remission) and non-response. This aligns broadly to the national guidelines which state that switching antidepressants should be undertaken if response is still not adequate at 8 weeks (NICE 2009) or where only minimal improvement has been achieved (British Association for Psychopharmacology (BAP), 2015). Through the questionnaire responses, and also on discussing with UK clinical experts at the advisory board to validate the model structure, it is clear that for some patients response (as defined in the model by a ≥50% reduction in symptoms) is an adequate treatment outcome and hence patients would be continued on treatment if in response at 8 and 12 weeks after initiation. This branch was explored in detail with the clinical experts who took part in the advisory board (see appendix 6.4 for full report). They agreed that the structure was reflective of the approach that would be taken in clinical practice.

3.6.2.3. Non-responders

The non-responder population incorporates patients with no response through to patients with less than a 50% reduction in symptoms.

The national guidelines (BAP and NICE) both suggest that if there is a complete absence of response a patient should be switched at 4 weeks. However the BAP guideline does suggest that a longer treatment period should be given if a patient has failed multiple previous treatments. Local guidelines agree with this to some extent, with one suggesting the dose should be increased at 4 weeks if advised in the British National Formulary (BNF), with the patient being reassessed 4 weeks later. In addition, both guidelines suggest that if there has been at least some level of improvement the patient should be continued for another 2-4 weeks (up to 6-8 weeks). In general the national and local guidelines are supported by clinical practice – the responses to the questionnaires highlighted the same range of around 4-8 weeks and the experts at the clinical advisory board felt 8 weeks was representative. If at this point a patient still has not achieved an adequate response then they should be switched.

In view of this insight, the model implements a switch due to initial non-response at week 8 in line with the clinical data available. The advisors at the advisory board also supported the switching of patients at week 8.

3.6.2.4. Withdrawals due to STAEs

All sources of clinical insight supported the switching of patients due to the STAEs at 4 weeks (though there was not a specific question regarding this in the clinical questionnaire surveyed/conducted).

In addition, an analysis of REVIVE was also undertaken which showed that of all the patients who had withdrawn due to adverse events at week 8, approximately 83% of those had withdrawn by week 4; this figure fell slightly to 76% of patients when looking at week 12 drop outs. In addition the mean time to withdrawal due to adverse events was 15 days in the 8 week population and 19 days in the 12 week population.

Patients withdrawing due to adverse events are assumed to be in the no response health state. This assumption is supported by an analysis of the REVIVE population where 100% of patients withdrawing due to adverse events were observed to be non-responders.

3.6.2.5. Length of maintenance treatment

The length of maintenance treatment in the model was also a point that the Committee requested to be explored. The guidelines provided limited recommendations, mainly stating that a patient should be reviewed after 6 months to assess whether treatment should be continued. NICE CG90 suggests that if a patient is high risk then up to 2 years of treatment should be considered. This is in line with the request from the Committee (ACD pg. 4).

The clinician's responses received to the questionnaire suggest that there is a mixture of opinion in clinical practice – some stating 4-6 months treatment is adequate and others stating up to 3-5yrs to lifetime depending on number of previous episodes.

In order to assess the average length of treatment overall, patients from IMS Heath's Longitudinal Patient Data set were analysed. The data shows that the average length of treatment for patients treated with an antidepressant, and who have a diagnosis of depression in their record, is 475.5 days – approximately 1 year and 3 months (IMS 2015).

Based on these sources, Lundbeck are presenting analyses looking at both up to 6 months (Analyses sets 1, 3, 4 and 6) and up to 22 months maintenance treatment (Analyses set 2 and 5).

3.6.2.6. Referrals to a specialist

The national and local guidelines provide recommendations suggesting that patients who are high risk or who have failed 2-3 previous treatments should be referred to a specialist. They give no guidance on when a patient should be referred back to primary care.

The clinicians' responses to the questionnaire indicate that patients would receive on average 2-3 treatments before being referred to a specialist. Based also on these responses, referral back out to primary care would generally occur when response to treatment has occurred.

Due to the model structure in place from the original model and the set time constraints on running the analyses, Lundbeck decided to run two scenario analyses: one with initiation and maintenance in primary care and the second, with initiation and continuation in secondary care.

3.6.3. Inputs

Patients entering the revised cost-effectiveness model are now assumed to have experienced inadequate response to 2 previous antidepressants. In addition, as the decision tree health states now include response (but not in remission) along with all other states included in the original structure, the re-parameterisation of the efficacy, costs and resource use inputs were necessary.

The tables with the inputs previously included in the Manufacturer's submission or within the ERG report are included in Appendix 6.8 for the sake of readability.

3.6.3.1. Efficacy

0-8 week efficacy

To calculate the relative efficacies at 3rd line the following steps were taken:

1) The vortioxetine rate of remission and no response were adjusted to 3rd line based on the proportional reduction observed in STAR *D between 2nd and 3rd line treatments as

Table 4: Adjustment of REVIVE remission and no response probabilities based on STAR*D

Line	Remission probability		No response (1-response) probability	
	STAR*D	REVIVE – vortioxetine	STAR*D	REVIVE – vortioxetine
2nd	30.6%	40.5%	71.5%	38.5%
3rd	13.7%	18.13%*	83.2%	44.8%*^

*Proportional reduction in efficacy from 2nd to 3rd line applied from STAR*D.
^rates of withdrawals due to AEs subtracted from this.

2) Odds ratios from the different sources explored were applied to the rates of remission and no response

3) 3rd line-adjusted response rates were calculated as follows:
   Pr(response) = 1- Pr(remission) – Pr(no response)

4) Rates of withdrawals due to AEs were subtracted directly from the proportion of patients in no-response based on clinical opinion and an analysis of REVIVE which showed all patients withdrawing due to AEs remained in no response.

Based on the above calculations Table 5 summarises the input parameters for the 0-8 week period of the decision tree.

Table 5: Model parameters – 0-8 weeks: efficacy and withdrawals due to AEs

Model parameter inputs: 0-8 week efficacy & withdrawals due to adverse events												
Efficacy data		**Patient population: Third-line**										
		Par efficacy		**SOLUTION (Wang et al 2015)**		**Switch Network (Manufacturer's submission, Feb 2015)**		**Llorca et al. (2014)**		**Pae et al. (2014)**		
		Rate (%)	**OR**	**Rate (%)**	**OR**	**Rate (%)**	**OR**	**Rate (%)**	**OR**	**Rate (%)**	**OR**	
REMISSION - 8 & 12 weeks	Vortioxetine	18.13%	-	18.13%	Ref	18.13%	Ref	18.13%	Ref	18.13%	Ref	
	Agomelatine	18.13%	-			11.96%	1.63	15.36%	1.22	10.49%	1.89	
	Sertraline	18.13%	-			10.25%	1.94					
	Venlafaxine	18.13%	-	17.15%	1.07	14.95%	1.26	24.33%	0.69	19.40%	0.92	
	Citalopram	18.13%	-			10.15%	1.96					
	Escitalopram	18.13%	-					18.28%	0.99			
	Duloxetine	18.13%	-					19.86%	0.89	24.04%	0.7	
RESPONSE, NO REMISSION at 8 weeks*	Vortioxetine	37.07%	-	37.07%		37.07%		37.07%		37.07%		Rates below are calculated from PAE OR applied to initial vortioxetine response rate
	Agomelatine	37.07%	-			28.87%		38.74%		29.90%		
	Sertraline	37.07%	-			18.66%						
	Venlafaxine	37.07%	-	32.49%		15.78%		36.64%		35.05%		
	Citalopram	37.07%	-			Not reported						

	Escitalopram	37.07%	-					41.09%				
	Duloxetine	37.07%	-					38.12%		40.39%		
NO RESPONSE at 8 weeks	Vortioxetine	44.80%	-	38.16%	Ref	38.87%	Ref	38.30%	Ref	38.87%	Ref	44.80%
	Agomelatine	44.80%	-			49.67%	1.80	41.50%	1	50.11%	0.55	59.61%
	Sertraline	44.80%	-			44.19%	3.00	82.62%	1.3			
	Venlafaxine	44.80%	-	36.20%	1.25	41.07%	2.80	21.42%	1.3	28.47%	0.97	45.55%
	Citalopram	44.80%	-			Not reported						
	Escitalopram	44.80%	-					34.85%	1.2			
	Duloxetine	44.80%	-					33.52%	1.12	29.02%	1.47	35.57%
Withdrawals due to Adverse events	Vortioxetine	5.93%		6.64%		5.93%		6.50%		5.93%	Ref	
	Agomelatine	9.50%				9.50%		4.39%		9.50%	0.6	
	Sertraline	26.90%				26.90%		17.38%				
	Venlafaxine	28.20%		14.16%		28.20%		17.62%		17.08%	0.306	
	Citalopram	28.20%				28.20%						
	Escitalopram	28.20%						5.77%				
	Duloxetine	28.20%						8.50%		6.55%	0.9	

*1-(Pr(no response, no remission)-Pr(remission)-Pr(withdrawal due to AE))

8-12 week efficacy

In order to populate the efficacy outcomes between 8 and 12 weeks for patients in response at week 8, Lundbeck reanalysed data from REVIVE, following the advice received from the ERG, NICE team and Committee. Table 6 details the conditional probabilities observed in REVIVE. Within the model these are applied to all treatments and therefore are not considered to be treatment specific.

An example of how to interpret the table is as follows: Patients in response at week 8 have a 59.52% probability of being in remission at week 12.

Table 6: Model parameter inputs: Conditional 12 week probabilities for response cohort at 8 weeks

	Efficacy data	Value	Source
Conditional 12 week probabilities	Remission	59.52%	REVIVE
	Response	32.14%	REVIVE
	No response	8.33%	REVIVE

Recurrence while in recovery

Recurrence was considered for patients who reach recovery. To inform recurrence a paper by Hardeveld (2013) was used. This publication was the only one identified through a literature search which provided data on recurrence rates after treatment. This was a study conducted in the Netherlands. It investigated the risk of recurrence after recovery from MDD. In this paper estimates were provided for periods over 5, 10 and 20 years. After investigating the data, the 10 year period was found to have the greatest certainty in results. The recurrence probability at 10 years was reported to be 23.20%. This value was adjusted for two months to reflect the cycles of the existing model. The two month probability applied in the model was 0.439% (See Equation 1 and Equation 2 below). It was assumed that all patients who reach recovery remained in this recovery state for two months before the risk of recurrence was applied.

Equation 1. Calculating the one month rate:

$$-[\mathbf{ln}(\mathbf{1}-\mathbf{23.20}\%)]/\mathbf{120}\ \boldsymbol{months}=\mathbf{0.0022}$$

Equation 2. Converting to a two month probability:

$$\mathbf{1}-\boldsymbol{EXP}(-\mathbf{0.0022}*\mathbf{2})=\mathbf{0.439}\%$$

3.6.3.2. Safety and tolerability

The safety and tolerability rates in the majority of analyses were taken from the same sources as in the ERG's and Manufacturer's original analyses (See Table 32 in Appendix 6.8). This is with the exception of the SOLUTION analyses for which the rates taken from the clinical trial, and hence the same source as the efficacy inputs for this analysis, are reported in Table 7. The assumptions applied by the ERG to the LTAEs for these comparators are used in the updated model structure.

Table 7: SOLUTION: Short-term adverse event rates

Side-effect	Treatment	Probability	Source
Sexual dysfunction	Vortioxetine	0.95%	SOLUTION
	Venlafaxine	3.10%*	SOLUTION
Dry mouth	Vortioxetine	5.69%	SOLUTION
	Venlafaxine	10.62%	SOLUTION
Nausea	Vortioxetine	24.17%	SOLUTION
	Venlafaxine	23.45%	SOLUTION
Sweating	Vortioxetine	1.42%	SOLUTION
	Venlafaxine	3.98%	SOLUTION
Somnolence	Vortioxetine	2.84%	SOLUTION
	Venlafaxine	4.87%	SOLUTION
Headache	Vortioxetine	8.06%	SOLUTION
	Venlafaxine	6.64%	SOLUTION
Diarrhoea	Vortioxetine	3.79%	SOLUTION
	Venlafaxine	2.21%	SOLUTION
Insomnia	Vortioxetine	2.37%	SOLUTION
	Venlafaxine	7.08%	SOLUTION
Dizziness	Vortioxetine	8.06%	SOLUTION
	Venlafaxine	12.83%	SOLUTION

Source: SOLUTION CSR (2013)

- A rate of zero has mistakenly been used in the modelling. This is expected to bias against vortioxetine and therefore provide conservative estimates of the cost-effectiveness vs. venlafaxine

3.6.3.3. Utility values

Due to the restructuring of the model to include both response and remission health states, REVIVE was reanalysed providing the utility values for all the health states in the revised model. The disutilities associated with adverse events have not been updated from the original submission and are therefore included in Appendix 6.8 in Table 33 .

Table 8: Response/remission model parameter inputs: healthcare resource utilisation

Utilities		Base-case	
		Value	Source
Acute phase 0-8 weeks	Depression at baseline	0.54	REVIVE
	Remission	0.85	REVIVE
	Response without remission	0.76	REVIVE

	No response	0.56	REVIVE
Acute phase 8-12 weeks	Remission	0.85	REVIVE
	Response without remission	0.76	REVIVE
	No response	0.56	REVIVE
Maintenance phase	Remission	0.85	REVIVE
	Response without remission	0.76	REVIVE
	Relapse	0.56*	REVIVE (no response)
	Recovery	0.85	REVIVE
	Recurrence	0.56*	REVIVE (no response)
	Dry mouth	0	
	Dizziness	0	
	Sweating	0	
	Weight gain	0.032	Dixon 2004, REVIVE CSR
*Please note, due to time constraints the formula could not be updated to return these patients to a baseline health states. Lundbeck do not believe this to have a material impact on the cost-effectiveness results.			

3.6.3.4. Costs

Treatment costs have not been updated from the previous models (both Manufacturer's and ERG's).

Table 9: Treatment acquisition costs

INN and pharmaceutical form	Dose in acute phase	Dose in maintenance phase	Daily cost in acute phase	Daily cost in maintenance phase
Vortioxetine	10mg	16,47mg	£0.99	£0.99
Agomelatine tablets including LFT**	25mg	42,93mg	£1.46	£2.10
Sertraline tablets	50mg	135,5mg	£0.06	£0.10
Venlafaxine modified-release tablets	100mg	192,3mg	£0.24	£0.46
Citalopram tablets	20mg	51mg	£0.04	£0.06
Escitalopram	10mg	20mg	£0.06	£0.09
Duloxetine	60mg	120mg	£0.99	£1.98
Costs remain unchanged from previous models – aligned with those used in Manufacturer's ERG's model.				

3.6.3.5. Resource use

In the acute phase resource use will be taken from the PERFORM study, consistent with resource use data in the original model that was part of the NICE submission. Nevertheless, the definition of response in PERFORM is as follows:

- Patients in remission at 2 months
- Or at least 50% decrease from baseline on PHQ-9
- And if PHQ-9 was not available, at least 50% decrease from baseline on MADRS score

Therefore, patients who are classified in the response category may also be in remission. When the analysis of the UK population was run splitting the patients into remitters, responders (but not in remission), and non-responders (as required for the model structure presented in Figure 2), no patients were found to be in the responders (but not in remission) subgroup. It was therefore not possible to estimate the UK resource use associated with responders using the PERFORM study.

This problem also exists for the maintenance phase of the model. The originally submitted model used the Byford (2011) publication to populate the resource use in the maintenance phase for patients in remission or not. This publication does not provide a resource use analysis for responders and Lundbeck was unable to identify an alternative source providing this in the literature.

Due to the influence of the healthcare system structure on estimations of resource use Lundbeck believe it relevant to use only UK estimates for resource use. Therefore, in order to populate the resource use in the model for patients who are responders (but not in remission), assumptions are required. In line with the implicit assumptions made in the cost-effectiveness models used to underpin the CG90 model (NCCMH & NICE, 2010), analyses 1a, 2a and 3a (See Table 10) will consider that resource use associated with the response health state is equal to the resource use associated with the remission health state. The use of these estimates may lead to an underestimation of resource use for patients in response.

Sensitivity analyses will also be performed by assuming that the resource use for responders (non-remitters) is 30% higher than for patients in remission. Tabulated inputs are included in Appendix 6.8, Table 34 and Table 35.

3.7. Presentation of cost-effectiveness results

The results of the analyses are presented in this section and Appendix 6.10 and 6.11. For clarity, Table 10 (analyses for the response and remission model) and Table 11 (analyses for the remission model) provide a summary of the analyses conducted.

Table 10: Response and remission model: summary of analyses presented in the response document and Appendix 6.11.

Structure/inputs	Response and remission model								
	Analyses Set 1 Up to 6 months maintenance treatment; probability of recurrence			**Analyses Set 2** Up to 22 months maintenance			**Analyses Set 3** Up to 6 months maintenance; no risk of recurrence		
	1a [BC]	1b [AA]	1c [AA]	2a [AA]	2b [AA]	2c [AA]	3a [AP]	3b [AP]	3c [AP]
Maintenance treatment length									
Up to 6 months	x	x	x				X	X	x
Up to 22 months				x	x	x			
Recurrence									
Risk of recurrence in the recovery phase	x	x	x						
Resource use									
Response = remission	x	x		x	x		X	X	
+30% for response over remission			x			x			x
Treatment setting									
Primary care initiation and maintenance	x		x	x		x	X		x
Secondary care initiation and maintenance		x			x			X	

BC = Base-case; AA = additional analyses presented in this section; AP = analyses included in Appendix 6.11.
All analyses will be run for all data sets: Par efficacy (base-case); SOLUTION; Switch network; Llorca (2014) and Pae (2014)

Response and remission model

Analysis Set 1: up to 6 months maintenance phase including the probability of recurrence in the recovery phase

Analysis 1a)

- Resource use assumed the same for responders and remitters;
- treatment initiation and maintenance in primary care

Analysis 1b)

- as in 1a, but treatment initiation and maintenance in secondary care

Analysis 1c)

- as in 1a, but resource use for responders is assumed to be 30% greater than resource use for remitters

Analysis Set 2: up to 22 months maintenance phase

These sensitivity analyses look to explore the impact of an increase in length of maintenance treatment on the cost-effectiveness of vortioxetine (in comparison to analysis set 1).

Analysis 2a, 2b and 2c have the same variations as explained above for analysis set 1.

Analysis Set 3: up to 6 months maintenance phase with no probability of recurrence in the recovery phase. These sensitivity analyses look to explore the impact of recurrence on the cost-effectiveness of vortioxetine (in comparison to analysis set 1).

Analysis 3a, 3b and 3c have the same variations as explained above for analysis set 1.

The results from Analysis Set 3 are included in Appendix 6.11.

In addition to the results from the model including response and remission in the decision tree, the results from the original model structure are presented in Appendix 6.10. An overview of the analyses to be conducted is included in Table 11. This model has been updated with all the changes applied to the response and remission model as described in Section 0 and 3.6 apart from the changes made in relation to including response.

Table 11: Remission only model - overview of analyses presented in Appendix 6.10.

Structure/inputs	Remission model					
	Analyses Set 4		Analyses Set 5		Analyses Set 6	
Maintenance treatment length	4a AP	4b AP	5a AP	5a AP	6a AP	6b AP
Up to 6 months	x	X			X	x
Up to 22 months			x	x		
Recurrence						
Risk of recurrence in the recovery phase	x	X				
Resource use						
Response = remission +30% for response over remission	x	X	x	x	X	x
Treatment setting						
Primary care initiation and maintenance	x		x		X	
Secondary care initiation and maintenance		X		x		x

BC = Base-case; AA = additional analyses presented in this section; AP = analyses included in Appendix 6.10
All analyses will be run for all data sets: Par efficacy (base-case); SOLUTION; Switch network; Llorca (2014) and Pae (2014)

Remission only model

Analysis Set 4: up to 6 months maintenance phase including the probability of recurrence in the recovery phase

Analysis 4a)

- treatment initiation and maintenance in primary care

Analysis 4b)

- as in 4a, but treatment initiation and maintenance in secondary care

Analysis Set 5: up to 22 months maintenance phase

Analysis 5a and 5b have the same variations as explained above for analysis set 4.

Analysis Set 6: up to 6 months maintenance phase with no probability of recurrence in the recovery phase

Analysis 6a and 6b have the same variations as explained above for analysis set 4.

In all of the tables presented in the response dossier, the results for the par-efficacy analyses are presented in black, with all other exploratory analyses sets presented in grey.

When discussing cost-effectiveness in this section the assumption will be that an ICER no more than £20-30k per QALY gained is acceptable.

Two incremental analyses will be presented for each Analysis Set, one including all comparators, and in line with the ERGs approach, another excluding SSRIs based on the findings of the Papakostas publication and the recommendation in CG90 to switch to an alternative class of treatment at 3rd line. This could have also supported an incremental analysis excluding SSRIs and SNRIs however the only comparator remaining would be agomelatine – therefore this has not been presented explicitly but should be borne in mind when considering the pairwise results of vortioxetine vs. agomelatine. Further discussion around comparators based on CG90 have been presented in Section 3.3.1 and 3.4.1.2.

3.7.1. Base-case: Analysis set 1a: up to 6 months maintenance with a risk of recurrence in the recovery phase

The results of the base-case analysis are presented in Table 12 as both pair-wise analyses and an incremental cost-utility analysis with all comparators and one without SSRIs in addition to the pair-wise PSA results for vortioxetine vs. comparators. This table also provides the results from the non-base-case data sets.

Sections 3.7.1.3 to 3.7.1.7 contain the incremental cost-effectiveness planes for vortioxetine vs. comparators for analysis set 1a. In addition, Appendix 6.9 contains the associated pair-wise cost-effectiveness acceptability curves.

Due to time constraints, PSA were only conducted for the base-case analysis set however this was run for all data sets.

3.7.1.1. Par efficacy

Pairwise comparisons

Vortioxetine is a cost-effective treatment option vs. citalopram, escitalopram, sertraline, venlafaxine (dominant) and duloxetine (dominant). The ICER vs. agomelatine is £243,078.85 represents a

willingness to accept QALYs lost, rather than willingness to pay for QALYs gained, as vortioxetine is 0.001 QALYs less effective but approximately £170 cheaper.

The probabilistic sensitivity analysis (PSA) pair-wise comparisons show vortioxetine to be the most likely to be cost-effective versus all comparators at a cost per QALY threshold of both £20k and £30k. It is most likely to be cost-effectiveness versus duloxetine (probability of 72%), around 60-70% likely to be cost-effective versus citalopram, escitalopram, sertraline, and venlafaxine, and just over 50% likely to be cost-effective versus agomelatine.

Incremental – all treatments

The comparator associated with the lowest expected costs was citalopram, followed by escitalopram, sertraline, venlafaxine, vortioxetine, duloxetine and agomelatine, in ascending order. Sertraline, venlafaxine and duloxetine, being more expensive and less effective than at least one comparator, were eliminated by dominance. Agomelatine had an ICER of £243k making it a non-cost-effective treatment option.

Incremental –without SSRIs

Vortioxetine was the most cost-effective treatment option, dominating both venlafaxine and duloxetine. Agomelatine had an ICER of £243k making it non-cost-effective.

3.7.1.2. Other data sources

There was variation in the cost-effectiveness of all treatments when considering the other sources of efficacy inputs.

- SOLUTION: Vortioxetine dominated venlafaxine; PSA results showed vortioxetine to have a 87-88% chance of being cost-effective versus venlafaxine at a threshold of £20-30k per QALY respectively.

- Switch: Vortioxetine dominated sertraline, venlafaxine and agomelatine. There was around an 100% likelihood that vortioxetine would be cost effective vs. all comparators at both cost per QALY thresholds.

- Llorca: vortioxetine dominated duloxetine and agomelatine and was dominated by escitalopram and venlafaxine in pairwise comparisons. Escitalopram was the most cost-effective in the incremental analysis compared with all comparators given a threshold of £20-£30k; venlafaxine was the most cost-effective treatment when SSRIs were excluded from the analysis. However, pairwise PSA revealed that vortioxetine had a substantial probability of being cost-effective versus all comparators ranging (based on a £20k and £30k cost per QALY threshold) from 38-40% vs. escitalopram, 40-41% vs. venlafaxine, 53% vs. duloxetine and 54% vs. agomelatine. The PSA results show that when considering the Llorca data there is much uncertainty – no one comparator is certain to be the most cost-effective.

- Pae: in pair-wise analysis vortioxetine is dominant versus venlafaxine and agomelatine. The ICER vs. duloxetine is £42,099.14 but falls into the south-west quadrant and hence may be considered cost-effective. Assuming a threshold of £20-30k in both incremental analyses (all treatments and without SSRIs) duloxetine is the most cost-effective treatment option. The results from the pairwise PSA show vortioxetine to have a 71% probability of being cost-effective vs. venlafaxine, 98% versus agomelatine and 25% vs. duloxetine.

Table 12: Base-case – Analysis Set 1a (up to 6 months maintenance & recurrence risk in recovery): primary care initiation and maintenance

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI	Pairwise PSA – Pr(vortioxetine being CE)	
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)	k = £20k	k = £30k
BASE-CASE: PAR EFFICACY									
Citalopram	£1,341.88	1.414	£4,589.85	Ref	Ref	Ref	NA	63%	65%
Escitalopram	£1,347.28	1.414	£3,956.04	£5.40	-0.001	Dominated	NA	62%	65%
Sertraline	£1,357.42	1.412	£2,746.00	£10.13	-0.002	Dominated	NA	65%	67%
Vortioxetine	£1,399.00	1.427	NA	£41.58	0.015	£2,746.00	Ref	NA	NA
Venlafaxine	£1,399.52	1.410	Dominant	£0.52	-0.017	Dominated	Dominated	65%	67%
Duloxetine	£1,548.77	1.411	Dominant	£149.25	0.002	Dominated	Dominated	72%	72%
Agomelatine	£1,567.40	1.428	£243,078.85*	£18.63	0.016	£243,078.85	£243,078.85	52%	52%
SOLUTION									
Vortioxetine	£1,393.04	1.427	NA	Ref	Ref	Ref	Ref	NA	NA
Venlafaxine	£1,442.62	1.399	Dominant	£49.59	-0.03	Dominated	Dominated	87%	88%
SWITCH									
Vortioxetine	£1,399.00	1.427	NA	Ref	Ref	Ref	Ref	NA	NA
Sertraline	£1,647.51	1.330	Dominant	£248.51	-0.097	Dominated	NA	100%	100%
Venlafaxine	£1,649.27	1.336	Dominant	£1.76	0.006	Dominated	Dominated	100%	100%
Agomelatine	£1,689.66	1.380	Dominant	£40.39	0.043	Dominated	Dominated	98%	98%
LLORCA									
Escitalopram	£1,298.73	1.431	Dominated	Ref	Ref	Ref	NA	38%	40%
Venlafaxine	£1,331.06	1.431	Dominated	£32.34	0.001	£41,999.32	Ref	40%	41%
Vortioxetine	£1,393.99	1.427	NA	£62.93	-0.005	Dominated	Dominated	NA	NA
Duloxetine	£1,525.85	1.424	Dominant	£131.86	-0.003	Dominated	Dominated	53%	53%
Agomelatine	£1,581.72	1.424	Dominant	£55.87	-0.000	Dominated	Dominated	54%	54%
PAE									
Vortioxetine	£1,399.00	1.427	NA	Ref	Ref	Ref	Ref	NA	NA
Venlafaxine	£1,403.64	1.410	Dominant	£4.64	-0.017	Dominated	Dominated	71%	71%
Duloxetine	£1,469.16	1.445	£42,099.14*	£65.53	0.035	£3,878.30	£3,878.30	25%	25%
Agomelatine	£1,695.58	1.378	Dominant	£226.41	-0.067	Dominated	Dominated	98%	98%

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

3.7.1.3. Incremental cost-effectiveness planes – Analysis Set 1a: Par efficacy

Figure 7: Incremental cost-effectiveness plane - Par/equivalent efficacy: vortioxetine vs. citalopram

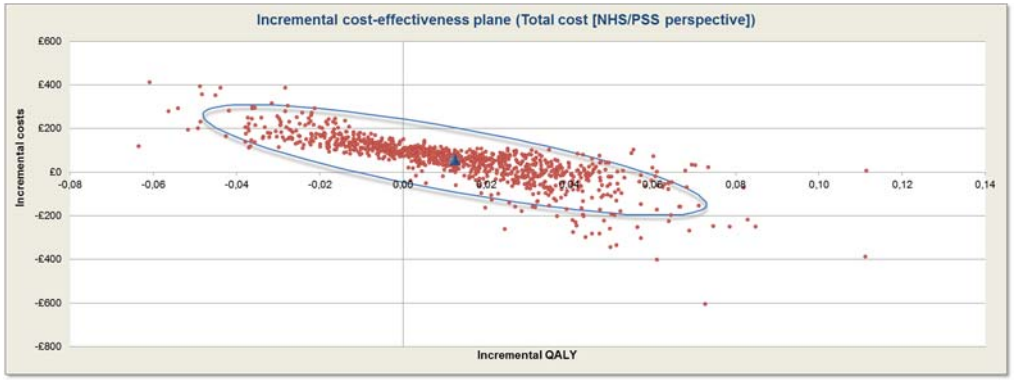


Figure 6: Incremental cost-effectiveness plane – Par/equivalent efficacy: Vortioxetine vs. escitalopram

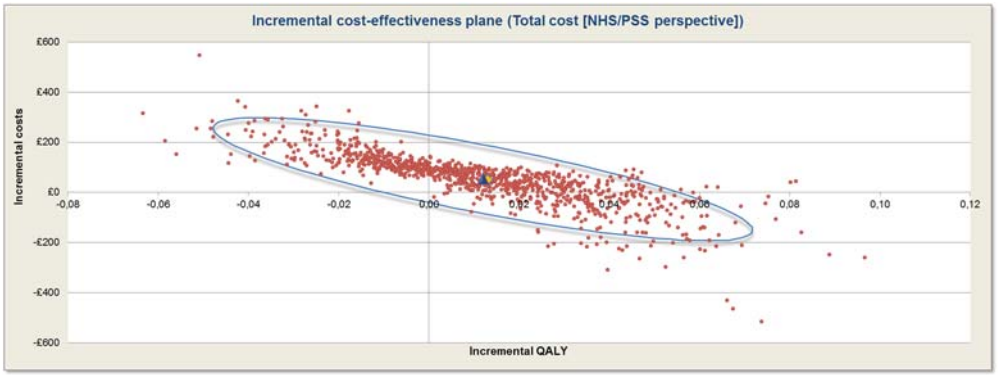


Figure 5: Incremental cost-effectiveness plane - Par/equivalent efficacy: vortioxetine vs. sertraline

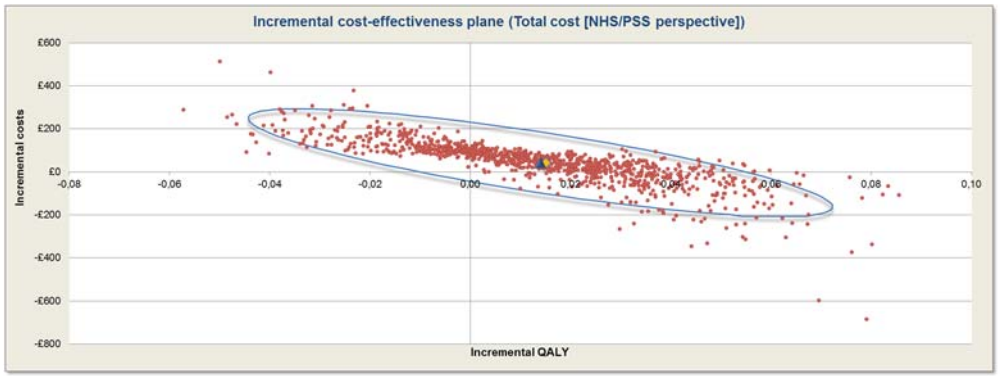


Figure 4: Incremental cost-effectiveness plane - Par/equivalent efficacy: vortioxetine vs. venlafaxine

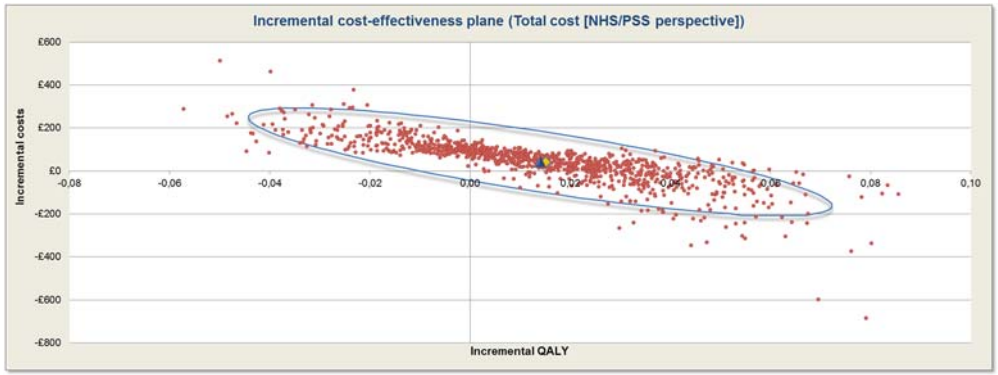


Figure 9: Incremental cost-effectiveness plane - Par/equivalent efficacy: vortioxetine vs. duloxetine

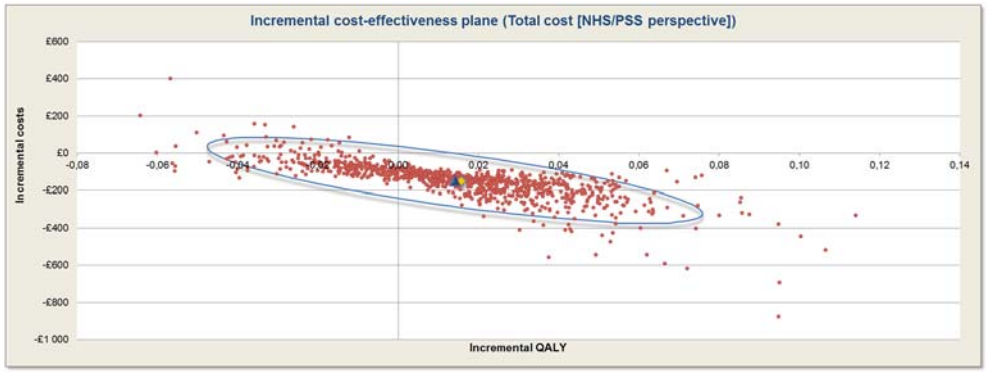
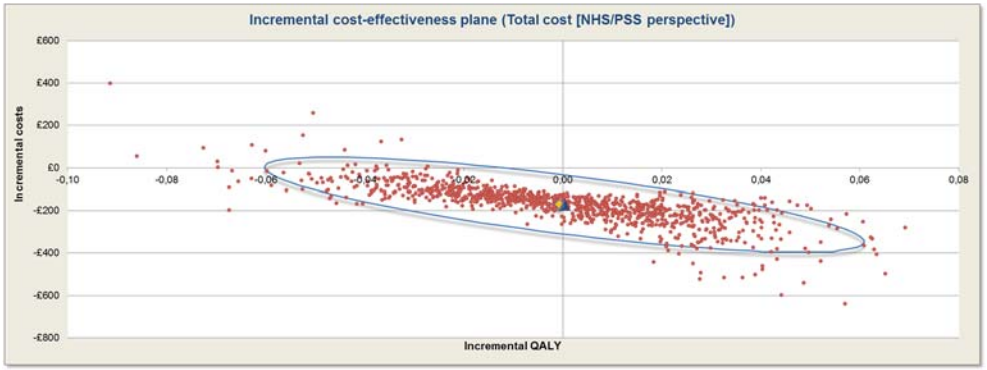
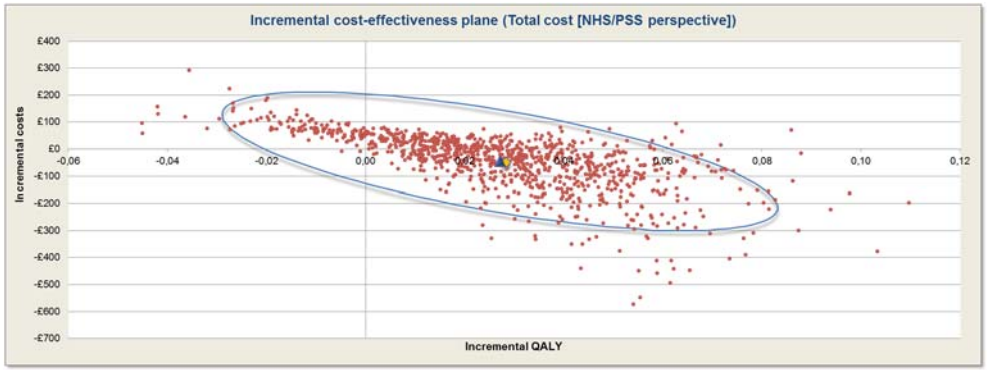


Figure 8: Incremental cost-effectiveness plane - Par/equivalent efficacy: vortioxetine vs. agomelatine



3.7.1.4. Incremental cost-effectiveness planes – Analysis Set 1a: SOLUTION

Figure 10: Incremental cost-effectiveness plane - Par/equivalent efficacy: vortioxetine vs. venlafaxine



3.7.1.5. Incremental cost-effectiveness planes – Analysis Set 1a: Switch network

Figure 12: Incremental cost-effectiveness plane – Switch network: vortioxetine vs. sertraline

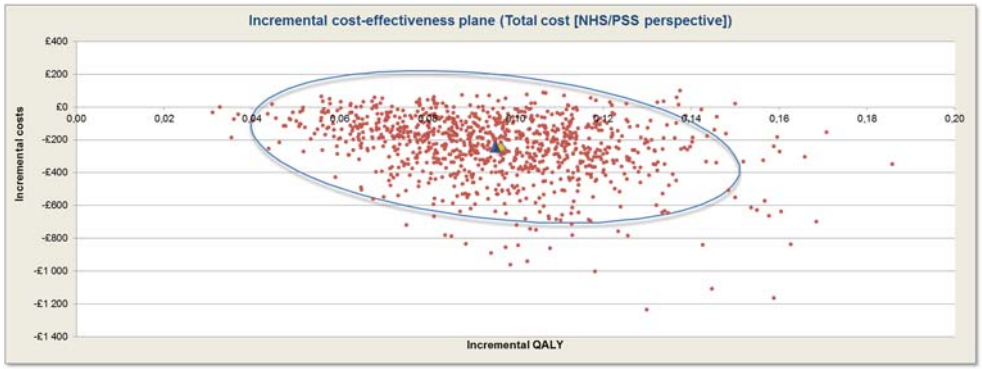


Figure 11: Incremental cost-effectiveness plane – Switch network: vortioxetine vs. venlafaxine

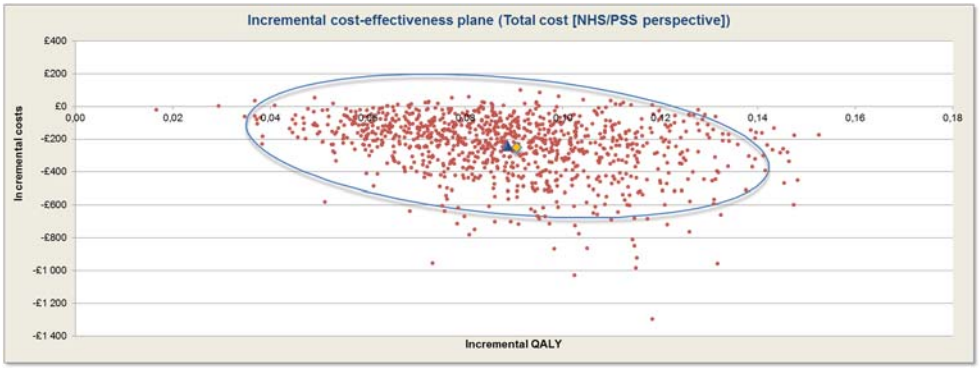
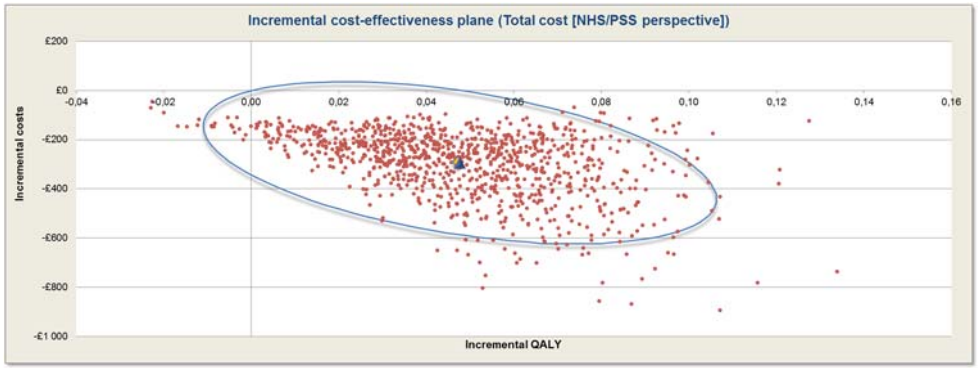


Figure 13: Incremental cost-effectiveness plane – Switch network: vortioxetine vs. venlafaxine



3.7.1.6. Incremental cost-effectiveness planes – Analysis Set 1a: Llorca

Figure 17: Incremental cost-effectiveness plane – Llorca: vortioxetine vs. escitalopram

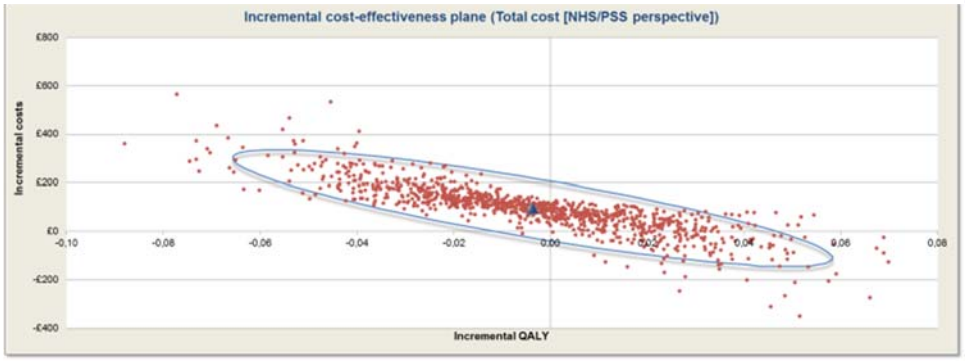


Figure 16: Incremental cost-effectiveness plane – Llorca: vortioxetine vs. venlafaxine

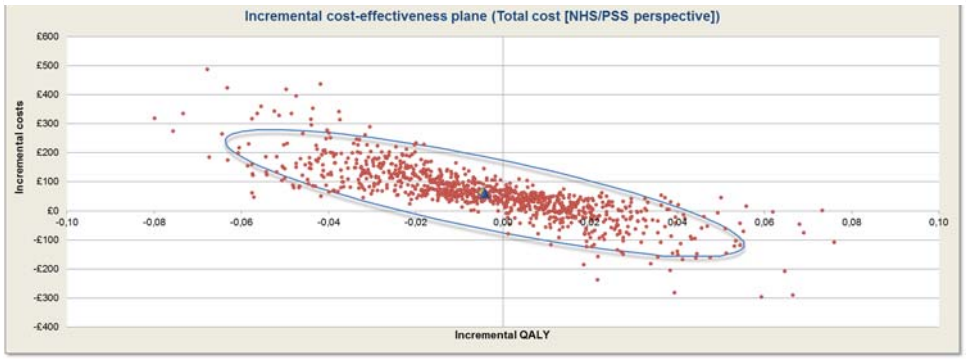


Figure 15: Incremental cost-effectiveness plane – Llorca: vortioxetine vs. duloxetine

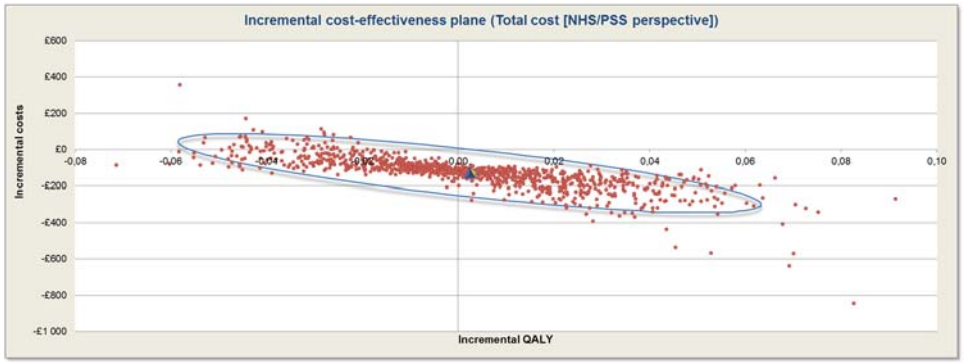
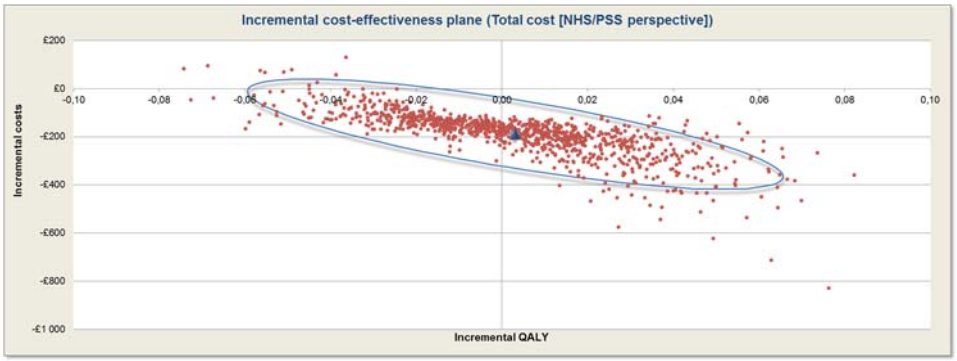


Figure 14 Incremental cost-effectiveness plane – Llorca: vortioxetine vs. agomelatine



3.7.1.7. Incremental cost-effectiveness planes – Analysis Set 1a: Llorca

Figure 18: Incremental cost-effectiveness plane - Pae: vortioxetine vs. duloxetine

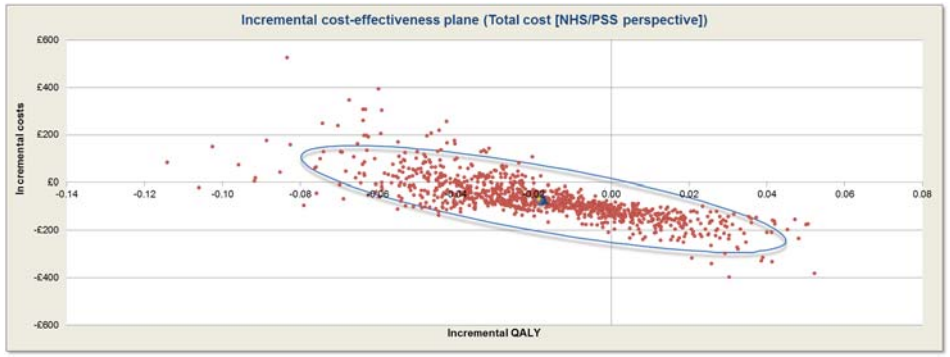


Figure 19: Incremental cost-effectiveness plane - Pae: vortioxetine vs. agomelatine

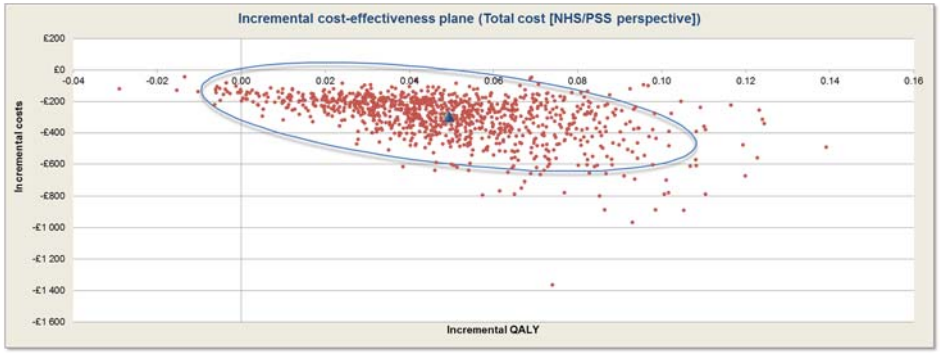
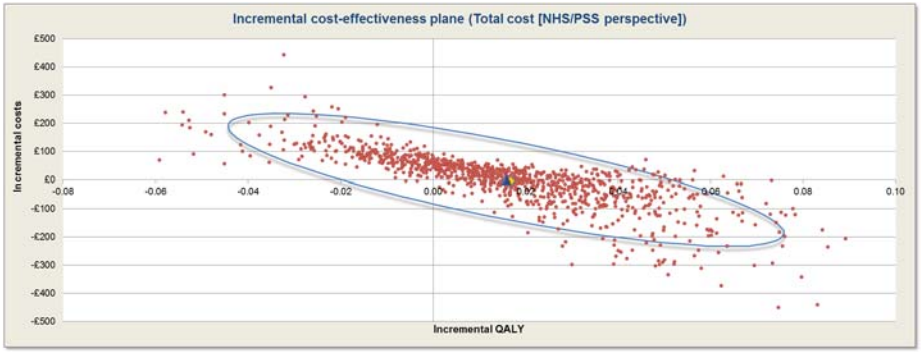


Figure 20: Incremental cost-effectiveness plane - Pae: vortioxetine vs. venlafaxine



3.7.2. Analysis set 2a: Maintenance treatment – up to 22 months – primary care treatment setting

Model 2a explores the impact of increasing maintenance treatment to 22 months, from 6 months in the base-case model. This increases the total cost of all treatments due to the increased drug acquisition costs and an increased risk of long-term adverse events (and associated cost), both due to the increased time of patients receiving medication. The total QALYs gained generally decreases due to the increase in long-term adverse events and also the increased cumulative risk of relapse (which has a higher probability than recurrence).

3.7.2.1. Par efficacy

The cost-effectiveness conclusions from all analyses in set 2a are similar to those in analysis 1a.

3.7.2.2. Other data sets

- SOLUTION – vortioxetine becomes cost-effective vs venlafaxine rather than dominating.
- Switch – vortioxetine is cost-effective versus sertraline and venlafaxine and dominant versus agomelatine. It remains the most cost-effective treatment option in the incremental analyses.
- Llorca – the cost-effectiveness conclusions remain unchanged.
- Pae – vortioxetine is cost-effective vs. venlafaxine and dominant vs. agomelatine. The ICER vs duloxetine shows vortioxetine to be non-cost effective as the £15k cost per QALY falls in the south-west quadrant. In incremental analyses duloxetine remains the most cost-effective option.

Table 13: Response and Remission Model Analysis 2a (up to 22 months maintenance): primary care initiation and maintenance

Technologies	Total costs	Total QALYs	Pairwise ICER ICER Vortioxetine vs. comparator	Incremental analyses Incremental costs	Incremental QALYs	All txs ICER incremental (QALYs)	w/o SSRI ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Citalopram	£1,658.91	1.408	£22,664.07	Ref	Ref	Ref	Ref
Escitalopram	£1,669.64	1.407	£20,627.65	£11	-0.001	Dominated	Ref
Sertraline	£1,682.31	1.405	£16,763.21	£13	-0.002	Dominated	Ref
Venlafaxine	£1,777.79	1.403	£8,845.57	£95	-0.002	Dominated	Ref
Vortioxetine	£1,922.57	1.419	NA	£145	0.016	£22,664.07	£8,845.57
Duloxetine	£2,184.44	1.404	Dominant	£262	-0.015	Dominated	Dominated
Agomelatine	£2,311.54	1.420	£700,807.02*	£127	0.015	£700,807.02	£700,807.02
SOLUTION							
Venlafaxine	£1,783.61	1.393	£5,054.16	Ref	Ref	Ref	Ref
Vortioxetine	£1,916.62	1.419	NA	£133	0.026	£5,054.16	£5,054.16
SWITCH							
Sertraline	£1,817.86	1.327	£1,135.15	Ref	Ref	Ref	NA
Venlafaxine	£1,864.53	1.334	£683.02	£47	0.007	£6,422.38	Ref
Vortioxetine	£1,922.58	1.419	NA	£58	0.085	£683.02	£683.02
Agomelatine	£2,236.79	1.373	Dominant	£314	-0.046	Dominant	Dominant
LLORCA							
Escitalopram	£1,644.46	1.423	Dominated	Ref	Ref	Ref	NA
Venlafaxine	£1,753.55	1.425	Dominated	£109	0.002	£45,253.84	Ref
Vortioxetine	£1,917.58	1.419	NA	£164	-0.006	Dominated	Dominated
Duloxetine	£2,195.07	1.417	Dominant	£277	-0.002	Dominated	Dominated
Agomelatine	£2,305.99	1.415	Dominant	£111	-0.002	Dominated	Dominated
PAE							
Venlafaxine	£1,778.38	1.404	£9,427.88	Ref	Ref	Ref	Ref
Vortioxetine	£1,922.58	1.419	NA	£144.20	0.015	£9,427.88	£9,427.88
Duloxetine	£2,216.33	1.438	£15,674.44*	£293.75	0.019	£15,674.44	£15,674.44
Agomelatine	£2,234.00	1.371	Dominant	£17.67	-0.067	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

3.7.3. Analysis set 1b: Maintenance treatment – up to 6 months & risk of recurrence – secondary care treatment setting

Table 14 presents a similar analysis to 1a however it assumes patients are initiated and treated in secondary care. This analysis increases overall costs however health gains remain the same. Comparators associated with a higher numbers health care visits are more affected than those associated with less.

The cost-effectiveness conclusions remain unchanged from analysis 1a.

Table 14: Response and Remission Model Analysis 1b (up to 6 months maintenance & recurrence risk in recovery): secondary care initiation and maintenance

Technologies	Total costs	Total QALYs	Pairwise ICER ICER Vortioxetine vs. comparator	Incremental analyses Incremental costs	Incremental QALYs	All txs ICER incremental (QALYs)	w/o SSRI ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Vortioxetine	£3,032.91	1.427	NA	Ref	Ref	Ref	Ref
Citalopram	£3,073.23	1.414	Dominant	40.32	-0.012	Dominated	NA
Escitalopram	£3,078.63	1.414	Dominant	5.40	-0.001	Dominated	NA
Sertraline	£3,088.12	1.412	Dominant	9.49	-0.002	Dominated	NA
Venlafaxine	£3,135.10	1.410	Dominant	46.98	-0.002	Dominated	Dominated
Agomelatine	£3,263.13	1.428	£332,296.24*	128.03	0.018	£332,296.24	£332,296.24
Duloxetine	£3,284.36	1.411	Dominant	21.23	-0.016	Dominated	Dominated
SOLUTION							
Vortioxetine	£3,019.63	1.427	NA	Ref	Ref	Ref	Ref
Venlafaxine	£3,237.77	1.399	Dominant	£218.13	-0.03	Dominated	Dominated
SWITCH							
Vortioxetine	£3,032.91	1.427	NA	Ref	Ref	Ref	Ref
Agomelatine	£3,572.27	1.380	Dominant	£539.36	-0.047	Dominated	NA
Venlafaxine	£3,675.55	1.336	Dominant	£103.29	-0.043	Dominated	Dominated
Sertraline	£3,700.94	1.330	Dominant	£25.38	-0.006	Dominated	Dominated
LLORCA							
Escitalopram	£2,969.83	1.431	Dominated	Ref	Ref	Ref	NA
Venlafaxine	£2,982.60	1.431	Dominated	£12.77	0.001	£16,582.45	Ref
Vortioxetine	£3,022.03	1.427	NA	£39.44	-0.005	Dominated	Dominated
Duloxetine	£3,216.05	1.424	Dominant	£194.02	-0.003	Dominated	Dominated
Agomelatine	£3,293.72	1.424	Dominant	£77.67	-0.000	Dominated	Dominated
PAE							
Vortioxetine	£3,032.91	1.427	NA	Ref	Ref	Ref	Ref
Duloxetine	£3,075.62	1.445	£169,992.40*	£42.71	0.018	£2,360.48	£2,360.48
Venlafaxine	£3,140.03	1.410	Dominant	£64.42	-0.035	Dominated	Dominated
Agomelatine	£3,586.41	1.378	Dominant	£446.38	-0.032	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

3.7.4. Analysis set 2b: Maintenance treatment – up to 22 months maintenance – secondary care treatment setting

As explained for analyses 1a vs. 2a the increase in maintenance treatment length, increase the costs associated with each comparator and decrease the QALYs gained. This pattern is observed between 1b and 2b. The change in treatment setting to secondary care (2b compared to 2a) also increases the cost but has no impact on the QALYs gained (see explanation for analysis 1a vs. 1b).

The cost-effectiveness conclusions remain the same.

Table 15: Response and Remission Model Analysis 2b (up to 22 months maintenance): secondary care initiation and maintenance

Technologies	Total costs	Total QALYs	Pairwise ICER ICER Vortioxetine vs. comparator	Incremental analyses Incremental costs	Incremental QALYs	All txs ICER incremental (QALYs)	w/o SSRI ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Citalopram	£3,907.74	1.408	£18,615.83	Ref	Ref	Ref	NA
Escitalopram	£3,918.47	1.407	£16,786.81	£11	-0.001	Dominated	NA
Sertraline	£3,930.50	1.405	£13,522.15	£12	-0.002	Dominated	NA
Venlafaxine	£4,021.38	1.403	£6,288.51	£91	-0.002	Dominated	Ref
Vortioxetine	£4,124.30	1.419	NA	£103	0.016	£18,615.83	£6,288.51
Duloxetine	£4,428.02	1.404	Dominant	£304	-0.015	Dominated	Dominated
Agomelatine	£4,583.74	1.420	£827,761.56*	£156	0.015	£827,761.56	£827,761.56
SOLUTION							
Venlafaxine	£4,036.69	1.393	£2,825.79	Ref	Ref	Ref	Ref
Vortioxetine	£4,111.06	1.419	NA	£74	0.026	£2,825.79	£2,825.79
SWITCH							
Vortioxetine	£4,124.32	1.419	NA	Ref	Ref	Ref	Ref
Sertraline	£4,142.80	1.327	Dominant	£18	-0.092	Dominated	NA
Venlafaxine	£4,179.96	1.334	Dominant	£37	0.007	Dominated	Dominated
Agomelatine	£4,543.14	1.373	Dominant	£363	0.039	Dominated	Dominated
LLORCA							
Escitalopram	£3,870.51	1.423	Dominated	Ref	Ref	Ref	NA
Venlafaxine	£3,972.46	1.425	Dominated	£102	0.002	£42,288.47	Ref
Vortioxetine	£4,113.46	1.419	NA	£141	-0.006	Dominated	Dominated
Duloxetine	£4,420.13	1.417	Dominant	£307	-0.002	Dominated	Dominated
Agomelatine	£4,579.07	1.415	Dominant	£159	-0.002	Dominated	Dominated
PAE							
Venlafaxine	£4,018.04	1.404	£6,949.16	Ref	Ref	Ref	Ref
Vortioxetine	£4,124.32	1.419	NA	£106.29	0.015	£6,949.16	£6,949.16
Duloxetine	£4,419.98	1.438	£15,775.70*	£295.65	0.019	£15,775.70	£15,775.70
Agomelatine	£4,541.84	1.371	Dominated	£121.87	-0.067	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

3.7.5. Analysis set 1c: Maintenance treatment – up to 6 months & risk of recurrence – primary care treatment setting & 30% increase in resource use for responders

Analysis 1c, as reported in Table 16, increases the resource use for responders by 30% compared to remitters. This increases the total costs slightly compared to analysis 1a and health gains remain the same. The cost-effectiveness conclusions for analyses 1c and 2c are equivalent to those for analysis set 2a.

Table 16: Response and Remission Model Analysis 1c (up to 6 months maintenance & recurrence risk in recovery): Primary care & increase in resource use by 30% for responders vs. remitters

Technologies	Total costs	Total QALYs	Pairwise ICER ICER Vortioxetine vs. comparator	Incremental analyses Incremental costs	Incremental QALYs	All txs ICER incremental (QALYs)	w/o SSRI ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Citalopram	£1,367.86	1.414	£4,655.74	Ref	Ref	Ref	NA
Escitalopram	£1,373.26	1.414	£4,018.77	5.40	-0.001	Dominated	NA
Sertraline	£1,383.39	1.412	£2,800.15	10.13	-0.002	Dominated	NA
Venlafaxine	£1,425.34	1.410	£26.02	41.95	-0.002	Dominated	Ref
Vortioxetine	£1,425.79	1.427	NA	0.45	0.017	£4,655.74	£26.02
Duloxetine	£1,574.59	1.411	Dominant	148.80	-0.016	Dominated	Dominated
Agomelatine	£1,594.34	1.428	£243,284.6*	19.75	0.016	£243,284.61	£243,284.61
SOLUTION							
Vortioxetine	£1,419.83	1.427	NA	Ref	Ref	Ref	Ref
Venlafaxine	£1,465.25	1.399	Dominant	45.42	-0.03	Dominated	Dominated
SWITCH							
Vortioxetine	£1,425.79	1.427	NA	Ref	Ref	Ref	Ref
Venlafaxine	£1,660.26	1.336	Dominant	£234.48	-0.091	Dominated	NA
Sertraline	£1,660.58	1.330	Dominant	£0.32	-0.006	Dominated	Dominated
Agomelatine	£1,710.64	1.380	Dominant	£50.06	0.050	Dominated	Dominated
LLORCA							
Escitalopram	£1,327.52	1.431	Dominated	Ref	Ref	Ref	NA
Venlafaxine	£1,356.58	1.431	Dominated	£29.07	0.001	£16,582.45	Ref
Vortioxetine	£1,420.79	1.427	NA	£64.20	-0.005	Dominated	Dominated
Duloxetine	£1,552.40	1.424	Dominant	£131.62	-0.003	Dominated	Dominated
Agomelatine	£1,609.87	1.424	Dominant	£57.47	-0.000	Dominated	Dominated
PAE							
Vortioxetine	£1,425.79	1.427	NA	Ref	Ref	Ref	Ref
Venlafaxine	£1,428.05	1.410	Dominant	£2.26	-0.017	Dominated	Dominated
Duloxetine	£1,497.30	1.445	£2,049.03*	£69.25	0.035	£3,952.24	£3,952.24
Agomelatine	£1,717.30	1.378	Dominant	£220.01	-0.067	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

3.7.6. Analysis set 2c: Maintenance treatment – up to 22months maintenance – primary care treatment setting & 30% increase in resource use for responders

Table 17: Response and Remission Model Analysis 2c (up to 22 months maintenance): Primary care & increase in resource use by 30% for responders vs. remitters

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Citalopram	£1,706.31	1.408	£22,910.75	Ref	Ref	Ref	NA
Escitalopram	£1,717.04	1.407	£20,861.69	£11	-0.001	Dominated	NA
Sertraline	£1,729.72	1.405	£16,963.44	£13	-0.002	Dominated	NA
Venlafaxine	£1,824.65	1.403	£9,053.99	£95	-0.002	Dominated	Ref
Vortioxetine	£1,972.84	1.419	NA	£148	0.016	£22,910.75	£9,053.99
Duloxetine	£2,231.30	1.404	Dominant	£258	-0.015	Dominated	Dominated
Agomelatine	£2,362.31	1.420	£701,705.97	£131	0.015	£701,705.97	£701,705.97
SOLUTION							
Venlafaxine	£1,824.68	1.393	£5,403.76	Ref	Ref	Ref	Ref
Vortioxetine	£1,966.90	1.419	NA	£142	0.026	£5,403.76	£5,403.76
SWITCH							
Sertraline	£1,841.72	1.327	£1,421.46	Ref	Ref	Ref	NA
Venlafaxine	£1,884.48	1.334	£1,039.87	£43	0.007	£5,883.88	Ref
Vortioxetine	£1,972.85	1.419	NA	£88	0.085	£1,039.87	£1,039.87
Agomelatine	£2,276.34	1.373	Dominant	£303	-0.046	Dominated	Dominated
LLORCA							
Escitalopram	£1,697.00	1.423	Dominated	Ref	Ref	Ref	NA
Venlafaxine	£1,799.87	1.425	Dominated	£103	0.002	£42,671.41	Ref
Vortioxetine	£1,967.85	1.419	NA	£168	-0.006	Dominated	Dominated
Duloxetine	£2,243.26	1.417	Dominant	£275	-0.002	Dominated	Dominated
Agomelatine	£2,359.05	1.415	Dominant	£116	-0.002	Dominated	Dominated
PAE							
Venlafaxine	£1,822.69	1.404	£9,817.86	Ref	Ref	Ref	Ref
Vortioxetine	£1,972.85	1.419	NA	£150.16	0.015	£9,817.86	£9,817.86
Duloxetine	£2,267.39	1.438	£15,716.37*	£294.54	0.019	£15,716.37	£15,716.37
Agomelatine	£2,274.95	1.371	Dominant	£7.56	-0.067	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

3.8. Discussion of cost-effectiveness results

Par/equivalent efficacy assumption

The base-case analysis shows vortioxetine to be the most cost-effective, and in cases, dominant, treatment option versus all comparators: citalopram, escitalopram, sertraline, venlafaxine, duloxetine and agomelatine. These results were consistent across scenario analyses. The greatest ICER (£23k) was vs. citalopram in Analysis set 2c – 22months maintenance treatment, primary care setting with 30% increase in resource use for responders over remitters.

In pairwise PSA analyses run on the base-case model (analysis set 1 a – up to 6 months maintenance treatment, risk of recurrence in the recovery phase, treatment setting in primary care) show that vortioxetine was the comparator with the highest probability of being be cost-effective (assuming a cost per QALY threshold of both £20k and £30k). Vortioxetine was most likely to be cost-effective versus duloxetine (probability of 72%), with a probability of 60-70% of being cost-effective versus citalopram, escitalopram, sertraline, and venlafaxine, with just over a 50% likelihood of being cost-effective versus agomelatine.

Other data sets

The cost-effectiveness results based on other data source should be viewed with the limitations of each source in mind (as discussed in Section 3.4.1).

Vortioxetine vs. agomelatine

Vortioxetine is a cost-effective treatment option versus agomelatine in all analyses (Switch, Llorca and Pae, in addition to par efficacy). Agomelatine was never the most cost-effective treatment option in incremental analyses.

The PSA pairwise results on analysis set 1a showed vortioxetine to have a probability of between 52-100% of being cost-effective versus agomelatine.

Vortioxetine Vs. citalopram

The comparison between vortioxetine and citalopram was only considered in the par efficacy set and was cost-effective in all scenario analyses. Citalopram was never the most cost-effective treatment option in incremental analyses given a cost per QALY threshold of £20-£30k.

The pairwise PSA results from the base-case model show vortioxetine to have a likelihood of 63-65% of being cost-effective vs. citalopram given a cost per QALY threshold of £20-£30k respectively.

That being said, this comparison may not be relevant as CG90 suggests changing treatment class at 3rd line. In addition, the Papakostas publication suggest the relative effects of SSRIs do not remain constant and the vast majority of patients at 3rd line in the UK will have already received 1 or 2 previous SSRIs.

Vortioxetine vs. escitalopram

An assessment of the cost-effectiveness of escitalopram is only available in the Llorca data set (apart from the par/equivalent efficacy assumption). Vortioxetine is dominated by escitalopram in all scenarios based on the Llorca data source. Incremental analyses including SSRIs in some scenarios escitalopram was the most cost-effective treatment option. Pairwise probabilistic analysis however shows that vortioxetine does have a 38-40% probability (depending on the threshold) of being cost-effective versus escitalopram in Analysis set 1a.

However, as stated in the section above comparing vortioxetine to citalopram, a comparison to SSRIs at 3rd line may be deemed to be of limited relevance.

Vortioxetine vs. sertraline

Apart from the par efficacy analysis, the assessment of the cost-effectiveness of vortioxetine was only available from the Switch network. In all scenarios vortioxetine dominated sertraline, supported by the pairwise PSA which showed that vortioxetine had an 100% probability of being cost-effective versus sertraline.

Due to the limitations of Llorca publication, a comparison of vortioxetine to sertraline was not possible due to a lack of data to populate the remission and response endpoint (see Section 3.4.1.4).

Given the 3rd line focus, as stated in the section above comparing vortioxetine to citalopram, a comparison to SSRIs may be deemed inappropriate.

Vortioxetine vs. venlafaxine

The cost-effectiveness conclusions for vortioxetine vs. venlafaxine are mixed, as are the conclusions that can be drawn from the incremental analyses including venlafaxine.

The analyses based on the head-to-head study, SOLUTION, show that vortioxetine is consistently cost-effective, if not dominant versus venlafaxine XR. These results are supported by the conclusions from the Switch network and Pae analyses where vortioxetine is always cost-effective or dominant vs. venlafaxine. Considering these data sets venlafaxine is never the most cost-effective treatment option in incremental analyses.

A comparison to venlafaxine is also possible through the results published in the Llorca manuscript. Based on this data source, venlafaxine consistently dominates vortioxetine in pairwise comparisons. In the incremental analyses considering all treatment options venlafaxine is not a cost-effective option in some scenarios. In the incremental analyses excluding SSRIs venlafaxine is always the most cost-effective treatment option.

The pairwise PSA show the probability of vortioxetine being cost-effective vs. venlafaxine is actually fairly substantial in all analyses including Llorca: Par efficacy -62%-65%; SOLUTION – 87-88%; Switch network – 100%; Llorca: 40-41%; Pae – 71% (figures shown for a £20k and £30k cost per QALY threshold).

Vortioxetine vs. duloxetine

As with venlafaxine, the cost-effectiveness conclusions for vortioxetine vs. duloxetine are mixed, as are the conclusions which can be drawn from the incremental analyses which include duloxetine.

The comparison of vortioxetine to duloxetine can be made using the data from Llorca and Pae.

Vortioxetine consistently dominates duloxetine using the Llorca data set. In around half of the scenarios using the Pae data set vortioxetine is cost-effective, and around half are not.

In the incremental analyses, using Llorca venlafaxine is sometimes the most cost-effective treatment option, and when considering Pae, duloxetine is sometimes the most cost effective treatment options vs. all other treatments.

As with the comparison to venlafaxine, the results of the pair-wise PSA from all dataset show vortioxetine to have a marked probability of being cost-effective vs. duloxetine in all analyses (ranging from 25% to 72%)

Influence of maintenance treatment length

Two scenarios were considered here (up to 6 months or 22 months maintenance treatment) to explore the influence of increased treatment length on the cost-effectiveness vortioxetine vs. other antidepressants. In general, the increase in length of treatment increases costs and reduces QALYs for reasons discussed in Section 3.7.2.

Clinical opinion and clinical guidelines such as CG90 and the BAP are in agreement that the length of maintenance treatment will depend on the patient, mainly being influenced by the number of previous episodes and the perceived risk of relapse.

This parameter had limited impact on the cost-effectiveness of vortioxetine.

Initiation and maintenance treatment setting

Two scenarios were considered to explore the impact of treatment setting on the cost-effectiveness of vortioxetine: initiation and maintenance in primary and secondary care. The impact of this is discussed in Section 3.7.3. The primary care scenario better reflects reality as clinical opinion including the responses to the questionnaire and the advisory board (see Appendix 6.7 and 6.4 respectively) suggest that in some areas of the UK patients may receive up to 3 or 4 treatments in primary care if the clinician is well experienced. From the same sources providing insight into clinical practice, it is clear that the majority of patients who are referred to secondary care are referred back out to primary care as soon as they are stable. Therefore, the secondary care scenario should be considered an extreme scenario and will overestimate the cost of treatment for all comparators, especially those associated with higher rates of health care contacts. Due to the time constraints for this response Lundbeck could not reflect this aspect in the model.

In any case, this had little impact on the cost-effectiveness conclusions.

Impact of the inclusion of response to the model

A comparison of the costs and QALYs accrued in the remission model vs. the response and remission model show that, in general, the latter is associated with higher costs and lower health gains for all comparators.

In the remission only model (results presented in Appendix 6.10) the health state "response" was not included. Responders in the remission only model are captured in the non-remission health state. Within this model patients who do not achieve remission at 8 weeks are assumed to switch. Within the updated model (including both response and remission as outcomes) patients in both the remission and response health state are assumed to continue treatment to at least week 12. In the response health state, they are then reassessed, at which point they are assigned a probability of continuing in response and entering the maintenance phase, moving to remission and entering the maintenance phase, or moving into no-response, in which case they will switch treatment.

Therefore in the response and remission model a lower proportion of patients switch treatment to 4th line and onwards (modelled in the Markov portion of the model). In addition, for those patients who do switch from their initial (3rd line) treatment in this model, the switch will on average take place at a later time point.

One of the reasons for a higher cost and lower QALY accrual in the response and remission model is that a lower proportion of patients switch (given that in the model with response and remission included, responders continue on treatment (at least to week 12, and in many cases into the maintenance phase), where as in then remission model they were switched at week 8). Therefore, as more patients continue on their 3rd line treatment, long-term adverse events are more likely. Consequently, there is a higher chance of disutilities associated with long-term adverse events being applied, and the costs associated with these will be greater (as these are not applied for treatments at 4th line and onwards). Within the response and remission model, the better-tolerated antidepressants such as vortioxetine, become more cost-effective when comparing the equivalent analyses results from the remission model.

In addition, the higher total cost in the revised model will be driven in part by the higher drug costs associated with initial treatments (relative to the assumption of drug costs at later lines), and as just stated, more patients are expected to continue on their initial treatment.

One of the primary concerns of the Committee with regards to the old model structure was that the faster switch associated with lack of efficacy based on remission as the outcome, disproportionately benefitted the comparators with a higher acquisition cost (i.e. vortioxetine). The analyses presented here show that when the base-case par efficacy assumption is applied, vortioxetine is consistently cost-effective when response is included as an efficacy outcome.

3.9. Summary of positioning of vortioxetine based on revised analyses

Vortioxetine is an antidepressant with a unique mechanism of action. It has been shown to be as efficacious, and generally better tolerated, than other antidepressants. This has been observed consistently in the full MDD population through both direct head-to-head and indirect evidence.

There are limitations associated with the available data sources in providing relative efficacy estimates of vortioxetine and comparators to populate a cost-effectiveness model, particularly one focusing on third line treatment. Given this, and the statements within CG90 and from the Committee suggesting that there is no difference in efficacy between vortioxetine and comparators, and antidepressant in general, the par efficacy assumption is proposed as the most appropriate source to inform the decision problem.

As requested by the Committee, the cost-effectiveness model has been updated to include the clinically relevant outcomes of response and remission, the structure of which has been validated by UK clinical experts.

The base-case analysis conducted using this revised model has shown that vortioxetine, with its tolerability benefits, is expected to be a cost-effective treatment option for patients experiencing an MDE who have failed on at least 2 previous antidepressants in England and Wales. When considering the base-case data source, this result is robust to the changes employed in scenario analyses conducted around treatment in both primary and secondary care, length of maintenance treatment and increased resource use for responders.

4. Comments on the ACD

4.1. Section 1: Appraisal Committee's preliminary recommendations

The above analyses are submitted in response to the committee's preliminary decision.

4.2. Section 2: The Technology

Section 2.2, Page 4: The summary of product characteristics lists the following 'common' and 'very common' adverse reactions for vortioxetine: abnormal dreams, constipation, decreased appetite, diarrhoea, dizziness generalised itching, nausea and vomiting. For full details of adverse reactions and contraindications, see the summary of product characteristics.

The adverse events listed above are no longer correct due to an update of the SmPC. Please see Table 18 for the latest adverse events included in the SmPC for vortioxetine (EMA, 17th June 2015).

Table 18: Adverse reactions associated with vortioxetine

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Psychiatric disorders	Common	Abnormal dreams
Nervous system disorders	Common	Dizziness
	Unknown	Serotonin Syndrome
Vascular disorders	Uncommon	Flushing
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, Constipation, Vomiting
Skin and subcutaneous tissue disorders	Common	Pruritus, including pruritus generalised
	Uncommon	Night sweats
Adverse reactions are listed using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).		

Section 2.3 Page 4: The recommended dosage is 10 mg once daily in adults younger than 65 years, and 5 mg once daily in adults 65 years and older.

This is incorrect and should read as per the SmPC: The starting dosage is 10 mg once daily in adults younger than 65 years, and 5 mg once daily in adults 65 years and older. Depending on individual patient response, the dose may be increased to a maximum of 20 mg vortioxetine once daily or decreased to a minimum of 5 mg vortioxetine once daily (EMA, 2015. SmPC Section 4.2).

4.3. Section 3: The Company's submission

Section 3.3, Page 6 (& Section 4.6, Page 36): Full Analysis Set (FAS) vs Intention to Treat (ITT)

The ACD documents that Lundbeck presented results of the REVIVE trial using the Full Analysis Set (FAS) population rather than the Intention to Treat (ITT) population.

A true ITT analysis is not straightforward since assumptions need to be made for patients without post-baseline data.

For this reason FAS is generally accepted as a modified ITT. In the current study the problem is small with 3 and 5 ITT patients respectively in the VOR and AGO group not qualifying for FAS. Assuming e.g. a 'no change score' for these patients did not have impact on the results

Section 3.3, Page 6: The company tested a primary hypothesis of non-inferiority, and a secondary hypothesis of superiority.

This statement is incorrect. The superiority test was not a secondary hypothesis but part of the primary hypothesis. It is well recognised that once non-inferiority is established in a non-inferiority study a superiority test can be performed under a closed test procedure (EMA 2000). Non-inferiority was established in REVIVE as the upper bound of the 95% CI for the vortioxetine and agomelatine comparison was -0.81 MADRS points. This was clearly below the non-inferiority margin of +2 MADRS points vs. 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 (mean difference for vortioxetine to agomelatine was 2.2 ({95% CI: 3.5 to 0.8; p = 0.0018}).

Section 3.5, Page 7: The company stated that vortioxetine statistically significantly improved outcomes compared with agomelatine across the analyses of response and relapse outcomes measured by MADRS score (see table 2).

This sentence is factually inaccurate. It should read as follows: The company stated that vortioxetine statistically significantly improved outcomes compared with agomelatine across the analyses of response and **remission** outcomes measured by MADRS score (see table 2).

Section 3.9 Page 9: "There are no head-to-head data comparing vortioxetine with comparators other than agomelatine in the second-line population."

This statement is incorrect. As stated in the submission there were two trials of vortioxetine in switch populations though 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 required a treatment switch due to experiencing TESD with their current treatment. Study 14178A (REVIVE) compared vortioxetine with agomelatine and Study 318 compared vortioxetine with escitalopram.

In addition to REVIVE and TAK318, a head-to-head study vs venlafaxine has also been conducted in patients with MDD. Further information about the study is provided in Appendix 4.46.3 and the results of this study are included in the cost-effectiveness analyses undertaken and reported in Section 3.7).

Section 3.14, Page 14 (& Section 3.36, Page 24; Section 4.16, Page 47) A half-cycle correction was applied to the health effects but not the costs in the Markov part of the model (cycle length 2 months).

Though Lundbeck does appreciate that a half cycle correction is usually applied to both the costs and health effects the rationale for not applying the half-cycle correction for the former was as follows:

- Resource use and costs were available for the period preceding the health state achieved after the acute phase, e.g. for remission the cost is available for the two-month period before achieving remission. This principle was applied for all cycles, i.e. in the Markov phase, the cost of the acute phase corresponds to the two-month cost associated with achieving remission or of remaining in non-remission depending on the outcome.

- Quality of life/utilities were available at the time of the health states, e.g. at 8 weeks utilities were available when patients should a patient achieve remission or not. Therefore to account for the transition between health states at different points in time, half-cycle correction was applied

As stated above, despite the rationale employed leading to the half-cycle correction to be applied to utilities and not costs it is recognised that a half-cycle correction is applied to both costs and outcomes. Therefore all additional analyses provided in this document apply a half-cycle correction to both costs and utilities.

Section 3.23, Page 19 (& Section 4.5, Page 35) The ERG commented that the population enrolled into REVIVE was broadly representative of the second-line population in England… However, the ERG noted that:

- *Most patients were white (99.8%), which is unlikely to be reflective of the second-line population in England…*
- *23% of patients had received an SNRI as initial treatment, which is not reflective of clinical practice in England, where SNRI use in first line is negligible…*

Lundbeck do not believe that either of these factors lessen the external validity of REVIVE. As stated in the submission, the efficacy of vortioxetine did not differ by race in subgroup analyses of the full

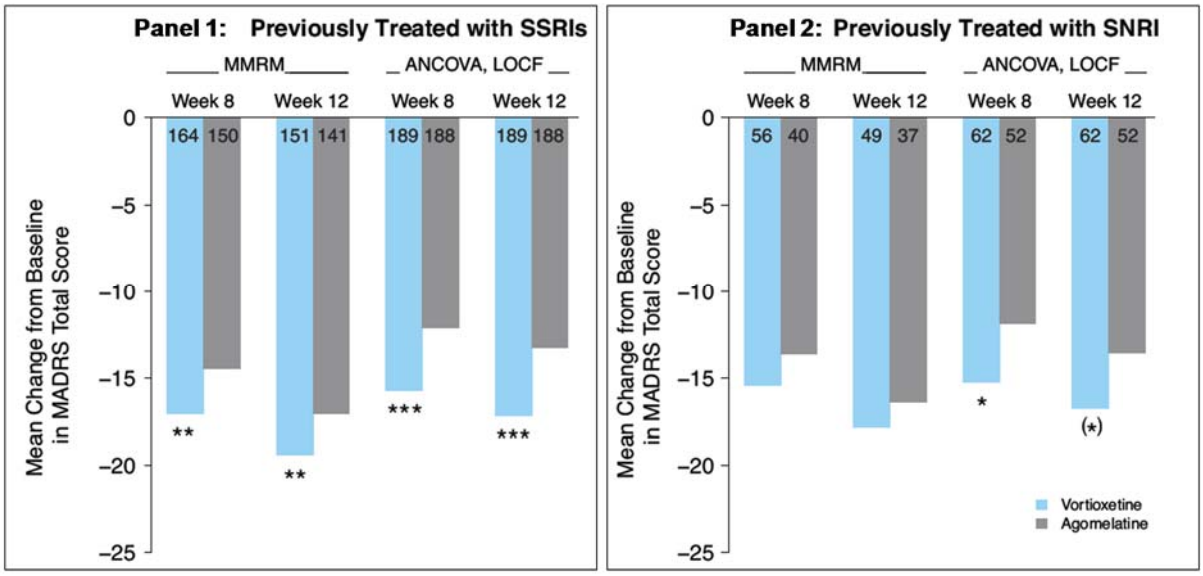
MDD package and therefore should not affect the generalisability of results (vortioxetine EPAR, 2013).

In addition, one of the subgroup analyses presented within the Manufacturer's submission 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 (Papakostas 2014).

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 21, 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 21, Panel 2).

It can be concluded that the efficacy advantage of vortioxetine over agomelatine is independent of previous treatments class (SSRI or SNRI). Therefore the SNRI pre-treatment of 23% of the population in REVIVE does not affect the generalisability of results.

Figure 21: Study 14178A (REVIVE). Subgroup analysis of primary efficacy endpoint by previous class of treatment



Source: Poster (Papakostas 2014). 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

Section 3.25, Page 19: The ERG commented that the results from the company's analysis of the primary and secondary outcomes from REVIVE had relatively wide confidence intervals, so the size of the difference in efficacy between vortioxetine and agomelatine was uncertain

Lundbeck do not agree that the confidence intervals around the results observed in REVIVE should be considered "relatively wide". A MADRS SD=7.6 was observed in the study which is lower than what is typically found in the other vortioxetine studies in MDD (SD=9.5). In addition with n~220 per group these confidence intervals are in fact narrower than what is typically found.

Section 3.27, Page 20 (& Section 4.7, Page 37): It also stated that time of outcome assessment between trials (varying from 6–14 weeks) may also affect the results because rates of remission and withdrawal are likely to be time-dependent.

As stated in the submission Lundbeck does not believe the variation in time points of outcome assessment between trials affects the results of the indirect comparison in switch. 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 (REVIVE CSR 2013), 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 Manufacturer's submission, Section 6.10.2.3)

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 (NHS Choices, 2013 & REVIVE analyses presented in Section 3.6.2.4).

Section 3.33, Page 22 (& Section 4.12, Page 41): The company used different modelling approaches in the maintenance and recovery periods, rather than an initial decision tree for the acute phase and then a separate Markov component for all people in the subsequent 10 month period.

The current model design was selected based on both expert recommendations and previously published cost-effectiveness models in MDD. Both sources used to inform the structure highlighted the high heterogeneity between patients and patient pathways in both the treatment and management of the disorder.

A decision tree was selected to reflect the different clinical (i.e. outcome) pathways a patient can have following the acute and maintenance phases of treatment. In order to reflect clinical practice patients could switch at different points in time depending on the reason (e.g. treatment discontinuation due to relapse or long-term adverse events). Therefore Lundbeck believed it was appropriate a to start the Markov component at the time of switch (rather than, for example, after the first 8 weeks of treatment) and adjust the time spent in the Markov up to the end of the time horizon.

4.4. Section 4: Consideration of the evidence

Section 4.3, Page 33: The clinical expert stated that most people in the NHS would receive escitalopram (also an SSRI) second line, but treatment choice was influenced by treatment history (for example, number of previous therapies, first or recurrent episode of depression) and presence of specific signs and symptoms.

Lundbeck support the clinical expert's view that the treatment of depression should consider aspects such as treatment history and an individual's symptoms as depression is a heterogeneous disorder. This is in line with the recommendations in CG90 which states that antidepressants are largely equal in efficacy therefore choice should be primarily dependant on safety, tolerability and patient preference.

However, prescribing data presented within the Manufacturer's submission (again presented in this document Figure 1) shows escitalopram not to be the most commonly used antidepressant at second line within the NHS.

Section 4.6, Page 36: The Committee heard from the clinical expert that the mean change from baseline in total MADRS score was not a useful outcome measure for judging whether a clinically important difference was observed because the MADRS included 10 items for measuring depressive symptoms. The clinical expert explained that a reduction in 1 item of the MADRS by 2 or more points would generally be considered clinically meaningful.

Lundbeck believes the clinical experts view has been misreported within the ACD.

Firstly, although Lundbeck recognise that the MADRS scale is not widely used in clinical practice, it is however recognised as a standard measurement of symptoms associated with depression, in clinical research, alongside HAM-D (Duru & Fantino 2008).

The Committee heard the clinical expert state that, although there is some debate as to what constitutes a clinically meaningful change in MADRS score it is generally accepted that 2 points are considered the threshold in a placebo-controlled trial. Within active-controlled trials this difference can be halved and is still considered clinical meaningful. This is in line with the literature provided by Lundbeck at the clarification question stage of the appraisal process which included the following:

Table 19 details what is considered a clinically meaningful change in symptom scores for the relevant scales as detailed in the literature. These clinically relevant differences are however in the context of assessing pharmacological compounds versus placebo. As discussed by Montgomery (2011), this clinically relevant difference versus placebo is not to be generalised for comparisons between two active drugs, and one rule that can be applied for the translation from placebo-control to active-control comparison is 50% of the difference judged as clinically relevant in placebo-controlled studies:

"The criteria used to establish a clinically relevant difference have almost all been focused on a comparison of drug and placebo. Comparing differences between two active treatments applying the

same criterion used to define a clinically relevant difference on the pivotal scale between active drug and placebo is very stringent, since this means that the difference to placebo of the superior treatment must be at least twice that of the comparator antidepressant. However, 50% of the difference between active drug and placebo has also been used as a criterion to indicate probable clinical relevance when comparing two established treatments."

The London New Drugs Group (LNDG) has accepted this criterion when assessing evidence to inform local decision-making (Denby 2009). This is demonstrated in their discussion of agomelatine and what should be considered a clinically relevant change in HAM-D_{17} score:

"The agomelatine/placebo difference in HAMD score was not always greater than 3 points (ref 8 and the active control studies), the difference considered to be clinically significant by NICE. The agomelatine/sertraline HAMD score difference was greater than 1.5 points, which is considered clinically significant."

Table 19: Clinical relevance of changes in symptom scores on depression rating scales

Scale	Clinically relevant difference in change in symptom score: active treatment versus placebo control		References
		Half of the score considered clinically relevant in active-controlled vs. placebo controlled studies based on Montgomery 2011[4]	
MADRS	2 points	1 point	Batterham 2009[6] Melander 2008[7] Bruce 1994[8]
	1.6 to 1.9 points	0.8 to 0.95 points	Duru 2008[9]
HAM-D_{24}	2 points	1 point	Duru 2008[9] Montgomery 2009[10]
HAM-D_{17}	3 point	1.5 points	Denby[5]
CGI-S/CGI-I	No clear consensus		Bandelow 2006[11]

The clinical expert did continue to state that at an individual patient level he would be able to observe a reduction in 1 item of the MADRS by 2 or more points.

Section 4.8, Page 38: The Committee heard from the company that, although there is a paucity of evidence for vortioxetine used second line, the company chose not to use data from its trials, including first-line treatment, because it claimed that the relativeness effectiveness changes across lines of treatment.

There is a typographical error in this sentence. "Relativeness" should be replaced with "relative".

Section 4.8, Page 38: The ERG acknowledged that the relative effectiveness may reduce in clinical practice at second or later lines of treatment compared with first-line treatment, particularly for SSRIs when compared with antidepressants of a different class. However, it emphasised that there was no evidence available to support a declining relative effect of treatment between drugs other than SSRIs.

Lundbeck conducted a systematic review to identify all data available to answer the research question of whether there are differences in relative treatment effects at different treatment lines. The full report can be found in Appendix 6.2.

The conclusions from this review were as follows:

"The systematic review demonstrates that there is limited evidence currently available allowing the assessment of relative efficacies of antidepressants across treatment lines.

Despite identifying a number of studies providing some evidence that may be used to interpret the difference in relative efficacy of antidepressants between lines of treatment, quantitative analysis would be extremely difficult to perform with the reported data

The Bauer publication (16) potentially provides the strongest evidence in answering the question of whether relative efficacies differ between treatment lines. Despite limitations associated with the design, as each treatment arm used as evidence consisted of at least 2,000 patients from several clinical trials, these can be considered robust results. Therefore, the reported odds ratio patterns may be indicative of a variation in relative treatment efficacy between the before-and after-switch populations.

Considering the evidence presented in Figure 13 in its totality, it appears that the general trend towards a difference in the number of patients achieving a response to treatment between before- and after-switch populations between interventions.
The findings of this review add to the understanding of relative efficacies gained from the findings of the Papakostas (1) publication; that across-class switch from SSRI to non-SSRI is more likely to result in remission than switching from one SSRI to another".

Section 4.9, Page 39: The Committee concluded that the estimates of relative effectiveness in each analysis were subject to uncertainty but, of the available sources, Llorca had the fewest weaknesses.

Lundbeck does not believe Llorca (2014) to provide the most robust evidence for populating the current cost-effectiveness model. See Section 3.4 for full rationale.

Section 4.10, Page 40: the Committee noted that the evidence for vortioxetine in people having second-line treatment included trials only of short duration, so the treatment effect of vortioxetine after 8 weeks was uncertain

The effect of vortioxetine in the switch population has been demonstrated in a trial longer than 8 weeks - the REVIVE study which was 12 weeks in duration.

Section 4.11, Page 40: The Committee understood that the dose of vortioxetine generally increases over time

Lundbeck are unclear on the evidence base used to substantiate this. Within the REVIVE study the starting dose for all patients randomised to vortioxetine was 10mg. This could be adjusted (either to 10mg or 20mg) at the weekly visits during the first 4 weeks only.

In clinical studies with flexible-dose design there is a tendency to increase the dose. In REVIVE, the proportion of patients on the high dose (approximately 2/3 of the patients) is in line with what has been observed in the clinical development programme for vortioxetine for other studies with a flexible-dose design (Study 11985A, Table 36 [open-label period], and open-label extension studies [Study 11492C, chapter 8, Study 11984B, chapter 8]). In REVIVE the investigator could only adjust the dose within the first 4 weeks of the treatment period, which might have affected the titration and the speed of up-titration as compared to what could be expected in clinical practice.

This phase IIIb study included a common and difficult-to-treat population than the studies in the MAA did. Being aware of this, and of the dose-response relationship of vortioxetine, the investigators may have tended to use higher doses in this particular population.

In addition, it is difficult to fully translate the observed dose pattern in these studies to what could be expected in clinical practice.

Based on the clinical trial data currently available it could be said that rather than the dose "generally increases over time" the likelihood is that a more substantial proportion of patients are up-titrated to the high dose. Again, whether this reflects reality is another question as it is often seen that within clinical trials, doses are more readily up-titrated than in usual clinical practice.

Section 4.13, Page 44: The Committee was also aware that the company's model assumed that all people with major depressive disorder remain in primary care after first-line treatment. It noted that, in clinical practice in England, this is not consistent with where vortioxetine is likely to be given (that is, secondary care; see section 4.4)

Lundbeck does not support the view that patients failing first-line antidepressant treatment are referred to secondary care or a community mental health trust is representative of clinical practice in the majority of the UK.

In line with NICE guidelines, the insight gained from clinicians both in primary, secondary and tertiary care is that in the main patients with depression are referred after inadequate response to 2-3 antidepressants in primary care. The exception to this is if a patient is suicidal, complex or has depression with psychotic symptoms. In these cases the patient would be automatically referred for specialist care (NICE 2009 and advisory board Appendix 6.4)

Section 4.21, Page 51: The Committee concluded that these benefits were sufficiently captured within the company's economic modelling.

Lundbeck believes the Committee to have overlooked the benefits associated with the lack of discontinuation symptoms experienced with treatment with vortioxetine. All antidepressants are

associated with discontinuation symptoms bar agomelatine and vortioxetine (Taylor et al. 2015). As stated in the submission poor adherence to antidepressant medication is common and patients are often seen to miss consecutive doses of treatment for several days (Demyttenaere et al. 2001). Haddad and Anderson (2007) note that such breaks in therapy can precipitate discontinuation symptoms. In their review of all antidepressants, they reported that the most common discontinuation symptoms included 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 due to disutilities of such side-effects being unavailable from the literature, the cost-effectiveness of vortioxetine may be underestimated versus treatments associated with such symptoms.

Section 4.21, Page 52: The Committee acknowledged that vortioxetine may be a valuable treatment option for people with a major depressive order experiencing cognitive dysfunction.

There is a typographical error in this sentence.

The sentence should read:

"The Committee acknowledged that vortioxetine may be a valuable treatment option for people with a major depressive **disorder** experiencing cognitive dysfunction"

Section 4.21, Page 52: The Committee…. noted that the EQ-5D data from REVIVE reported for the vortioxetine and agomelatine groups did not suggest that the average utility was notably different between treatments.

This statement is not correct. Statistically significant differences in EQ-5D scores in favour of vortioxetine over agomelatine were observed in REVIVE. As reported in the submission the EQ-5D profile data were scored on a summary index, using the UK tariff (Dolan 1997); summary statistics of index scores at each assessment point are shown in Table 20. 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).

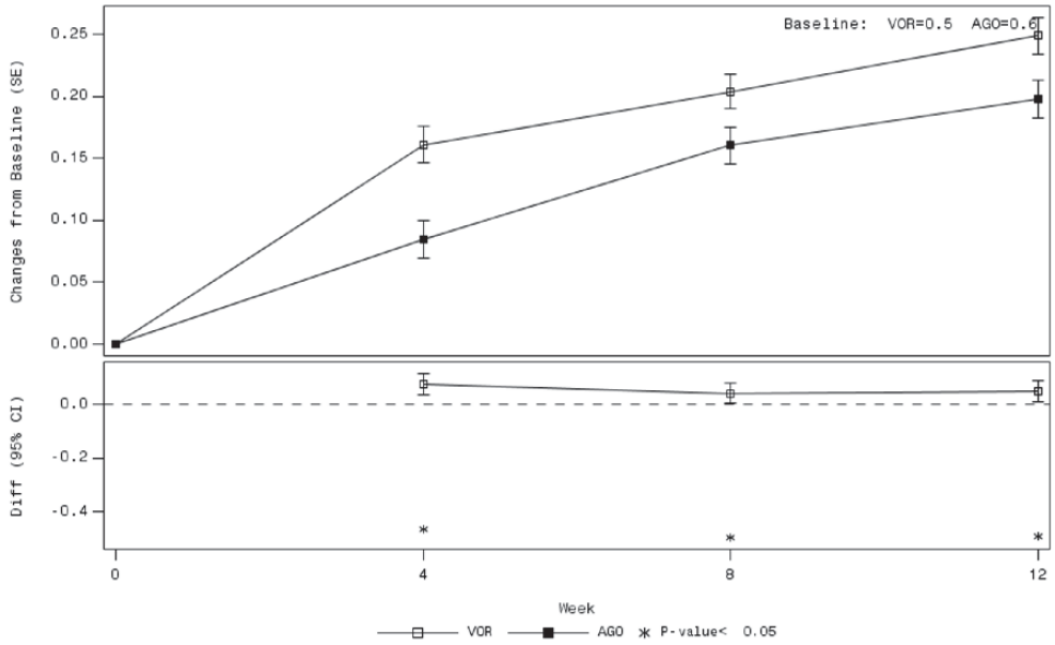
Table 20: Study 14178A (REVIVE). EQ-5D Summary index scores (FAS, OC)

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: REVIVE CSR 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 22. 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).

Figure 22: Study 14178A (REVIVE). Mean changes from baseline in EQ-5D summary index and mean treatment differences to agomelatine (FAS, MMRM)[27]



Source: CSR, 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 22). The area between these curves thus represents the mean quality-adjusted survival difference between the two treatments over 12 weeks of treatment.

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6. Appendices

6.1. Appendix 1: Market shares for individual treatment strategies (CPRD analysis used for Lamy 2015 publication)

Table 21: Market shares for individual treatment strategies in CPRD analysis (unpublished data)

		1st line	2nd line	3rd line	4th line or more
Treatment (detail)	Nb of valid values	123662	62901	37602	63399
	agomelatine	1 (0.00%)	0	2 (0.01%)	36 (0.06%)
	agomelatine-citalopram	0	0	0	10 (0.02%)
	agomelatine-citalopram-other	0	0	0	1 (0.00%)
	agomelatine-duloxetine	0	0	1 (0.00%)	4 (0.01%)
	agomelatine-escitalopram	0	0	0	2 (0.00%)
	agomelatine-escitalopram-mirtazapine	0	0	0	1 (0.00%)
	agomelatine-fluoxetine	0	0	0	1 (0.00%)
	agomelatine-mirtazapine	0	0	0	2 (0.00%)
	agomelatine-mirtazapine-venlafaxine	0	0	0	1 (0.00%)
	agomelatine-other	0	0	0	7 (0.01%)
	agomelatine-other-venlafaxine	0	0	0	1 (0.00%)
	agomelatine-sertraline	0	1 (0.00%)	0	2 (0.00%)
	agomelatine-venlafaxine	0	0	0	4 (0.01%)
	citalopram	55093 (44.55%)	19389 (30.82%)	11288 (30.02%)	13709 (21.62%)
	citalopram-duloxetine	0	89 (0.14%)	38 (0.10%)	98 (0.15%)
	citalopram-duloxetine-fluoxetine	0	0	0	1 (0.00%)
	citalopram-duloxetine-mirtazapine	0	0	0	2 (0.00%)
	citalopram-duloxetine-mirtazapine-other	0	0	0	1 (0.00%)
	citalopram-duloxetine-other	0	0	2 (0.01%)	10 (0.02%)
	citalopram-duloxetine-other-other	0	0	0	1 (0.00%)
	citalopram-duloxetine-venlafaxine	0	0	1 (0.00%)	0
	citalopram-escitalopram	0	177 (0.28%)	55 (0.15%)	96 (0.15%)
	citalopram-escitalopram-fluoxetine	0	0	3 (0.01%)	2 (0.00%)
	citalopram-escitalopram-mirtazapine	0	0	1 (0.00%)	4 (0.01%)
	citalopram-escitalopram-other	0	0	4 (0.01%)	5 (0.01%)
	citalopram-escitalopram-sertraline	0	0	0	1 (0.00%)
	citalopram-escitalopram-venlafaxine	0	0	1 (0.00%)	0
	citalopram-fluoxetine	0	1367 (2.17%)	232 (0.62%)	315 (0.50%)
	citalopram-fluoxetine-mirtazapine	0	0	9 (0.02%)	7 (0.01%)
	citalopram-fluoxetine-other	0	6 (0.01%)	26 (0.07%)	21 (0.03%)
	citalopram-fluoxetine-paroxetine	0	0	2 (0.01%)	0
	citalopram-fluoxetine-sertraline	0	0	1 (0.00%)	4 (0.01%)
	citalopram-fluoxetine-venlafaxine	0	0	3 (0.01%)	2 (0.00%)
	citalopram-fluvoxamine	0	3 (0.00%)	0	0
	citalopram-fluvoxamine-other	0	0	0	1 (0.00%)
	citalopram-mirtazapine	0	738 (1.17%)	228 (0.61%)	568 (0.90%)
	citalopram-mirtazapine-other	0	2 (0.00%)	17 (0.05%)	26 (0.04%)
	citalopram-mirtazapine-other-other	0	0	0	1 (0.00%)
	citalopram-mirtazapine-paroxetine	0	0	2 (0.01%)	0
	citalopram-mirtazapine-sertraline	0	0	3 (0.01%)	3 (0.00%)
	citalopram-mirtazapine-venlafaxine	0	1 (0.00%)	0	2 (0.00%)
	citalopram-other	0	2385 (3.79%)	652 (1.73%)	2175 (3.43%)
	citalopram-other-other	0	0	18 (0.05%)	20 (0.03%)
	citalopram-other-other-venlafaxine	0	0	0	1 (0.00%)
	citalopram-other-paroxetine	0	1 (0.00%)	0	1 (0.00%)
	citalopram-other-sertraline	0	0	8 (0.02%)	12 (0.02%)
	citalopram-other-venlafaxine	0	0	8 (0.02%)	17 (0.03%)
	citalopram-paroxetine	0	122 (0.19%)	26 (0.07%)	47 (0.07%)
	citalopram-paroxetine-venlafaxine	0	0	0	1 (0.00%)
	citalopram-sertraline	0	404 (0.64%)	110 (0.29%)	181 (0.29%)
	citalopram-sertraline-venlafaxine	0	1 (0.00%)	1 (0.00%)	2 (0.00%)
	citalopram-venlafaxine	0	216 (0.34%)	59 (0.16%)	141 (0.22%)
	duloxetine	392 (0.32%)	712 (1.13%)	634 (1.69%)	1807 (2.85%)
	duloxetine-escitalopram	0	18 (0.03%)	13 (0.03%)	23 (0.04%)
	duloxetine-escitalopram-fluoxetine	0	0	1 (0.00%)	0
	duloxetine-escitalopram-mirtazapine	0	0	0	1 (0.00%)
	duloxetine-escitalopram-other	0	0	0	2 (0.00%)
	duloxetine-escitalopram-other-venlafaxine	0	0	0	1 (0.00%)

duloxetine-fluoxetine	0	73 (0.12%)	24 (0.06%)	62 (0.10%)
duloxetine-fluoxetine-mirtazapine	0	0	1 (0.00%)	2 (0.00%)
duloxetine-fluoxetine-other	0	0	4 (0.01%)	4 (0.01%)
duloxetine-mirtazapine	0	16 (0.03%)	32 (0.09%)	137 (0.22%)
duloxetine-mirtazapine-other	0	0	0	19 (0.03%)
duloxetine-mirtazapine-other-other-other	0	0	0	1 (0.00%)
duloxetine-mirtazapine-venlafaxine	0	0	0	5 (0.01%)
duloxetine-other	0	35 (0.06%)	54 (0.14%)	298 (0.47%)
duloxetine-other-other	0	0	1 (0.00%)	9 (0.01%)
duloxetine-other-paroxetine	0	0	0	2 (0.00%)
duloxetine-other-sertraline	0	0	1 (0.00%)	4 (0.01%)
duloxetine-other-venlafaxine	0	0	1 (0.00%)	9 (0.01%)
duloxetine-paroxetine	0	4 (0.01%)	1 (0.00%)	8 (0.01%)
duloxetine-sertraline	0	14 (0.02%)	12 (0.03%)	38 (0.06%)
duloxetine-venlafaxine	0	11 (0.02%)	11 (0.03%)	50 (0.08%)
escitalopram	5223 (4.22%)	2366 (3.76%)	1487 (3.95%)	2324 (3.67%)
escitalopram-fluoxetine	0	134 (0.21%)	28 (0.07%)	51 (0.08%)
escitalopram-fluoxetine-venlafaxine	0	0	1 (0.00%)	0
escitalopram-fluvoxamine	0	1 (0.00%)	0	1 (0.00%)
escitalopram-mirtazapine	0	81 (0.13%)	49 (0.13%)	144 (0.23%)
escitalopram-mirtazapine-other	0	0	0	13 (0.02%)
escitalopram-mirtazapine-paroxetine	0	0	1 (0.00%)	0
escitalopram-mirtazapine-sertraline	0	0	0	1 (0.00%)
escitalopram-other	0	173 (0.28%)	74 (0.20%)	308 (0.49%)
escitalopram-other-other	0	0	2 (0.01%)	2 (0.00%)
escitalopram-other-sertraline	0	0	0	2 (0.00%)
escitalopram-other-venlafaxine	0	0	0	2 (0.00%)
escitalopram-paroxetine	0	15 (0.02%)	2 (0.01%)	8 (0.01%)
escitalopram-sertraline	0	53 (0.08%)	21 (0.06%)	23 (0.04%)
escitalopram-venlafaxine	0	26 (0.04%)	17 (0.05%)	44 (0.07%)
fluoxetine	40833 (33.02%)	13999 (22.26%)	8314 (22.11%)	11082 (17.48%)
fluoxetine-fluvoxamine	0	1 (0.00%)	0	3 (0.00%)
fluoxetine-mirtazapine	0	446 (0.71%)	144 (0.38%)	334 (0.53%)
fluoxetine-mirtazapine-other	0	1 (0.00%)	7 (0.02%)	21 (0.03%)
fluoxetine-mirtazapine-sertraline	0	0	0	4 (0.01%)
fluoxetine-mirtazapine-venlafaxine	0	0	3 (0.01%)	6 (0.01%)
fluoxetine-other	0	1417 (2.25%)	434 (1.15%)	1515 (2.39%)
fluoxetine-other-other	0	0	9 (0.02%)	19 (0.03%)
fluoxetine-other-paroxetine	0	2 (0.00%)	0	5 (0.01%)
fluoxetine-other-sertraline	0	1 (0.00%)	3 (0.01%)	14 (0.02%)
fluoxetine-other-venlafaxine	0	1 (0.00%)	3 (0.01%)	5 (0.01%)
fluoxetine-paroxetine	0	73 (0.12%)	16 (0.04%)	44 (0.07%)
fluoxetine-sertraline	0	222 (0.35%)	73 (0.19%)	149 (0.24%)
fluoxetine-sertraline-venlafaxine	0	0	0	1 (0.00%)
fluoxetine-venlafaxine	0	132 (0.21%)	62 (0.16%)	128 (0.20%)
fluvoxamine	16 (0.01%)	16 (0.03%)	8 (0.02%)	22 (0.03%)
fluvoxamine-mirtazapine	0	0	2 (0.01%)	0
fluvoxamine-other	0	0	0	4 (0.01%)
fluvoxamine-paroxetine	0	0	0	1 (0.00%)
fluvoxamine-sertraline	0	1 (0.00%)	0	0
fluvoxamine-venlafaxine	0	0	0	2 (0.00%)
mirtazapine	4410 (3.57%)	4417 (7.02%)	2922 (7.77%)	5654 (8.92%)
mirtazapine-other	0	205 (0.33%)	180 (0.48%)	605 (0.95%)
mirtazapine-other-other	0	0	4 (0.01%)	12 (0.02%)
mirtazapine-other-other-other-venlafaxine	0	0	0	1 (0.00%)
mirtazapine-other-other-venlafaxine	0	0	0	1 (0.00%)
mirtazapine-other-sertraline	0	0	1 (0.00%)	19 (0.03%)
mirtazapine-other-sertraline-venlafaxine	0	0	0	1 (0.00%)
mirtazapine-other-venlafaxine	0	0	0	14 (0.02%)
mirtazapine-paroxetine	0	28 (0.04%)	26 (0.07%)	66 (0.10%)
mirtazapine-paroxetine-sertraline	0	0	2 (0.01%)	0
mirtazapine-paroxetine-venlafaxine	0	0	0	2 (0.00%)
mirtazapine-sertraline	0	116 (0.18%)	80 (0.21%)	284 (0.45%)
mirtazapine-sertraline-venlafaxine	0	0	4 (0.01%)	3 (0.00%)
mirtazapine-venlafaxine	0	76 (0.12%)	96 (0.26%)	440 (0.69%)
other	7194 (5.82%)	5190 (8.25%)	4264 (11.34%)	8162 (12.87%)
other-other	0	130 (0.21%)	88 (0.23%)	294 (0.46%)
other-other-other	0	0	1 (0.00%)	2 (0.00%)
other-other-other-paroxetine	0	0	0	2 (0.00%)
other-other-paroxetine	0	0	1 (0.00%)	5 (0.01%)

	other-other-sertraline	0	0	9 (0.02%)	7 (0.01%)
	other-other-venlafaxine	0	0	0	17 (0.03%)
	other-paroxetine	0	69 (0.11%)	36 (0.10%)	168 (0.26%)
	other-paroxetine-sertraline	0	1 (0.00%)	0	1 (0.00%)
	other-sertraline	0	358 (0.57%)	155 (0.41%)	661 (1.04%)
	other-sertraline-venlafaxine	0	0	0	7 (0.01%)
	other-venlafaxine	0	79 (0.13%)	99 (0.26%)	483 (0.76%)
	paroxetine	1992 (1.61%)	1152 (1.83%)	814 (2.16%)	1356 (2.14%)
	paroxetine-sertraline	0	17 (0.03%)	10 (0.03%)	32 (0.05%)
	paroxetine-venlafaxine	0	8 (0.01%)	11 (0.03%)	24 (0.04%)
	sertraline	7163 (5.79%)	4254 (6.76%)	2861 (7.61%)	4961 (7.83%)
	sertraline-venlafaxine	0	37 (0.06%)	23 (0.06%)	66 (0.10%)
	venlafaxine	1345 (1.09%)	1818 (2.89%)	1564 (4.16%)	3735 (5.89%)
Treatment group (detail)	Nb of valid values	123662	62901	37602	63399
	Other AD excl Mirt & Ago	200 (0.16%)	117 (0.19%)	118 (0.31%)	299 (0.47%)
	Other AD excl Mirt & Ago-Other AD excl Mirt & Ago	0	0	0	5 (0.01%)
	Other AD excl Mirt & Ago-Other AD excl Mirt & Ago-SNRI	0	0	0	1 (0.00%)
	Other AD excl Mirt & Ago-Other AD/Mirt & Ago	0	10 (0.02%)	5 (0.01%)	44 (0.07%)
	Other AD excl Mirt & Ago-Other AD/Mirt & Ago-SNRI	0	0	0	4 (0.01%)
	Other AD excl Mirt & Ago-Other AD/Mirt & Ago-SNRI-SSRI	0	0	0	1 (0.00%)
	Other AD excl Mirt & Ago-Other AD/Mirt & Ago-SNRI-TCA	0	0	0	2 (0.00%)
	Other AD excl Mirt & Ago-Other AD/Mirt & Ago-SSRI	0	0	2 (0.01%)	11 (0.02%)
	Other AD excl Mirt & Ago-Other AD/Mirt & Ago-SSRI-TCA	0	0	0	1 (0.00%)
	Other AD excl Mirt & Ago-Other AD/Mirt & Ago-TCA	0	0	3 (0.01%)	7 (0.01%)
	Other AD excl Mirt & Ago-SNRI	0	10 (0.02%)	11 (0.03%)	47 (0.07%)
	Other AD excl Mirt & Ago-SNRI-SNRI	0	0	0	1 (0.00%)
	Other AD excl Mirt & Ago-SNRI-SSRI	0	0	0	5 (0.01%)
	Other AD excl Mirt & Ago-SNRI-SSRI-TCA	0	0	0	1 (0.00%)
	Other AD excl Mirt & Ago-SNRI-TCA	0	0	0	10 (0.02%)
	Other AD excl Mirt & Ago-SSRI	0	147 (0.23%)	41 (0.11%)	182 (0.29%)
	Other AD excl Mirt & Ago-SSRI-SSRI	0	0	1 (0.00%)	3 (0.00%)
	Other AD excl Mirt & Ago-SSRI-TCA	0	0	7 (0.02%)	15 (0.02%)
	Other AD excl Mirt & Ago-SSRI-TCA-TCA	0	0	0	2 (0.00%)
	Other AD excl Mirt & Ago-TCA	0	12 (0.02%)	11 (0.03%)	49 (0.08%)
	Other AD/Mirt & Ago	4411 (3.57%)	4417 (7.02%)	2924 (7.78%)	5690 (8.97%)
	Other AD/Mirt & Ago-Other AD/Mirt & Ago	0	0	0	2 (0.00%)
	Other AD/Mirt & Ago-Other AD/Mirt & Ago-SNRI	0	0	0	1 (0.00%)
	Other AD/Mirt & Ago-Other AD/Mirt & Ago-SSRI	0	0	0	1 (0.00%)
	Other AD/Mirt & Ago-SNRI	0	92 (0.15%)	129 (0.34%)	585 (0.92%)
	Other AD/Mirt & Ago-SNRI-SNRI	0	0	0	5 (0.01%)
	Other AD/Mirt & Ago-SNRI-SSRI	0	1 (0.00%)	8 (0.02%)	18 (0.03%)
	Other AD/Mirt & Ago-SNRI-SSRI-TCA	0	0	0	1 (0.00%)
	Other AD/Mirt & Ago-SNRI-TCA	0	0	0	30 (0.05%)
	Other AD/Mirt & Ago-SNRI-TCA-TCA	0	0	0	1 (0.00%)
	Other AD/Mirt & Ago-SSRI	0	1410 (2.24%)	529 (1.41%)	1411 (2.23%)
	Other AD/Mirt & Ago-SSRI-SSRI	0	0	18 (0.05%)	19 (0.03%)
	Other AD/Mirt & Ago-SSRI-TCA	0	3 (0.00%)	23 (0.06%)	69 (0.11%)
	Other AD/Mirt & Ago-TCA	0	195 (0.31%)	175 (0.47%)	568 (0.90%)
	Other AD/Mirt & Ago-TCA-TCA	0	0	1 (0.00%)	5 (0.01%)
	SNRI	1737 (1.40%)	2530 (4.02%)	2198 (5.85%)	5542 (8.74%)
	SNRI-SNRI	0	11 (0.02%)	11 (0.03%)	50 (0.08%)
	SNRI-SNRI-SSRI	0	0	1 (0.00%)	0
	SNRI-SNRI-SSRI-TCA	0	0	0	1 (0.00%)
	SNRI-SNRI-TCA	0	0	1 (0.00%)	8 (0.01%)
	SNRI-SSRI	0	617 (0.98%)	260 (0.69%)	634 (1.00%)
	SNRI-SSRI-SSRI	0	1 (0.00%)	7 (0.02%)	7 (0.01%)
	SNRI-SSRI-TCA	0	1 (0.00%)	18 (0.05%)	48 (0.08%)
	SNRI-SSRI-TCA-TCA	0	0	0	1 (0.00%)
	SNRI-TCA	0	104 (0.17%)	142 (0.38%)	734 (1.16%)
	SNRI-TCA-TCA	0	0	1 (0.00%)	15 (0.02%)
	SSRI	110320 (89.21%)	41176 (65.46%)	24772 (65.88%)	33454 (52.77%)
	SSRI-SSRI	0	2590 (4.12%)	573 (1.52%)	951 (1.50%)
	SSRI-SSRI-SSRI	0	0	6 (0.02%)	7 (0.01%)
	SSRI-SSRI-TCA	0	11 (0.02%)	40 (0.11%)	59 (0.09%)
	SSRI-TCA	0	4255 (6.76%)	1310 (3.48%)	4649 (7.33%)
	SSRI-TCA-TCA	0	0	32 (0.09%)	38 (0.06%)
	TCA	6994 (5.66%)	5073 (8.07%)	4146 (11.03%)	7863 (12.40%)

TCA-TCA	0	118 (0.19%)	77 (0.20%)	240 (0.38%)
TCA-TCA-TCA	0	0	1 (0.00%)	2 (0.00%)

Appendix 9: Summary report: Responses to the questionnaire regarding clinical practice to inform a cost-effectiveness model in MDD to be submitted to NICE

A questionnaire was distributed to 7 clinicians in June-July 2015 to try to establish current clinical practice in the NHS. Of the 7 clinicians, 6 were psychiatrists and 1 was a GP with a special interest in mental health, particularly depression. The participants were not incentivised to provide their feedback.

The questionnaire was specifically designed to inform the revised structure and potential parameterisation of the cost-effectiveness model. Hence, the questions focussed on triggers for clinical decisions, in particular around the switching of antidepressants.

The responses to the questionnaire have been summarised below under each question. The responses were then used to inform the key questions to be discussed in more detail at the advisory board held to inform the cost-effectiveness model and gain a consensus of opinion.

QUESTIONS

Referral to specialists

1. How many antidepressants does a patient receive within primary care for the treatment of a single major depressive episode before they are referred to a specialist?

Only 1 respondent advised that referral would take place after 1 antidepressant. The majority felt it was usually 2, although 1 respondent felt this might be higher in actual clinical practice.

2. If a patient is referred to a specialist for the treatment of their depression, at what point will they be referred back out to primary care?

In general referral back to primary care was when the patient had "started to respond to treatment". But this depended on severity and was based on clinical judgement. The responses also varied in the length of time before referral back to primary care ranging from as soon as possible (on average 8 weeks) to 6-12 months in remission. Service capacity was also mentioned as a reason for less frequent follow up than ideal and sooner referral back to primary care.

Treatment switching

Please think about a patient who has failed on 2 previous antidepressants (at a therapeutic dose for an adequate trial period) for the treatment of their current episode.

3. What would you consider an adequate "trial period" of an antidepressant (used as a third treatment) to determine efficacy (if the patient could tolerate the product)?
    a. And how would you define "efficacy"? E.g. response (>50% reduction in symptoms), remission, something else?

The time to switching varied for respondents, who also made comments about checking compliance and ensuring proper dose titration. 3-4 weeks was deemed the minimum adequate trial of a 3rd line antidepressant, the majority of respondents suggested between 6 and 8 weeks, and the maximum stated in a response was 8-12 weeks. Response was generally defined as a 50% reduction in symptoms and how efficacy was defined.

4 weeks of treatment

4. If a patient has shown no improvement/minimal improvement after 4 weeks of treatment on their 3rd antidepressant would you continue their treatment or stop/change it?

    a. If you would continue, how long would you continue for before reassessment and would you adjust the dose?
    b. If you would stop/change treatment, what approach would you take? E.g. switch treatment, augmentation, combination.

A number of respondents said they would change treatment at 4 weeks if there was no response to treatment, others mentioned a need to titrate the dose upwards. Some respondents stated they would augment or combine treatment at 4 weeks.

5. Would your answers differ to the above if the patient had:
    a. Responded (50% reduction in symptom score)?

Most respondents would continue treatment and potentially increase the dose if a patient had responded at 4 weeks.

    b. Remitted?

The responses to this question were inconsistent probably due its dependence on the previous responses and the wording of the questions. However, along with completing the questionnaire the clinicians were asked to talk through their responses; from this it was clear that if a patient was in remission they would be continued on treatment.

8 weeks of treatment (similar questions to the above at 4 weeks)

6. If a patient has shown no improvement/minimal improvement after 8 weeks of treatment on their 3rd antidepressant would you continue their treatment or stop/change it?

    a. If you would continue, how long would you continue for before reassessment and would you adjust the dose?
    b. If you would stop/change treatment, what approach would you take? E.g. switch treatment, augmentation, combination

Two respondents felt patients would not get to 8 weeks of treatment if no improvement or minimal effect had been seen at 4 weeks. Treatment options for these patient patients with minimal improvement would be augmentation or combination. The other respondents suggested that at 8 weeks a patient would be switched due to lack of efficacy.

7. Would your answers differ to the above if the patient had:

    c. Responded (50% reduction in symptom score)?

One respondent felt if it had taken 8 weeks to get to response then generally the patient would have had their treatment switched or augmentation/combination treatment by then. Others felt at 8 weeks treatment should be continued and some felt treatment augmentation/combination would take place.

d. Remitted?

The responses to this question were inconsistent probably due its dependence on the previous responses and the wording of the questions. However, along with completing the questionnaire the clinicians were asked to talk through their responses; from this it was clear that if a patient was in remission they would be continued on treatment.

12 weeks of treatment

8. If a patient has shown no improvement/minimal after 12 weeks of treatment on their 3rd antidepressant would you continue their treatment or stop/change it?

    a. If you would continue, how long would you continue for before reassessment and would you adjust the dose?
    b. If you would stop/change treatment, what approach would you take? E.g. switch treatment, augmentation, combination

If a patient had got to 12 weeks with no improvement/minimal response all would stop/change therapy, this would primarily be switch or augmentation/combination.

9. Would your answers differ to the above if the patient had:

    e. Responded (50% reduction in symptom score)?

Some respondents suggested that response was an adequate outcome for the majority of their patients and therefore they would be continued on treatment. Other respondents felt remission is the ultimate goal, however these patients would have already have been switched at week 9.

i. If you would continue this patient on treatment how long would they be continued for?

For patients with a 50% response at 12 weeks respondents confirmed they would stay on treatment for a minimum of 6 months. However not all answered this question as they previously answered that patients would not get to 12 weeks with only response as an outcome. One respondent noted that the length of time on maintenance treatment would depend on the number of previous episodes the patient had experienced.

ii. In addition, if continued on treatment would you ever expect them to achieve remission and subsequent recovery?
    1. If so, as an average how long would you expect (on average) each of these milestones to take?

Responses were mixed to this question, some stated full recovery was rare, another commented that effective treatment has a quick response but the effective treatment may take a while to find.

f. Remitted?

The responses to this question were inconsistent probably due its dependence on the previous responses and the wording of the questions. However, along with completing the questionnaire the clinicians were asked to talk

through their responses; from this it was clear that if a patient was in remission they would be continued on treatment.

General question:

Would you expect a patient who does not achieve response at week 8 to achieve the following at week 12, if so, what proportion?

Remission:
Response:
No response:

All respondents felt that if a patient had no achieved any response at week 8 then they were unlikely to achieve response or remission at 12 weeks. Some respondents felt that no patients would reach remission or response if no response had been achieved at 8 weeks and advised stopping treatment.

How long is the average patient continued on treatment for once symptom resolution has been achieved?

The respondents varied in their responses. The majority answered around 6 months maintenance was standard. However, some respondents felt the length of maintenance treatment increased when patients had experienced multiple previous episodes.

6.2. Appendix 2: Relative efficacies systematic review report

The relative efficacy of antidepressants in different lines of treatment in major depressive disorder (MDD): a systematic review

Version: 3.0

Date prepared: 15th July 2015

Abbreviations

ADM	Antidepressant medication
APA	American Psychiatric Association
AS	After switch
BDI	Beck Depression Inventory
BS	Before switch
CDRS	Cornell Dysthymia Rating Scale
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CI	Confidence interval
CPRS	Comprehensive Psychopathological Rating Scale
DARE	Database of Abstracts of Reviews of Effects
ECNP	European College of Neuropsychopharmacology
HAM-D	Hamilton rating scale for depression
HTA	Health technology assessment
ITT	Intention to treat
MADRS	Montgomery–Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
MDE	Major depressive episode
NASSA	Noradrenergic and specific serotonergic antidepressant
NICE	National Institute for Health and Care Excellence
NR	Not reported
NRI	Norepinephrine reuptake inhibitors
NS	Not significant
OR	Odds ratio
PP	Per protocol
RCT	Randomised controlled trial
RDS	Raskin Depression Scale
SD	Standard deviation
SE	Standard error
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRE	Selective serotonin reuptake enhancer
SSRI	Selective serotonin reuptake inhibitor
STA	Single technology appraisal
TCA	Tricyclic antidepressant
TeCA	Tetracyclic antidepressant
TRD	Treatment resistant depression

Objective

The objective of this qualitative systematic review was to identify publications reporting evidence demonstrating whether the relative efficacy of individual antidepressants or classes of antidepressant differs between lines of treatment, when patients in later lines have been switched to an alternative antidepressant due to lack of efficacy on previous treatment.

Methodology

Data sources

Electronic database search

The following electronic databases were searched via the OVID platform on 22nd April 2015:

- MEDLINE® In-Process & Other Non-Indexed Citations and MEDLINE® 1946 to present
- Embase 1980 to present
- The Cochrane Library, incorporating:
  - The Cochrane Central Register of Controlled Trials (CENTRAL)
  - The Health Technology Assessment (HTA) Database
  - Cochrane Database of Systematic Reviews (Cochrane Reviews)
  - Database of Abstracts of Reviews of Effects (DARE)

The search strings used to identify relevant studies are detailed in Appendix A.

Identification of relevant publications

Citations identified by the electronic database search were reviewed on the basis of title and abstract. A detailed hierarchy system was used to assess whether citations should be excluded at this stage and, if so, documented according to specific exclusion criteria. Studies comparing one individual antidepressant with placebo that could not be excluded for any other reason were excluded and tagged to allow further assessment if required at a later date. Full publications of references deemed to be potentially relevant were obtained and examined in full to identify the studies eligible for inclusion in the systematic review.

Hand searching

To supplement the electronic database search, the following conferences' proceedings were searched for 2012 to 2014:

- American Psychiatric Association (APA) Annual Meeting
- European College of Neuropsychopharmacology (ECNP) Congress

The following search terms were used to identify the relevant sessions within the conference proceedings:

- "MDD"
- "M.D.D"
- "Major depressi"
- "Clinical depression"
- "Resistant depression"

In addition, reference lists of included studies, and review papers included after title and abstract screening that contained any discussion of switching strategies or crossover trials, were searched by hand to identify potentially relevant publications that were not identified in the electronic database searches.

Selection criteria

The eligibility criteria for studies to be included in the systematic review are detailed in Table 22.

Table 22. Eligibility criteria

Criteria	Include	Exclude

Population	• Adults (≥18 years), with
	• Major depressive disorder (MDD)
	  o Major depression
	  o Clinical depression
	  o Unipolar depression
	  o Treatment resistant depression
	  o Unipolar disorder
		• Patients <18 years.
		• Mixed populations excluded if <80% meet the inclusion criteria.
		• If it is unclear whether the population meets inclusion criteria, it will be excluded.

Interventions/ Comparators	At least 2 antidepressants, or classes of antidepressants, including at least 1 from: Selective serotonin reuptake inhibitors (SSRIs) • Citalopram • Sertraline • Escitalopram • Fluvoxamine • Fluoxetine • Dapoxetine • Paroxetine Seratonin norepinephrine reuptake inhibitors (SNRIs) • Desvenlafaxine • Levomilnacipran • Duloxetine • Tofenacin • Milnacipran • Venlafaxine Tricyclic antidepressants (TCAs) • Amitriptyline • Lofepramine • Amitriptylinoxide • Melitracen • Clomipramine • Nitroxazepine • Desipramine • Nortriptyline • Dibenzepin • Noxiptiline • Dosulepin • Protriptyline • Doxepin • Trimipramine • Imipramine Tetracyclic antidepressant (TeCAs) • Amoxapine • Mirtazapine • Maprotiline • Setiptiline/Teciptiline • Mianserin Monoamine oxidase inhibitors (MAOIs) • Isocarboxazid • Metralindole • Phenelzine • Moclebemide • Tranylcypromine • Pirlindole • Selegiline (Emsam) • Toloxatone Other • Agomelatine • Teniloxazine • Bupropion/Amfebutamone • Trazodone • Etoperidone • Vilazodone • Nefazodone • Viloxazine • Reboxetine • Vortioxetine • Tandospirone	• Any interventions not currently used for the treatment of MDD • 1 individual antidepressant or class of antidepressant only (including different doses of same antidepressant) • Studies with 1 antidepressant vs placebo will be excluded but tagged
Outcomes	• Any study reporting at least one of the following: • Comparison of the relative efficacy of individual antidepressants, or classes of antidepressants, between lines of treatment. • Efficacy, or relative efficacy, of individual antidepressants, or classes of antidepressants, at different lines of treatment (no comparison reported). • (Patients in the later line(s) of treatment [‘after-switch’ patients] must have been switched to an alternative antidepressant due to lack of efficacy on previous treatment for the current MDE) • (If results of different treatment lines from one study are reported in separate publications, the study will still be eligible.)	• No reporting or review of efficacy or relative efficacy o Studies with efficacy results in one line of treatment only will be excluded but tagged • (Results of different studies reported in separate publications will not be eligible to be compared)
Study designs	Crossover trials, RCTs, cohort studies, systematic reviews, meta-analyses, reviews	Protocol only, economic evaluations, cost studies, utility studies, single-patient case studies

Criteria	Include	Exclude
Other limitations	English language publications	Non-English language publications

Abbreviations: MDD, major depressive disorder; MDE, major depressive episode; RCT, randomised controlled trial.

Data extraction

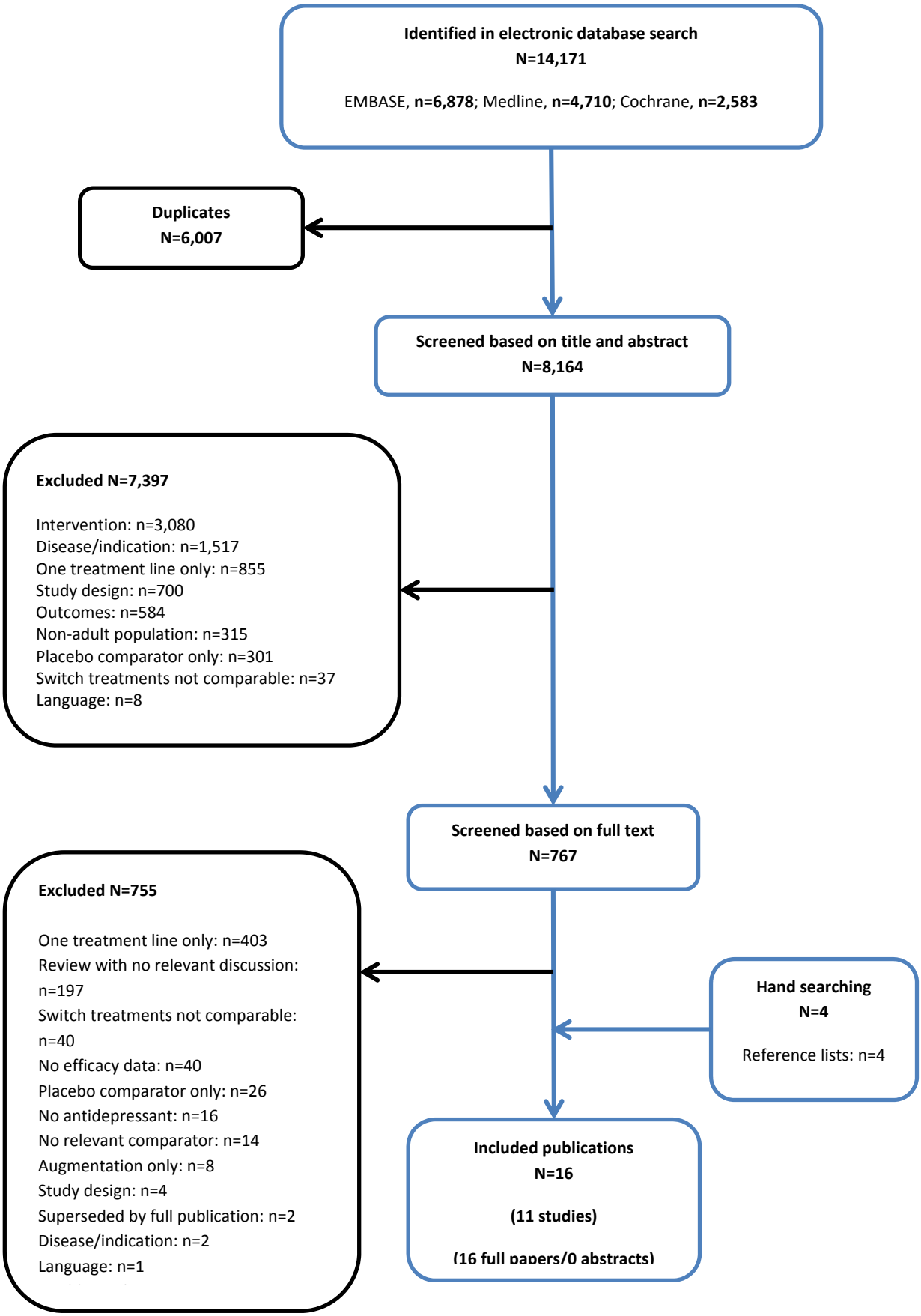
Details of study design, baseline characteristics and relative efficacy results of included studies were extracted into a pre-designed table. Results data were only extracted for efficacy outcomes reported in both lines of treatment. Where results for within-treatment line differences (relative efficacy) between interventions were not reported, the differences were calculated by the analyst by subtracting the efficacy result for one intervention from the other.

Results

Identification of included studies

The electronic searches identified 14,171 citations. After removal of 6,007 duplicates, 8,164 citations were then screened based on title and abstract using the inclusion criteria detailed in Table 22. Following this initial screening, 767 citations were deemed potentially relevant and screened on the basis of the full publications. Following this, 16 publications of 11 individual studies met the eligibility criteria and were included in the systematic review. Figure 23 details the flow of included and excluded studies.

Figure 23: Study flow



Included studies

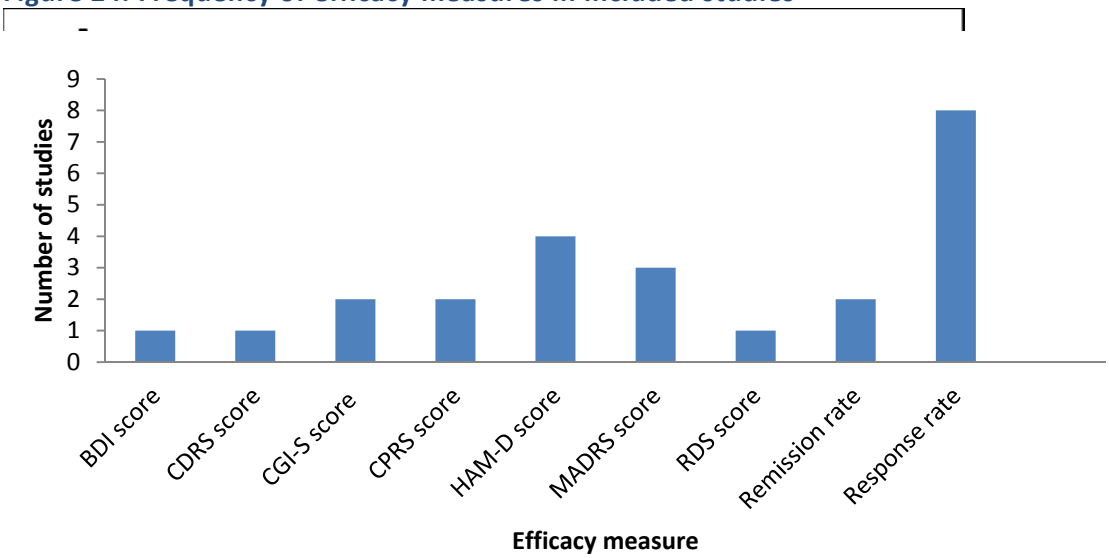
This systematic review identified 16 publications of 11 studies reporting data that could be used to demonstrate whether the relative efficacy of different antidepressants, or classes of antidepressants, differs between lines of treatment, when later lines follow a treatment switch due to lack of or inadequate efficacy. Relative efficacy data from the included studies are summarised in Table 23.

There were no publications that compared the relative efficacy of antidepressants between treatment lines. Instead, the majority of the evidence came from nine crossover trials reported in 14 publications (2-15), in addition to one meta-analysis (16) and one post-hoc subpopulation analysis of a randomised controlled trial (RCT) (17).

Efficacy outcomes were reported in a number of formats; **only efficacy outcomes reported for both before- and after-switch (when patients switched treatment due to lack of or inadequate efficacy) populations were relevant in this systematic review**. These were: response rate, remission rate, Hamilton Rating Scale for Depression (HAM-D), Montgomery–Åsberg Depression Rating Scale (MADRS), Clinical Global Impression-Severity (CGI-S) scale, Comprehensive Psychopathological Rating Scale (CPRS), Beck Depression Inventory (BDI), Cornell Dysthymia Rating Scale (CDRS) and the Raskin Depression Scale (RDS). The most frequently reported efficacy outcome was response rate, reported in eight studies (eleven publications), (based on a ≥50% reduction in HAM-D score (2, 6-8, 11-13, 15, 17), at least a 'much improved' rating on the Clinical Global Impression-Improvement (CGI-I) scale (5, 11, 12, 17), or as an odds ratio (16)), followed by HAM-D score in four studies (six publications) (3, 11-14, 17). The MADRS score was reported in three studies (five publications) (3, 11-14), and the CPRS score, the CGI-S score and remission rates were reported in two studies each (3, 4, 10-14, 16). The BDI, CDRS, and RDS scores were reported in one study (in two publications) each (3, 11, 12, 14). This is illustrated in Figure 24.

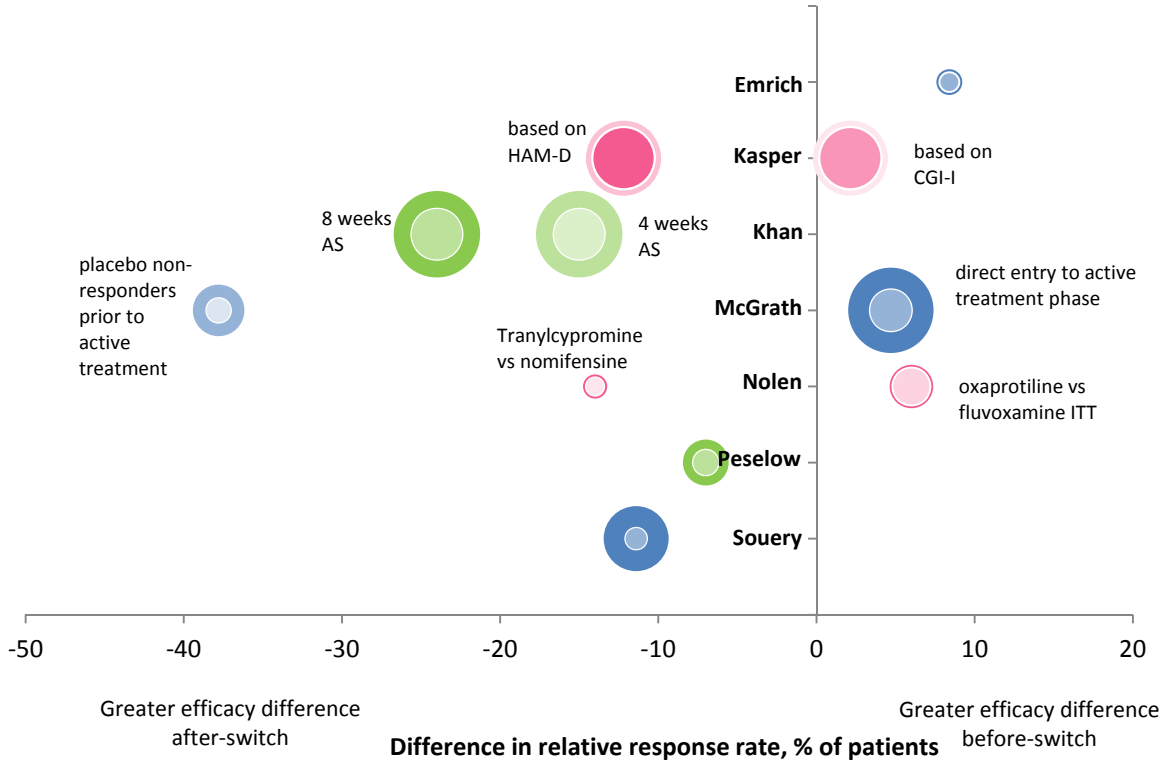
Results for difference in relative efficacy of antidepressants between lines of treatment for the response rate outcome (the most frequently reported) are illustrated in Figure 25. Although eight studies reported on response rate, only the seven that reported response to treatment as number of patients and/or percentage of patients are displayed in the figure; Bauer 2009 (16) reported response as an odds ratio only, and therefore this study cannot be presented on the same scale. Difference in relative efficacy was calculated as: before-switch efficacy difference minus after-switch efficacy difference. The bubble areas are sized to represent the total number of patients in the study; the outer circles represent the before-switch population sizes, the inner circles represent the after-switch population sizes; the larger the bubble, the larger the sample size. This should be taken into consideration as sample size is likely to affect the reliability of the results. In addition, population sizes were always smaller in the after-switch samples than in the before-switch samples, which may affect the reliability of the after-switch efficacy difference used in the relative efficacy difference calculation. Other outcomes have not been displayed graphically as each was only reported in a few studies.

Figure 24. Frequency of efficacy measures in included studies



Abbreviations: BDI, Beck Depression Inventory; CDRS, Cornell Dysthymia Rating Scale; CGI-S, Clinical Global Impression-Severity; CPRS, Comprehensive Psychopathological Rating Scale; HAM-D, Hamilton rating scale for depression; MADRS, Montgomery–Åsberg Depression Rating Scale; RDS, Raskin Depression Scale.
Only measures reported in both before-switch and after-switch populations have been used in this systematic review.

Figure 25. Difference in relative response rate between lines of treatment



Abbreviations: AS, after switch; CGI-I, Clinical Global Impression – Improvement; ITT, intention to treat; HAM-D, Hamilton rating scale for depression.
Difference in relative response rate has been calculated as: before-switch efficacy difference minus after-switch efficacy difference. Bubble areas are representative of the sample sizes: the darker shade represents the before-switch population size, the lighter shade represents the after-switch population size. The larger the bubble, the larger the sample size. The further

from zero, the higher the relative effect size. Only studies reporting response to treatment as number of patients or percentage of patients are shown. Measures of uncertainty or statistical significance are not represented.

Table 23: Summary of included studies

Reference	Study type	Treatment duration	Intervention (class)	Type of efficacy outcome	Measure of efficacy	Before switch				After switch			
						Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value	Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value
Bauer 2009 (16)	Meta-analysis	NR	Venlafaxine (SNRI)	Response	Random effects OR (95% CI)	NR	29 trials *N=3,598*	NR	1.15 (1.02, 1.29) p=NR	NR	NR	NR	NR
			SSRIs				29 trials *N=2,952*	NR			NR	NR	
			Venlafaxine (SNRI)	Remission	Random effects OR (95% CI)		23 trials *N=3,047*	NR	1.19 (1.06, 1.34) p=NR		NR	NR	NR
			SSRIs				23 trials *N=2,392*	NR			NR	NR	
			Venlafaxine (SNRI)	Response	Random effects OR (95% CI)	NR	NR	NR	NR	TRD	4 trials *N=2,150*	NR	1.38 (0.67, 3.38) p=NR
			Other ADMs (mostly SSRIs)				NR	NR			4 trials, *N=2,000*	NR	
			Venlafaxine (SNRI)	Remission	Random effects OR (95% CI)		NR	NR	NR		5 trials *N=2,400*	NR	1.36 (0.99, 2.10) p=NR
			Other ADMs (mostly SSRIs)				NR	NR			5 trials *N=2,477*	NR	
Emrich 1987 (2)	Randomised double-blind crossover trial	BS: 3 weeks AS: 3 weeks	Fluvoxamine (SSRI)	Response rate (based on ≥50% reduction in HAM-D score)	%	1 week washout	N=12	N (%) 4 (*33.3%*)	*-16.7%* p=NR	Non-responders to BS treatment undergone 1 week placebo washout	N=6	N (%) 1 (*16.7%*)	*-8.3%* p=NR
			Oxaprotiline (TCA)				N=12	N (%) 6 (*50%*)			N=8	N (%) 2 (*25%*)	
Kasper	Post-hoc sub-	BS: 6	Agomelatine	HAM-D	Mean (SD)	Not previously	N=130[†]	9.3 (6.9)	1.10[‡]	Treated with ADM	N=176[†]	11.1 (7.0)	1.63[‡]

Reference	Study type	Treatment duration	Intervention (class)	Type of efficacy outcome	Measure of efficacy	Before switch				After switch			
						Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value	Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value
2013 (17)	population analysis of RCT	weeks AS: 6 weeks	Sertraline (SSRI)	score	endpoint score	treated with ADMs in the year prior to trial	Number of episodes: 2.0 HAM-D: 26.1 (2.8) CGI-I: 4.7 (0.7)	10.5 (7.3)	[-1.20, 3.39] p=0.347	in the year prior to trial: SSRIs, venlafaxine, tianeptine, mianserin, mirtazapine or amitriptyline (unclear whether prior treatment refers to current MDE)	Number of episodes: 3.0 HAM-D: 26.5 (3.0) CGI-I: 4.7 (0.7)	13.0 (8.7)	[-0.45, 3.71] p=0.124
			Agomelatine	Response rate (based on HAM-D score)	%			73%	*0.1%* p=NS[§]			67.5%	*12.3%* p=NS[§]
			Sertraline (SSRI)					72%				55.2%	
			Agomelatine	Response rate (based on CGI-I score)	n (%)			61 (87.1%)	-7.14[¶] [-19.95, 5.66] p=0.270			64 (80.0%)	-5.00[¶] [-17.32, 7.32] p=0.431
			Sertraline (SSRI)					48 (80.0%)				72 (75.0%)	
Keller 1998 (3) and Thase 2002 (14)	Initial RCT (3) and subsequent crossover trial (14)	BS: 12 weeks AS: 12 weeks	Sertraline (SSRI)	HAM-D score	Mean (SE) change from baseline	43% ADM naïve; 20% prior adequate ADM	N=426 HAM-D: 25.0	-11.5	*0.4* p=NS	Non-responders to BS treatment	N=50 HAM-D: 25.0	-12.1 (9.3)	*2.8* p=NS
			Imipramine (TCA)				N=209 HAM-D: 25.1	-11.1			N=117 HAM-D: 24.6	-9.3 (11.0)	
			Sertraline (SSRI)	MADRS score	Mean (SE) change from baseline		N=426 MADRS: 25.4	-12.8	*-0.1* p=NS		N=50 MADRS: 25.8	-12.8 (11.5)	*2.9* p=NS
			Imipramine (TCA)				N=209 MADRS: 25.7	-12.9			N=117 MADRS: 24.8	-9.9 (12.7)	
			Sertraline (SSRI)	CDRS score	Mean (SE) change from baseline		N=426 CDRS: 40.7	-19.7	*1.0* p=NS		N=50 CDRS: 39.7	-17.8 (15.7)	*4.3* p=NS
			Imipramine (TCA)				N=209 CDRS: 40.6	-18.7			N=117 CDRS: 38.7	-13.5 (17.4)	
			Sertraline (SSRI)	BDI score	Mean (SE) change		N=426 BDI: 24.7	-11.6	*0.8* p=NS		N=50 BDI: 22.3	-9.8 (10.0)	*2.3* p=NS

Reference	Study type	Treatment duration	Intervention (class)	Type of efficacy outcome	Measure of efficacy	Before switch				After switch			
						Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value	Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value
			Imipramine (TCA)		from baseline		N=209 BDI: 24.3	-10.8			N=117 BDI: 22.8	-7.5 (10.6)	
			Sertraline (SSRI)	CGI-S score	Mean (SE) change from baseline		N=426 CGI-S: 4.2	-1.6	*0.2* p=NS		N=50 CGI-S: 4.3	-1.7 (1.2)	*0.4* p=NS
			Imipramine (TCA)				N=209 CGI-S: 4.2	-1.4			N=117 CGI-S: 4.2	-1.3 (1.3)	
Khan 2009 (15)	Randomised double-blind crossover trial	BD: 6 weeks AS: 4 and 8 weeks	Mirtazapine (TeCA)	Response rate (based on ≥50% reduction in HAM-D score)	n (%)	7 day placebo washout from any previous psychotropic medication	N=133	74 (56%)	*-7%* p=NS	Non-responders to BS treatment, undergone 1 week washout	N=46 HAM-D: 22.7	4 weeks: (39%) 8 weeks: 25 (54%)	4 weeks: *8%* 8 weeks: *17%* p=NR
			Amitriptyline (TCA)				N=136	86 (63%)			N=51 HAM-D: 21.0	4 weeks: (31%) 8 weeks: 19 (37%)	
Lingjaerde 1983 (4)	Randomised double-blind crossover trial	BS: 3 weeks AS: 3 weeks	Desipramine (TCA)	CPRS score	Mean change from baseline	≥5 days washout for any recently treated patients	N=12 CPRS: 17.3 Previous ADM, n: 6	*-7.0*	*4.5* p=NS	Non-responders to BS treatment	N=6 CPRS: 16.3	*-12.2*	*5.1* p=NS
			Zimelidine (SSRI)				N=12 CPRS: 19.0 Previous ADM, n: 4	*-2.5*			N=4 CPRS: 13.4	*-7.1*	
McGrath 1993 (5)	Randomised crossover trial	BS: 6 weeks AS: 6	Phenelzine (MAOI)	Response rate (based on	n (%)	10 day single-blind placebo washout	N=127	96 (*75.6%*)	*23.7%* p=NR	Non-responders to BS treatment, undergone 5 days of	N=41	21 (51%)	*19%* p=NS

Reference	Study type	Treatment duration	Intervention (class)	Type of efficacy outcome	Measure of efficacy	Before switch				After switch			
						Population details	**Baseline data** **Population size, N** **Severity measure, mean (SD)**	**Absolute efficacy**	**Efficacy difference** **p-value**	**Population details**	**Baseline data** **Population size, N** **Severity measure, mean (SD)**	**Absolute efficacy**	**Efficacy difference** **p-value**
		weeks	Imipramine (TCA)	CGI-I score of 'much improved' or greater)			N=135	70 (*51.9%*)		drug tapering and 9 day washout (ITT analysis); CGI-S: 3.9 (0.6) HAM-D: 14.6 (3.9)	N=25	8 (32%)	
			Phenelzine (MAOI)			Non-responders to 6 weeks placebo treatment	N=48	26 (*54.2%*)	*16.7%* p=NR	Non-responders to BS treatment (ITT analysis)	N=15	10 (67%)	*54.5%* P<0.05
			Imipramine (TCA)				N=48	18 (*37.5%*)			N=8	1 (12.5%)	
Nolen 1985 (6), Nolen 1988a (8) and Nolen 1988b (7)	Randomised crossover trial	BS: 2-4 weeks AS: 2-4 weeks	Oxaprotiline (TeCA)	Response rate (based on ≥50% reduction in HAM-D score, lasting for ≥6 months)	n (%)	ITT population: Non responders to ≥4 weeks ADM at adequate dose, majority non-responders to 2-3 ADMs. ≥1 week washout prior to study	N=33	5 (15%)	*15%* p=significant	Non responders to 2-4 weeks BS treatment, in addition to at least one other ADM pre-study	N=31	6 (19%)	*9%* p=NR
			Fluvoxamine (SSRI)				N=35	0 (0%)			N=21	2 (10%)	
		BS: 4 weeks AS: 4 weeks	Oxaprotiline (TeCA)	Response rate (based on ≥50% reduction in HAM-D score, lasting for ≥6 months)	n (%)	PP population: Non responders to ≥4 weeks ADM at adequate dose, majority non-responders to 2-3 ADMs. ≥1 week washout prior to study	N=19	2 (*10.5%*)	*6.3%* p=NR	Non responders to 4 weeks BS treatment, in addition to at least one other ADM pre-study	N=22	3 (*13.6%*)	*-6.4%* p=NR
			Fluvoxamine (SSRI)				N=24	1 (*4.2%*)			N=15	3 (*20%*)	
		BS: 4 weeks AS: 4	Tranylcy-promine (MAOI)	Response rate (based on ≥50%	n (%)	Non responders to oxaprotiline or fluvoxamine in above crossover	N=11	4 (36%)	*36%* p=significant	Non responders to 4 weeks BS treatment, in addition to at least	N=8	4 (50%)	*50%* p=NR

Reference	Study type	Treatment duration	Intervention (class)	Type of efficacy outcome	Measure of efficacy	Before switch				After switch			
						Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value	Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value
		weeks	Nomifensine	reduction in HAM-D score, lasting for ≥6 months)		trial, in addition to at least one other ADM pre-study	N=10	0 (0%)		one other ADM pre-study	N=5	0 (0%)	
Nyström 1985 (9) and Nyström 1987 (10)	Randomised double-blind crossover trial	BS: 4 weeks AS: 4 weeks	Maprotiline (TCA)	CPRS score	% (SD) change from baseline	Some patients previously treated; ≥4–7 days washout from any previous ADM. CPRS ≥10 following washout	N=35 CPRS: NR Severity, n: Mild, 1 Moderate, 23 Marked, 10 Severe, 1	-29% (26)	*10%* p=NR	Non-responders to BS treatment	N=7 CPRS: NR Severity, n: Mild, 0 Moderate, 5 Marked, 1 Severe, 1	-46% (19)	*-1%* p=NR
			Zimelidine (SSRI)				N=40 CPRS: NR Severity, n: Mild, 0 Moderate, 20 Marked, 14 Severe, 6	-19% (27)			N=7 CPRS: NR Severity, n: Mild, 0 Moderate, 5 Marked, 2 Severe, 0	-47% (29)	
Peselow 1989a (11) and 1989b (12)[††]	Randomised double-blind crossover trial	BS: 6 weeks AS: NR	Paroxetine (SSRI)	Response rate (based on ≥50% reduction in HAM-D score or CGI-I score of 'much improved' or greater)	n (%)	Reported data for patients who completed ≥1 week of treatment	N=40 HAM-D: ≥18 RDS: ≥9	19 (48%)	*-16%* p=NR	Non-responders to BS treatment	N=10	5 (50%)	*-23%* p=NR
			Imipramine (TCA)				N=36 HAM-D: ≥18 RDS: ≥9	23 (64%)			N=15	11 (73%)	

Reference	Study type	Treatment duration	Intervention (class)	Type of efficacy outcome	Measure of efficacy	Before switch				After switch			
						Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value	Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value
			Paroxetine (SSRI)	HAM-D score	Change from baseline		N=40 HAM-D: ≥18 RDS: ≥9	-10.05	*-5.51* p=0.016		N=10	-8.4	*-4.73* p=significant
			Imipramine (TCA)				N=36 HAM-D: ≥18 RDS: ≥9	-15.56			N=15	-13.13	
			Paroxetine (SSRI)	RDS score	Change from baseline		N=40 HAM-D: ≥18 RDS: ≥9	-2.78	*-1.66* p=0.017		N=10	-2.4	*-1.6* p=significant
			Imipramine (TCA)				N=36 HAM-D: ≥18 RDS: ≥9	-4.44			N=15	-4.00	
			Paroxetine (SSRI)	CGI-S score	Change from baseline		N=40 HAM-D: ≥18 RDS: ≥9	-1.03	*-0.75* p=0.011		N=10	-0.7	*-1.1* p=significant
			Imipramine (TCA)				N=36 HAM-D: ≥18 RDS: ≥9	-1.78			N=15	-1.80	
			Paroxetine (SSRI)	MADRS score	Change from baseline		N=40 HAM-D: ≥18 RDS: ≥9	-12.05	*-5.26* p=0.041		N=10	-7.8	*-6.4* p=NS
			Imipramine (TCA)				N=36 HAM-D: ≥18 RDS: ≥9	-17.31			N=15	-14.20	

Reference	Study type	Treatment duration	Intervention (class)	Type of efficacy outcome	Measure of efficacy	Before switch				After switch			
						Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value	Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value
Souery 2011 (13)	Randomised crossover trial	BS: 4 weeks AS: 4 weeks	Citalopram (SSRI)	Response rate (based on ≥50% change in HAM-D score)	%	Non-response to ≥4 weeks adequate treatment with ≥1 ADM (other than study ADMs): mainly SSRIs, TCAs, SNRIs; some NASSAs, NRIs, MAOIs, SSREs, trazodone; Reported data for 4-week completers only	N=85 HAM-D: 24.19 (4.31) MADRS: 31.38 (6.61)	n (%) 46 (54.12)	*-1.10* p=0.89	Non-responders to BS treatment; Reported data for 4-week completers only	N=8 HAM-D: 23.12 (7.00) MADRS: 31.00 (5.38)	N (%) 3 (37.50)	*-12.5* p=0.45
			Desipramine (TCA)				N=67 HAM-D: 24.35 (5.30) MADRS: 31.51 (7.05)	n (%) 37 (55.22)			N=10 HAM-D: 22.60 (5.97) MADRS: 31.67 (9.58)	N (%) 5 (50)	
			Citalopram (SSRI)	Remission rate (based on HAM-D score ≤7)	%		N=85 HAM-D: 24.19 (4.31) MADRS: 31.38 (6.61)	n (%) 16 (18.82)	*-12.52* p=0.07		N=8 HAM-D: 23.12 (7.00) MADRS: 31.00 (5.38)	N (%) 0 (0.00)	*0* p=0.22
			Desipramine (TCA)				N=67 HAM-D: 24.35 (5.30) MADRS: 31.51 (7.05)	n (%) 21 (31.34)			N=10 HAM-D: 22.60 (5.97) MADRS: 31.67 (9.58)	N (%) 0 (0.00)	
			Citalopram (SSRI)	HAM-D score	Mean change from baseline		N=85 HAM-D: 24.19 (4.31) MADRS: 31.38 (6.61)	*-8.36*	*-1.9* p=NS		N=8 HAM-D: 23.12 (7.00) MADRS: 31.00 (5.38)	*-0.08*	*-5.18* p=NR
			Desipramine (TCA)				N=67 HAM-D: 24.35 (5.30) MADRS: 31.51 (7.05)	*-10.26*			N=10 HAM-D: 22.60 (5.97) MADRS: 31.67 (9.58)	*5.10*	

Reference	Study type	Treatment duration	Intervention (class)	Type of efficacy outcome	Measure of efficacy	Before switch				After switch			
						Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value	Population details	Baseline data Population size, N Severity measure, mean (SD)	Absolute efficacy	Efficacy difference p-value
			Citalopram (SSRI)	MADRS score	Mean change from baseline		N=85 HAM-D: 24.19 (4.31) MADRS: 31.38 (6.61)	*-11.71*	*-2.29* p=NR		N=8 HAM-D: 23.12 (7.00) MADRS: 31.00 (5.38)	*5.40*	*-2.44* p=NR
			Desipramine (TCA)				N=67 HAM-D: 24.35 (5.30) MADRS: 31.51 (7.05)	*-14.00*			N=10 HAM-D: 22.60 (5.97) MADRS: 31.67 (9.58)	*7.84*	

Italics indicate independent calculation by the analyst using data provided by source publication. No statistical analysis has been performed, therefore significance values cannot be assessed. Positive efficacy difference values favour first intervention; negative values favour second intervention.

Abbreviations: ADM, antidepressant medication; AS, after switch; BDI, Beck Depression Inventory; BS, before switch; CDRS, Cornell Dysthymia Rating Scale; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; CI, confidence interval; CPRS, Comprehensive Psychopathological Rating Scale; HAM-D, Hamilton rating scale for depression; ITT, intention to treat; MADRS, Montgomery–Åsberg Depression Rating Scale; MAOI, monoamine oxidase inhibitor; MDE, major depressive episode; NASSA, noradrenergic and specific serotonergic antidepressant; NR, not reported; NRI, norepinephrine reuptake inhibitor; NS, not significant; OR, odds ratio; PP, per protocol; RCT, randomised controlled trial; RDS, Raskin Depression Scale; SD, standard deviation; SE, standard error; SNRI, serotonin norepinephrine reuptake inhibitor; SSRE, selective serotonin reuptake enhancer; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TRD, treatment-resistant depression.

†Baseline data not reported separately for treatment groups; ‡Estimate of difference between treatment mean, calculated as sertraline minus agomelatine [95% CI], and analysed using a two-way analysis of covariance with factors treatment, centre and baseline HAM-D score as covariate; §Analysed using Chi-square test; ¶ Estimate of difference between treatments, calculated as the sertraline minus agomelatine [95% CI], and analysed using Chi-square test; ††Study also contains a placebo arm in the before-switch phase of the trial – data for these patients has not been extracted into this table.

Discussion

Despite a sensitive search approach, this systematic review identified limited evidence regarding the relative efficacy of antidepressants between treatment lines. In particular, no study was identified that aimed specifically to answer or provide evidence for this study question.

In the absence of previously published evidence on this topic, other sources of evidence were used to facilitate limited assessment of the study question. The majority of such identified evidence came from crossover trials that reported efficacy data both after the initial treatment period and after the second treatment period following the crossover. In all nine crossover studies, (reported in 14 publications) included in this review (2-15), only non-responders to the initial treatment (assessed after the pre-specified treatment period [four to six weeks in most studies, but ranging from three to 12 weeks]) were crossed over to the alternate intervention, therefore these patients may represent a switch population. For each study, follow-up times before and after-switch were the same (with the exception of Khan 2009 (15)), allowing within-trial comparison of efficacy outcomes between treatment lines. Crossover trials may provide useful data for investigating the study question, provided that the treatment switch is as a result of lack of efficacy of the before-switch treatment (as is the case in all the included crossover trials), as the methodology, patient characteristics, and compared interventions are homogenous in both periods of the trial, while comparisons between lines of treatment taken from separate individual trials (i.e. a trial with an initial treatment population vs another trial with a switch population) would likely be subject to some degree of heterogeneity.

In addition, a post-hoc subpopulation analysis of an RCT (Kasper 2013 (17)) reported data for two patient populations that could represent before- and after switch populations: those previously treated and those not previously treated. The previously treated population is defined as patients who had received antidepressants in the year prior to inclusion in the trial, not specifically that they had been previously treated for their current major depressive episode, and therefore there is some uncertainty as to whether they can be used to represent a switch population. However, as this was published as a pre-treated subgroup we must assume that the authors had additional information regarding the validity of the subgroup as a proxy for previous treatment that was not reported in the publication. Lundbeck have attempted to contact the study authors to obtain further clarification, but have had no response. A relatively large number of patients were enrolled in the study (both the before and after-switch populations consist of more than 100 patients), therefore, assuming that the previously treated patients are sufficiently representative of a switch population, the results are likely to be more reliable than the smaller studies.

The data presented in Figure 25, illustrating calculated difference in relative response rate before- and after-switch in seven of the included studies, indicate that there is variability in this difference between studies. Taking into account population sizes, and using the four weeks after-switch value for Khan 2009 (15) (as the majority of studies had four to six weeks follow-up times), it appears that the general trend towards a difference in the number of patients achieving a response to treatment between before- and after-switch populations between interventions. Although not substantiated by any statistical analysis, this assessment provides a subjective impression of trends in the data of a difference in relative efficacy of antidepressants between lines of treatment.

This systematic review also identified a meta-analysis (Bauer 2009) (16) that reported odds ratios for response and remission with venlafaxine compared with SSRIs (before-switch population), and compared with other antidepressants (mostly SSRIs) in patients with treatment resistant depression (TRD) (after-switch population). Of the included studies, this meta-analysis is the closest to providing a quantitative answer to the study question. There are certain considerations that should be borne in mind when considering the evidence. Comparison should be viewed with caution as the after-switch comparator ('other antidepressants', comprised mainly of SSRIs) is not the same as the before-switch comparator, SSRIs. Given that SSRIs still make up the majority of the 'other antidepressant' category, it was assumed that the interventions (venlafaxine vs SSRIs before-switch groups and venlafaxine vs 'mainly SSRIs' after-switch groups) were sufficiently similar to allow comparison. However, as each treatment arm used as evidence consisted of at least 2,000 patients from several clinical trials, these can be considered robust results. Therefore, the reported odds ratio patterns may be indicative of a variation in relative treatment efficacy between the before-and after-switch populations.

When interpreting the data identified in this systematic review it is important to take into account the variation in population sizes across the included studies. Larger studies that enrolled greater numbers of patients are likely to have more reliable data (due to less uncertainty) and therefore, assuming robust study design and methodology, their results can be considered to have greater validity than trials with smaller sample sizes (more uncertainty). As such, results from the larger studies in this systematic review (Bauer 2009 (16), Kasper 2013 (17), Keller 1998 (3) and Thase 2002 (14), Khan 2009 (15), and McGrath 1993 (5)), which have more than 100 patients in each treatment arm before-switch, can be considered to carry greater evidence weighting than studies with smaller numbers of patients. Emrich 1987 (2) and Lingjaerde 1983(4) included only 12 patients in each treatment arm before switch; even one or two patients achieving a different outcome could significantly alter the overall results and associated efficacy differences for those studies. It should also be noted that in crossover trials, which comprised nine of the eleven studies included in this systematic review, the after-switch population sizes were usually considerably smaller than the before-switch sample sizes as only non-responders to initial treatment crossed over. This may mean that the after-switch efficacy differences for these studies are less reliable than the corresponding before-switch differences.

Despite identifying a number of studies providing some evidence that may be used to interpret the difference in relative efficacy of antidepressants between lines of treatment, quantitative analysis (out of the scope of this review) would be extremely difficult to perform with the reported data. A wide range of efficacy outcomes was reported, however these were not reported consistently across all included studies. Response rate, the most frequently reported outcome, was only reported in eight of the eleven included studies and the remaining eight outcomes were only reported in up to four studies each, precluding meaningful comparisons between studies. Furthermore, the conclusions of each study could be dependent on the efficacy outcome used to inform those conclusions. This is illustrated by Kasper 2013 (17), where reported response rate was very different depending on whether response was measured using the HAM-D score or the CGI-I score (Figure 25). In addition, in the majority of studies, within-treatment line efficacy differences were calculated for the purposes of this review, so no measures of uncertainty or statistical significance were present. Therefore there was insufficient data available to perform further quantitative analysis. Difference in relative efficacy between specific lines of treatment (first or second or third line) rather than before- or after-switch could not be assessed, because baseline information regarding patients' treatment histories that would inform the line of

treatment they were receiving in the studies was often either unclear or not reported, or patients who had received different numbers of previous antidepressants were pooled into one treatment arm.

In addition, in most included studies, results were only reported as within-group efficacy, with no values directly demonstrating relative efficacy. To allow any interpretation of the results it was necessary to calculate these relative efficacy values. Without individual patient data or accounting for measures of uncertainty (such as standard deviation [SD] or standard error [SE]) in a statistical analysis, such calculations can be used only as indications of the relative efficacy. In addition, as no statistical analysis was performed, the significance of any potential within-treatment line differences in efficacy between interventions cannot be determined and therefore the evidence obtained from each study should be used to inform only an overall impression of whether any difference in relative efficacy between lines of treatment is present.

Furthermore, the evidence identified in this systematic review represents data for only a small proportion of the antidepressants available for the treatment of MDD, and therefore may not be representative of the relationship of relative efficacy of all, or even the majority of, currently available antidepressants between lines of treatment. In addition, only a few specific combinations of interventions are directly compared; any potential efficacy difference between a given intervention and a comparator is unlikely to be the same with an alternative comparator and therefore any efficacy difference is only meaningful if it relates to the interventions of interest to the investigator. For the purposes of this review however, identifying whether a difference in efficacy between lines of treatment *can* exist in any treatment comparisons is sufficient. In three of the included studies (six publications) (4, 6-10) interventions not currently used for the treatment of MDD (zimelidine or oxaprotiline) were studied. It is worth noting that the research recommendations in the 2009 NICE Clinical Guideline 90 (Treatment and management of depression in adults) state that further clinical trials of antidepressants and treatment switching strategies, in patients who have an inadequate response to initial treatment with an SSRI, are required. Such trials may also help provide further data that could contribute to the evidence identified in this systematic review.

In the STA submission to NICE, Lundbeck referenced a meta-analysis by Papakostas et al (1) as support for the rationale used to restrict their systematic review to the switch population. That meta-analysis was not included in the current study as it did not strictly meet the specific inclusion criteria for this systematic review. The Papakostas study (1) investigated the relative benefits of two switching strategies for patients who had initially been treated with an SSRI; switching patients either within-class to an alternative SSRI, or out-of-class to a non-SSRI. As such there is no comparison between SSRIs and non-SSRIs in initial usage, therefore the relative efficacy of the two treatment classes *between* lines of treatment cannot be assessed. Consequently the study does not meet the eligibility criteria for reporting relative outcomes for this systematic review (see Table 22). However, this meta-analysis does provide useful results suggesting that an across-class switch from SSRI to non-SSRI is more likely to result in remission than switching from one SSRI to another. As SSRIs are generally considered the preferred first-line treatment for MDD (18, 19) this result has relevance to clinical practice, suggesting that in switch usage non-SSRIs should be preferred over SSRIs and therefore that the relative efficacy of SSRIs to non-SSRIs in switch usage is different to initial usage, where SSRIs are preferred. Following this rationale a switch to an alternative class after an SNRI may also be preferred, though no evidence has been identified to explicitly support this.

Conclusions

The systematic review demonstrates that there is limited evidence currently available allowing the assessment of relative efficacies of antidepressants across treatment lines.

Despite identifying a number of studies providing some evidence that may be used to interpret the difference in relative efficacy of antidepressants between lines of treatment, quantitative analysis would be extremely difficult to perform with the reported data

The Bauer publication (16) potentially provides the strongest evidence in answering the question of whether relative efficacies differ between treatment lines. Despite limitations associated with the design, as each treatment arm used as evidence consisted of at least 2,000 patients from several clinical trials, these can be considered robust results. Therefore, the reported odds ratio patterns may be indicative of a variation in relative treatment efficacy between the before-and after-switch populations.

Considering the evidence presented in Figure 13 in its totality, it appears that the general trend towards a difference in the number of patients achieving a response to treatment between before- and after-switch populations between interventions.

The findings of this review add to the understanding of relative efficacies gained from the findings of the Papakostas (1) publication suggesting that across-class switch from SSRI to non-SSRI is more likely to result in remission than switching from one SSRI to another.

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Appendix A: Search strategy

Embase 1980 to 2015 Week 16. Searched 22nd April 2015

#	Searches	Results
1	exp major depression/	39739
2	((clinical or major or unipolar or resistant) adj depression).mp.	55747
3	(((major depressive or unipolar) adj disorder*) or MDD).mp.	21264
4	or/1-3	60827
5	exp antidepressant agent/	312449
6	antidepressant*.mp.	120764
7	exp serotonin uptake inhibitor/	147890
8	(selective serotonin reuptake inhibitor* or SSRI*).mp.	17824
9	exp citalopram/	18131
10	(citalopram or Celexa or Cipramil or Cipram or Dalsan or Recital or Emocal or Sepram or Seropram or Citox or Cital).mp.	18576
11	exp escitalopram/	7474
12	(escitalopram or Lexapro or Cipralex or Seroplex or Esertia).mp.	7707
13	exp fluoxetine/	38095
14	(fluoxetine or Depex or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Flutop or Fluctin or Fluox or Depress or Lovan or Prodep).mp.	44914
15	exp paroxetine/	23437
16	(paroxetine or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Deparoc).mp.	23911
17	exp sertraline/	20446
18	(sertraline or Zoloft or Lustral or Serlain or Asentra or Tresleen).mp.	20781
19	exp fluvoxamine/	11438
20	(fluvoxamine or Luvox or Fevarin or Faverin or Dumyrox or Favoxil or Movox or Floxyfral).mp.	12390
21	exp dapoxetine/	388
22	(dapoxetine or Priligy).mp.	406
23	exp serotonin noradrenalin reuptake inhibitor/	71239
24	(serotonin noradrenalin reuptake inhibitor* or serotonin norepinephrine reuptake inhibitor* or SNRI* or non-SSRI*).mp.	4779
25	exp desvenlafaxine/ or exp duloxetine/ or exp milnacipran/ or exp tofenacin/ or exp venlafaxine/	21958
26	(desvenlafaxine or duloxetine or levomilnacipran or milnacipran or tofenacin or venlafaxine).mp.	22339
27	(Pristiq or Khedezla or Cymbalta or Fetzima or Ixel or Savella or Dalcipran or Toledomin or Elamol or Tofacine or Tofalin or Effexor or Efexor or Alventa or Bonilux or Depefex or Foraven or Rodomel or Sunveniz or Tonpular or Venaxx or Venlablue or Venlalic or Venlaneo or Vensir or Vexarin or ViePax).mp.	2448
28	exp serotonin antagonist/	108153
29	(reuptake inhibitor* or SMS* or SARI* or NRI* or NDRI*).mp.	32360
30	exp vilazodone/ or exp vortioxetine/ or exp etoperidone/ or exp trazodone/ or exp reboxetine/ or exp viloxazine/	13587
31	(vilazodone or vortioxetine or etoperidone or trazodone or reboxetine or viloxazine).mp.	13777
32	(Viibryd or Brintellix or Trintellix or Axiomin or Etonin or Oleptro or Desyrel or Edronax or Vivalan).mp.	1288
33	exp tricyclic antidepressant agent/	92716

#	Searches	Results
34	(tricyclic* or TCA*).mp.	49654
35	exp amitriptyline/ or exp amitriptylinoxide/ or exp clomipramine/ or exp desipramine/ or dibenzepin/ or exp dosulepin/ or exp doxepin/ or exp imipramine/ or exp lofepramine/ or exp melitracen/ or exp nitroxazepine/ or exp nortriptyline/ or exp noxiptiline/ or exp protriptyline/ or exp trimipramine/	73900
36	(amitriptyline or amitriptylinoxide or clomipramine or desipramine or dibenzepin or dosulepin or doxepin or imipramine or lofepramine or melitracen or nitroxazepine or nitroxazepine or nortriptyline or noxiptiline or pipofezine or protriptyline or trimipramine).mp.	76160
37	(Elavil or Endep or Vanatrip or Amioxid or Ambivalon or Equilibrin or Anafranil or Norpramin or Pertofrane or Noveril or Victoril or Prothiaden or Adapin or Sinequan or Tofranil or Lomont or Gamanil or Dixeran or Melixeran or Sintamil or Pamelor or Aventyl or Agedal or Elronon or Nogedal or Azafen or Azaphen or Vivactil or Surmontil).mp.	5529
38	exp tetracyclic antidepressant agent/	19017
39	(tetracyclic antidepressant* or TeCA* or tetracyclic*).mp.	4341
40	exp amoxapine/ or exp maprotiline/ or exp mianserin/ or exp mirtazapine/ or exp teciptiline/	19498
41	(amoxapine or maprotiline or mianserin or mirtazapine or setiptiline or teciptiline).mp.	19881
42	(Asendin or Ludiomil or Bolvidon or Norval or Tolvon or Remeron or Tecipul).mp.	1890
43	exp agomelatine/ or exp amfebutamone/ or exp tandospirone/ or exp teniloxazine/ or exp nefazodone/	19159
44	(agomelatine or bupropion or amfebutamone or tandospirone or teniloxazine or nefazodone).mp.	19696
45	(Valdoxan or Thymanax or Aplenzin or Budeprion or Forfivo or Wellbutrin or Sediel or Lucelan or Metatone or Dutonin or Nefadar or Serzone).mp.	2092
46	exp monoamine oxidase inhibitor/	39199
47	(monoamine oxidase inhibitor* or MAOI*).mp.	17075
48	exp isocarboxazid/ or exp phenelzine/ or exp tranylcypromine/ or exp selegiline/ or exp metralindole/ or exp moclobemide/ or exp pirlindole/ or exp toloxatone/	19352
49	(isocarboxazid or phenelzine or tranylcypromine or selegiline or metralindole or moclobemide or pirlindole or toloxatone).mp.	19834
50	(Marplan or Nardil or Parnate or Eldepryl or Zelapar or Emsam or Inkazan or Aurorix or Manerix or Pirazidol or Pyrazidol or Humoryl).mp.	1891
51	or/5-50	423127
52	(switch* or chang* or swap*).tw.	2732773
53	(crossover or cross-over or cross over or crossed).mp.	103199
54	manag*.tw.	1152054
55	efficac*.tw.	752283
56	or/52-55	4382052
57	meta-analys*.mp.	140014
58	search*.tw.	320611
59	review.pt.	2023738
60	(random* or double-blind*).tw.	997395
61	placebo*.mp.	334761
62	exp crossover procedure/	42297
63	(crossover or cross-over or cross over).tw.	71753
64	Clinical study/	65348
65	Case control study/	90420
66	Family study/	10719

#	Searches	Results
67	Longitudinal study/	75793
68	Retrospective study/	393772
69	Prospective study/	285117
70	Cohort analysis/	197212
71	(Cohort adj (study or studies)).mp.	135404
72	(Case control adj (study or studies)).tw.	82783
73	(follow up adj (study or studies)).tw.	45961
74	(observational adj (study or studies)).tw.	74603
75	(epidemiologic$ adj (study or studies)).tw.	77156
76	(cross sectional adj (study or studies)).tw.	99040
77	or/57-76	4424562
78	4 and 51 and 56 and 77	7244
79	limit 78 to english	6878

MEDLINE® In-Process & Other Non-Indexed Citations and MEDLINE® 1946 to Present. Searched 22nd April 2015

#	Searches	Results
1	exp Depressive Disorder, Major/	20299
2	((clinical or major or unipolar or resistant) adj depression).mp.	23446
3	(((major depressive or unipolar) adj disorder*) or MDD).mp.	15473
4	or/1-3	43190
5	exp Antidepressive Agents/	122995
6	antidepressant*.mp.	48565
7	exp Serotonin Uptake Inhibitors/	32073
8	(selective serotonin reuptake inhibitor* or SSRI*).mp.	11630
9	exp Citalopram/	3872
10	(citalopram or Celexa or Cipramil or Cipram or Dalsan or Recital or Emocal or Sepram or Seropram or Citox or Cital).mp.	5546
11	(escitalopram or Lexapro or Cipralex or Seroplex or Esertia).mp.	1546
12	exp Fluoxetine/	7825
13	(fluoxetine or Depex or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Flutop or Fluctin or Fluox or Depress or Lovan or Prodep).mp.	17340
14	exp Paroxetine/	3576
15	(paroxetine or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Deparoc).mp.	5466
16	exp Sertraline/	2483
17	(sertraline or Zoloft or Lustral or Serlain or Asentra or Tresleen).mp.	3946
18	exp Fluvoxamine/	1725
19	(fluvoxamine or Luvox or Fevarin or Faverin or Dumyrox or Favoxil or Movox or Floxyfral).mp.	2631
20	(dapoxetine or Priligy).mp.	144
21	exp Adrenergic Uptake Inhibitors/	62220
22	(serotonin noradrenalin reuptake inhibitor* or serotonin norepinephrine reuptake inhibitor* or SNRI* or non-SSRI*).mp.	1324
23	(desvenlafaxine or duloxetine or levomilnacipran or milnacipran or tofenacin or venlafaxine).mp.	5368
24	(Pristiq or Khedezla or Cymbalta or Fetzima or Ixel or Savella or Dalcipran or Toledomin or Elamol or Tofacine or Tofalin or Effexor or Efexor or Alventa or Bonilux or Depefex or Foraven or Rodomel or Sunveniz or Tonpular or Venaxx or Venlablue or Venlalic or Venlaneo or Vensir or Vexarin or ViePax).mp.	113
25	exp Serotonin Antagonists/	46049
26	(reuptake inhibitor* or SMS* or SARI* or NRI* or NDRI*).mp.	21017
27	exp Trazodone/ or exp Viloxazine/	1364
28	(vilazodone or vortioxetine or etoperidone or trazodone or reboxetine or viloxazine).mp.	2941
29	(Viibryd or Brintellix or Trintellix or Axiomin or Etonin or Oleptro or Desyrel or Edronax or Vivalan).mp.	66
30	exp Antidepressive Agents, Tricyclic/	29085
31	(tricyclic* or TCA*).mp.	27918
32	exp Amitriptyline/ or exp Clomipramine/ or exp Desipramine/ or exp Dothiepin/ or exp Doxepin/ or exp Imipramine/ or exp Lofepramine/ or exp Nortriptyline/ or exp Protriptyline/ or exp Trimipramine/	22932
33	(amitriptyline or amitriptylinoxide or clomipramine or desipramine or dibenzepin or dosulepin or doxepin or imipramine or lofepramine or melitracen or nitroxazepine or nortriptyline or noxiptiline or	29797

#	Searches	Results
	pipofezine or protriptyline or trimipramine).mp.	
34	(Elavil or Endep or Vanatrip or Amioxid or Ambivalon or Equilibrin or Anafranil or Norpramin or Pertofrane or Noveril or Victoril or Prothiaden or Adapin or Sinequan or Tofranil or Lomont or Gamanil or Dixeran or Melixeran or Sintamil or Pamelor or Aventyl or Agedal or Elronon or Nogedal or Azafen or Azaphen or Vivactil or Surmontil).mp.	766
35	(tetracyclic antidepressant* or TeCA* or tetracyclic*).mp.	2314
36	exp Amoxapine/ or exp Maprotiline/ or exp Mianserin/	3381
37	(amoxapine or maprotiline or mianserin or mirtazapine or setiptiline or teciptiline).mp.	5131
38	(Asendin or Ludiomil or Bolvidon or Norval or Tolvon or Remeron or Tecipul).mp.	158
39	exp Bupropion/	2494
40	(agomelatine or bupropion or amfebutamone or tandospirone or teniloxazine or nefazodone).mp.	5019
41	(Valdoxan or Thymanax or Aplenzin or Budeprion or Forfivo or Wellbutrin or Sediel or Lucelan or Metatone or Dutonin or Nefadar or Serzone).mp.	100
42	exp Monoamine Oxidase Inhibitors/	19661
43	(monoamine oxidase inhibitor* or MAOI*).mp.	11111
44	exp Isocarboxazid/ or exp Phenelzine/ or exp Tranylcypromine/ or exp Selegiline/ or exp Moclobemide/	5707
45	(isocarboxazid or phenelzine or tranylcypromine or selegiline or metralindole or moclobemide or pirlindole or toloxatone).mp.	7199
46	(Marplan or Nardil or Parnate or Eldepryl or Zelapar or Emsam or Inkazan or Aurorix or Manerix or Pirazidol or Pyrazidol or Humoryl).mp.	269
47	or/5-46	264850
48	(switch* or chang* or swap*).tw.	2371499
49	(crossover or cross-over or cross over or crossed).mp.	92318
50	manag*.tw.	887413
51	efficac*.tw.	557285
52	or/48-51	3650886
53	meta analysis.mp,pt.	89212
54	search*.tw.	264793
55	review.pt.	1963869
56	randomized controlled trial.pt.	391545
57	(randomized or placebo).mp.	649760
58	exp Cross-Over Studies/	35738
59	(crossover or cross-over or cross over).tw.	63669
60	Epidemiologic studies/	6152
61	exp case control studies/	707159
62	exp cohort studies/	1420010
63	Case control.tw.	84381
64	(cohort adj (study or studies)).tw.	99411
65	Cohort analy$.tw.	4172
66	(Follow up adj (study or studies)).tw.	38907
67	(observational adj (study or studies)).tw.	51656
68	Longitudinal.tw.	152902
69	Retrospective.tw.	303045
70	Cross sectional.tw.	190173

#	Searches	Results
71	Cross-sectional studies/	190723
72	or/53-71	4509896
73	4 and 47 and 52 and 72	4903
74	limit 73 to english	4710

EBM Reviews - Cochrane Central Register of Controlled Trials March 2015; **EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to March 2015; **EBM Reviews - Database of Abstracts of Reviews of Effects** 1st Quarter 2015; **EBM Reviews - Health Technology Assessment** 1st Quarter 2015. Searched 22nd April 2015

#	Searches	Results
1	exp Depressive Disorder, Major/	2160
2	((clinical or major or unipolar or resistant) adj depression).mp.	4788
3	(((major depressive or unipolar) adj disorder*) or MDD).mp.	3264
4	or/1-3	7539
5	exp Antidepressive Agents/	9603
6	antidepressant*.mp.	7915
7	exp Serotonin Uptake Inhibitors/	4626
8	(selective serotonin reuptake inhibitor* or SSRI*).mp.	2287
9	exp Citalopram/	741
10	(citalopram or Celexa or Cipramil or Cipram or Dalsan or Recital or Emocal or Sepram or Seropram or Citox or Cital).mp.	1480
11	(escitalopram or Lexapro or Cipralex or Seroplex or Esertia).mp.	794
12	exp Fluoxetine/	1116
13	(fluoxetine or Depex or Prozac or Fontex or Seromex or Seronil or Sarafem or Ladose or Motivest or Flutop or Fluctin or Fluox or Depress or Lovan or Prodep).mp.	3102
14	exp Paroxetine/	728
15	(paroxetine or Paxil or Seroxat or Sereupin or Aropax or Deroxat or Divarius or Rexetin or Xetanor or Paroxat or Loxamine or Deparoc).mp.	2145
16	exp Sertraline/	602
17	(sertraline or Zoloft or Lustral or Serlain or Asentra or Tresleen).mp.	1728
18	exp Fluvoxamine/	343
19	(fluvoxamine or Luvox or Fevarin or Faverin or Dumyrox or Favoxil or Movox or Floxyfral).mp.	890
20	(dapoxetine or Priligy).mp.	36
21	exp Adrenergic Uptake Inhibitors/	3851
22	(serotonin noradrenalin reuptake inhibitor* or serotonin norepinephrine reuptake inhibitor* or SNRI* or non-SSRI*).mp.	362
23	(desvenlafaxine or duloxetine or levomilnacipran or milnacipran or tofenacin or venlafaxine).mp.	1991
24	(Pristiq or Khedezla or Cymbalta or Fetzima or Ixel or Savella or Dalcipran or Toledomin or Elamol or Tofacine or Tofalin or Effexor or Efexor or Alventa or Bonilux or Depefex or Foraven or Rodomel or Sunveniz or Tonpular or Venaxx or Venlablue or Venlalic or Venlaneo or Vensir or Vexarin or ViePax).mp.	39
25	exp Serotonin Antagonists/	4298
26	(reuptake inhibitor* or SMS* or SARI* or NRI* or NDRI*).mp.	3177
27	exp Trazodone/ or exp Viloxazine/	200
28	(vilazodone or vortioxetine or etoperidone or trazodone or reboxetine or viloxazine).mp.	928
29	(Viibryd or Brintellix or Trintellix or Axiomin or Etonin or Oleptro or Desyrel or Edronax or Vivalan).mp.	27
30	exp Antidepressive Agents, Tricyclic/	3348
31	(tricyclic* or TCA*).mp.	2405
32	exp Amitriptyline/ or exp Clomipramine/ or exp Desipramine/ or exp Dothiepin/ or exp Doxepin/ or exp Imipramine/ or exp Lofepramine/ or exp Nortriptyline/ or exp Protriptyline/ or exp Trimipramine/	3089

#	Searches	Results
33	(amitriptyline or amitriptylinoxide or clomipramine or desipramine or dibenzepin or dosulepin or doxepin or imipramine or lofepramine or melitracen or nitroxazepine or nortriptyline or noxiptiline or pipofezine or protriptyline or trimipramine).mp.	6293
34	(Elavil or Endep or Vanatrip or Amioxid or Ambivalon or Equilibrin or Anafranil or Norpramin or Pertofrane or Noveril or Victoril or Prothiaden or Adapin or Sinequan or Tofranil or Lomont or Gamanil or Dixeran or Melixeran or Sintamil or Pamelor or Aventyl or Agedal or Elronon or Nogedal or Azafen or Azaphen or Vivactil or Surmontil).mp.	181
35	(tetracyclic antidepressant* or TeCA* or tetracyclic*).mp.	118
36	exp Amoxapine/ or exp Maprotiline/ or exp Mianserin/	535
37	(amoxapine or maprotiline or mianserin or mirtazapine or setiptiline or teciptiline).mp.	1479
38	(Asendin or Ludiomil or Bolvidon or Norval or Tolvon or Remeron or Tecipul).mp.	79
39	exp Bupropion/	456
40	(agomelatine or bupropion or amfebutamone or tandospirone or teniloxazine or nefazodone).mp.	1572
41	(Valdoxan or Thymanax or Aplenzin or Budeprion or Forfivo or Wellbutrin or Sediel or Lucelan or Metatone or Dutonin or Nefadar or Serzone).mp.	51
42	exp Monoamine Oxidase Inhibitors/	838
43	(monoamine oxidase inhibitor* or MAOI*).mp.	767
44	exp Isocarboxazid/ or exp Phenelzine/ or exp Tranylcypromine/ or exp Selegiline/ or exp Moclobemide/	605
45	(isocarboxazid or phenelzine or tranylcypromine or selegiline or metralindole or moclobemide or pirlindole or toloxatone).mp.	1222
46	(Marplan or Nardil or Parnate or Eldepryl or Zelapar or Emsam or Inkazan or Aurorix or Manerix or Pirazidol or Pyrazidol or Humoryl).mp.	45
47	or/5-46	27850
48	(switch* or chang* or swap*).tw.	148437
49	(crossover or cross-over or cross over or crossed).mp.	63042
50	manag*.tw.	54538
51	efficac*.tw.	143342
52	or/48-51	324740
53	meta analysis.mp,pt.	27960
54	search*.tw.	25812
55	review.pt.	2538
56	randomized controlled trial.pt.	351779
57	(randomized or placebo).mp.	392744
58	exp Cross-Over Studies/	26185
59	(crossover or cross-over or cross over).tw.	55199
60	Epidemiologic studies/	34
61	exp case control studies/	8770
62	exp cohort studies/	107493
63	Case control.tw.	4394
64	(cohort adj (study or studies)).tw.	6272
65	Cohort analy$.tw.	256
66	(Follow up adj (study or studies)).tw.	5338
67	(observational adj (study or studies)).tw.	5719
68	Longitudinal.tw.	6854

#	Searches	Results
69	Retrospective.tw.	8296
70	Cross sectional.tw.	5375
71	Cross-sectional studies/	2945
72	or/53-71	576493
73	4 and 47 and 52 and 72	2837
74	limit 73 to english [Limit not valid in DARE; records were retained]	2583

6.3. Appendix 3: The SOLUTION Study

6.3.1. Methods

6.3.1.1. Study 13692A (SOLUTION)

SOLUTION was an interventional, prospective, multi-national, multi-site, randomised, double-blind, parallel-group, active-comparator (venlafaxine XR), 8-week fixed-dose study.

The study aimed to compare the efficacy, safety and tolerability to venlafaxine XR. The primary analysis tested for non-inferiority of vortioxetine to venlafaxine XR using the change from baseline in MADRS total score at Week 8 based on the FAS using last observation carried forward (LOCF.

A total of 410 patients (205 patients per treatment group) with recurrent MDD as the primary diagnosis according to DSM-IV-TR™ (classification code 296.3x) criteria were planned for randomisation.

Patients were randomised equally (1:1) to fixed doses of either vortioxetine (10mg/day) or venlafaxine XR (150mg/day). The patients randomised to vortioxetine received 10mg/day of vortioxetine for the entire 8-week Core Treatment Period, followed by placebo during the 1-week Down-taper Period. The patients randomised to venlafaxine XR received 75mg/day of venlafaxine XR for 4 days and 150mg/day for the rest of the 8-week Core Treatment Period, followed by 75mg/day during the 1-week Down-taper Period.

Patients were seen for efficacy and safety assessments weekly during the first 2 weeks of treatment and then every 2 weeks until the end of the 8-week Core Treatment Period.

A Safety Follow-up Visit was scheduled for 4 weeks after completion of the 8-week Core Treatment Period. If possible, patients who withdrew were seen for a Withdrawal Visit as soon as possible, and were contacted for a safety follow-up assessment 4 weeks after withdrawal.

Figure 26: SOLUTION Study design

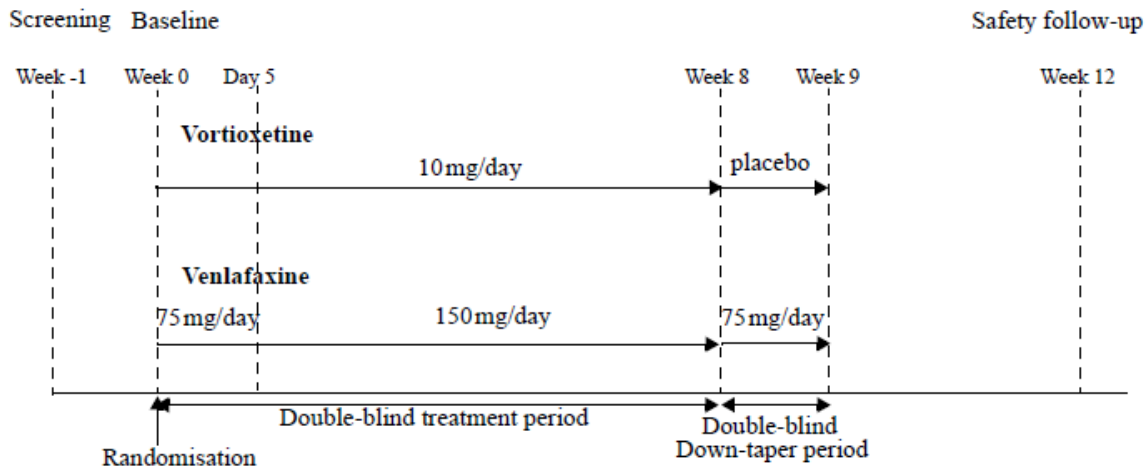


Table B1. Comparative summary of methodology of the relevant RCTs

SOLUTION		
Location	China, South Korea, Taiwan and Thailand	
Design	Double-blind, parallel group, active comparator	
Duration of study	8 weeks double-blind period	
Method of randomisation	At the Screening Visit, the patients were assigned a screening number in the range from S1001 to S1555. At the Baseline Visit, patients who fulfilled the selection criteria were assigned to treatment with either vortioxetine or venlafaxine XR in a 1:1 ratio. Randomisation was executed using an IVRS according to a randomisation list that was computer generated by H.Lundbeck A/S. Randomisation numbers (between R5001 and R6200) were prepared for a total of 1200 patients, with 600 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.	
Method of blinding (care provider, patient and outcome assessor)	Global Pharmacovigilance (GPV), H.Lundbeck A/S, and the investigator or pharmacist at the site had access to the details of the double-blind treatment for each patient. Access to these details was via IVRS. The randomisation code could be be broken by the investigator only in an emergency situation in order to give the patient optimal treatment. The randomisation code was not broken for any patient during the study.	
Numbers of subjects	All patients treated set (Full analysis set)	
	Vortioxetine 211 (209)	Venlafaxine XR 226 (215)
Primary outcomes (including scoring methods and timings of assessments)	Non-inferiority to venlafaxine XR: Change from baseline in Montgomery and Åsberg Depression Rating Scale (MADRS) total score after 8 weeks of treatment in patients with Major Depressive Disorder (MDD)	
Secondary outcomes (including scoring methods and timings of assessments)	The following secondary endpoints were defined: • change from baseline in MADRS total score at other weeks assessed • change from baseline in CGI-S score at each week assessed • CGI-I score at each week assessed • change from baseline in HAM-A total score at each week assessed • MADRS response at each week assessed (response defined as a ≥50% decrease in the MADRS total score) • MADRS remission at each week assessed (remission defined as a MADRS total score ≤10) • changes from baseline in MADRS single item scores at each week assessed • CGI-S remission at each week assessed (remission defined as a CGI-S score ≤2) • •CGI-I response at each week assessed (response defined as a CGI-I score ≤2)	

	• SDS total score • SDS family life subscale • SDS work subscale • SDS social life subscale • Q-LES-Q total score • Q-LES-Q item 15 – satisfaction with medication item • Q-LES-Q item 16 – overall life satisfaction and contentment item • Post-hoc analysis: MADRS total score - ANCOVA, APTS, LOCF analysis
Duration of 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.	

6.3.2. Participants

Table B2: SOLUTION: Eligibility criteria for recruitment

Inclusion criteria	Exclusion criteria
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 an inpatient in a psychiatric hospital or an outpatient at a psychiatric setting at the time of study entry. 5. The patient has recurrent Major Depressive Disorder as the primary diagnosis according to DSM-IV-TRTM criteria (classification code 296.3x). The current Major Depressive Episode (MDE) should be confirmed using the Mini International Neuropsychiatric Interview (MINI). 6. The patient has a MADRS total score ≥26. 7. The patient has a CGI-S score ≥4. 8. The reported duration of the current MDE is ≥3 months. 9. The patient is a man or woman, aged ≥18 years and ≤65 years. a. For South Korea only (SCA01): the patient is a man or woman, aged >18 and ≤65 years 10. The patient, if a woman, must: a. 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, some intrauterine devices, sexual abstinence, vasectomised partner), OR b. have had her last natural menstruation ≥24 months prior to the Screening Visit, OR c. have been surgically sterilised prior to the Screening Visit, OR d. have had a hysterectomy prior to the Screening Visit.	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 any of the investigational medicinal product(s) [IMP(s)] or their excipients. 5. The patient has hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase insufficiency. 6. The patient has a history of lack of response to previous adequate treatment with venlafaxine XR (including current episode). 7. The patient has an identified high risk of a serious cardiac ventricular arrhythmia (form example, those with a significant left ventricular dysfunction, NYHA Class III/IV) or uncontrolled hypertension. 8. The current depressive symptoms are considered by the investigator to have been resistant to 2 adequate antidepressant treatments of at least 6 weeks duration each at the recommended dose. 9. The patient has any current anxiety psychiatric disorder (DSM-IV-TR™ criteria), as assessed using the MINI. 10. 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, personality disorders, mental retardation, organic mental disorders, or mental disorders due to a general medical condition (DSM-IV-TR™ criteria). 11. 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 at least 2 years prior to the Screening Visit. 12. The patient has any other disorder for which the treatment takes priority over treatment of MDD or is likely to interfere with study treatment or impair treatment compliance. 13. The patient has a significant risk of suicide according to the investigators opinion or has a score ≥5 on Item 10 (suicidal thoughts) of the MADRS, or has attempted suicide within 6 months prior to the Screening Visit. 14. The patient is currently receiving formal cognitive or behavioural therapy or systematic psychotherapy, or plans to start such therapy during the study. 15. The patient has received electroconvulsive therapy within 6 months prior to the Screening Visit. 16. The patient has a history of moderate or severe head trauma or other neurological disorders or systemic medical diseases that are, in the opinion of the investigator, likely to affect central nervous

Inclusion criteria	Exclusion criteria
	system functioning. 17. 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 MP. 18. The patient has a clinically significant unstable illness, for example: • cardiovascular disease • seizure disorder or encephalopathy • congestive heart failure • cardiac hypertrophy • arrhythmia • bradycardia (pulse <50 beats per minute [bpm]) • respiratory disease • hepatic impairment or renal insufficiency • metabolic disorder • endocrinological disorder • gastrointestinal disorder • haematological disorder • infectious disorder • any clinically significant immunological condition • dermatological disorder • venereal disease • elevated intra-ocular pressure or is at risk of acute narrow-angle glaucoma 19. The patient takes or has taken disallowed recent or concomitant medication (specified in Table 1) or it is anticipated that the patient will require treatment with at least one of the disallowed concomitant medications during the study. 20. The patient has been treated with any investigational medicinal product within 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit. 21. The patient has clinically significant abnormal vital signs at the Screening Visit. 22. 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 in the investigator's opinion, 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. 23. The patient has a value of thyroid stimulating hormone (TSH) outside the normal range at the Screening Visit. 24. 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,

Inclusion criteria	Exclusion criteria
	where QTcF = QT/RR0.33) 25. 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. 26. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason. 27. The patient has previously been exposed to vortioxetine.

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.

6.3.3. Patient characteristics at baseline

6.3.3.1. Study 13926A (SOLUTION)

Table 24 provides baseline patient demographic and clinical characteristics for Study 13926A (SOLUTION).

Table 24: Study 13926A (SOLUTION): Baseline characteristics of participants

Baseline characteristic	Vortioxetine	Venlafaxine XR	Total
Number of patients: APTS[1]	211	226	437
Mean (median) age (years)[1]	39.6 (39.00)	40.65 (42.0)	40.14 (41.0)
Sex (% female)[1]	58.3%	61.5%	60.0%
Race (% Asian)	100%	100.0%	100%
Mean ± sd (median) MADRS total baseline score[2]	32.27 ± 4.64 (32.0)	32.29 ± 4.49 (32.0)	32.28 ± 4.56 (32.0)
Mean CGI-S ± sd (median) total baseline score[2]	4.84 ± 0.71 (5.0)	4.87 ± 0.69 (5.0)	4.85 ± 0.7 (5.0)
Mean ± sd (median) HAM-A total baseline score[2]	20.58 ± 7.28 (20.0)	21.12 ± 6.97 (22.0)	20.85 ± 7.12 (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 6.3.4.1.1 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 32 for both groups (ranging from 26-48 points) was consistent with patients experiencing moderate to severe MDD.

6.3.4. Statistical analysis and definition of study groups

6.3.4.1. Study 13926A (SOLUTION)

6.3.4.1.1. Analysis sets

The following analysis sets were defined either in the protocol or in the Statistical Analysis

Plan:

- 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 IMP
- 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 MADRS total score

- per-protocol set (PPS) – all patients in the FAS who:
  - had no major protocol violations that could interfere with the efficacy outcomes
  - had >14 days IMP exposure
  - had >70% IMP compliance in the Core Treatment Period
  - did not have a drug holiday during treatment for >6 consecutive days

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 before the code was broken.

6.3.4.1.2. Hypotheses

The primary analysis tested for non-inferiority of vortioxetine to venlafaxine XR using the change from baseline in MADRS total score at Week 8 based on the FAS using last observation carried forward (LOCF). Comparison between vortioxetine and venlafaxine XR was performed using an analysis of covariance (ANCOVA) with treatment and grouped site as fixed factors and the baseline MADRS total score as a covariate. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Vortioxetine was declared to be non-inferior to venlafaxine XR if the upper limit of the calculated two-sided 95% confidence interval for the treatment difference at Week 8 between vortioxetine and venlafaxine XR was less than +2.5 MADRS versus venlafaxine XR.

6.3.4.1.3. Power and sample size calculations

A minimum of 410 patients (205 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 +2.5 points. Assuming a standard deviation of 9.0 points and an expected true mean difference between treatments of 0 points, a total of 410 patients (205 per treatment group) were needed to provide a power of 80% for correctly concluding non-inferiority. The calculation was based on a standard t-test from an ANCOVA.

6.3.4.1.4. Handling of missing data and withdrawals

Data from all post-baseline visits were assigned to a nominal (scheduled) visit using the visit windows defined in Table 25. It was then possible to have two competing assessments with the same nominal visit. The originally observed visit was kept for by-visit analyses, whereas the 'Withdrawal Visit' (which, by definition, was always the latest of the two) was used for LOCF. For the final visit at Week 8, this would not result in conflict between by-visit and LOCF analyses, since it is not possible for a patient to have a regular final assessment together with a 'Withdrawal' assessment. For each visit, a window was defined such that the lower and upper bounds of each window was the midpoint between 2 consecutive study visits. The visit windows and applicable study day ranges are presented in Table 25.

Table 25: Study 13926A (SOLUTION): Study windows

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	MADRS, HAM-A, CGI-I, CGI-S	Q-LES-Q (SF), SDS, HEA	Lab, Vital Signs, ECG, Weight
Visit 2 (Baseline)	0	0	≤0	≤0	≤0
Visit 3 (Treatment)	1	7	1 to 10		
Visit 4 (Treatment)	2	14	11 to 21		
Visit 5 (Treatment)	4	28	22 to 35		1 to 42
Visit 6 (Treatment)	6	42	36 to 49		
Visit 7 (Completion/Withdrawal)	8	56	≥50	≥1	≥43
Visit 8 (Discontinuation)	9	63	NA	NA	NA
Visit 9 (Safety Follow-up)	12	84	NA	NA	NA

NA = not applicable

Baseline measurements/assessments were not carried forward in LOCF analyses.

In general, the baseline value for a variable was defined as the last observation prior to the first dose of double-blind study medication (visit date ≤ first dose start), including the screening value, if necessary.

For the health-related Quality of Life and overall functioning, and pharmacoeconomic variables, since these assessments were only performed at the baseline and completion visits, the OC analysis only included patients that had an assessment at the Completion Visit. In contrast, the LOCF analysis included both patients that had an assessment at the Completion Visit, as well as those that did not. The assessment at the early withdrawal visit was carried forward in the LOCF analysis for the patients that did not have an assessment at the Completion Visit due to early withdrawal.

6.3.5. Subgroup analyses

6.3.5.1. Study 13926A (SOLUTION)

The analysis of the primary efficacy endpoint based on the FAS was repeated for the following subgroups:

- Sex
- Age (≤50 vs. >50 years)
- Baseline severity (MADRS score <30 vs. ≥30)
- Baseline anxiety (HAM-A score <20 vs. ≥20)
- Number of previous episodes (1 or 2 previous MDEs vs ≥3 previous MDEs)
- Length of current MDE (current MDE < 21 weeks vs. ≥21 weeks)

6.3.6. Participant flow

6.3.6.1. Study 13926A (SOLUTION)

A modified CONSORT flow diagram of the disposition of patients in Study 13926A (SOLUTION) is provided in Figure 27. Five-hundred and forty nine patients were screened for potential participation. In the vortioxetine group, 18% of the patients (APRS) withdrew from the study compared to 27% in the venlafaxine XR group. The most frequent primary reason for withdrawal was adverse events (10.5%) (14/211 [6.6%] [vortioxetine] and 32/226 [14.2%] [venlafaxine XR]).

There was a high number of patients in the venlafaxine XR group who were excluded from the FAS (11 patients [5%] versus 2 patients [1%] in the vortioxetine group). All patients who were excluded from the FAS, were excluded due to the lack of a valid post-baseline assessment of the MADRS, arising as a result of early withdrawal. There is no single prevailing primary reason for early withdrawal among the patients in the venlafaxine XR group who were excluded from the FAS: 5 were withdrawn due to adverse event(s), 4 due to withdrawal of consent, 1 due to protocol violation, and 1 due to other reasons (Listing 5). In the vortioxetine group, the 2 patients who were excluded from the FAS had adverse event(s) and withdrawal of consent, respectively, as the primary reason for withdrawal.

The withdrawals from study by primary reason (APTS) are shown in Table 26.

Table 26: SOLUTION: Withdrawals from study by primary reason

	VOR		VLF		Total	
	n	%	n	%	n	%
All Patients Treated Set	211		226		437	
Completed	173	(82.0)	164	(72.6)	337	(77.1)
Withdrawn	38	(18.0)	62	(27.4)	100	(22.9)
Primary Reason						
Adverse Event(s)	14	(6.6)	32	(14.2)	46	(10.5)
Lack of Efficacy	8	(3.8)	3	(1.3)	11	(2.5)
Non-compliance with IMP	2	(0.9)	4	(1.8)	6	(1.4)
Protocol Violation	1	(0.5)	5	(2.2)	6	(1.4)
Withdrawal of Consent	5	(2.4)	13	(5.8)	18	(4.1)
Lost to Follow-up	4	(1.9)	2	(0.9)	6	(1.4)
Administrative or other reason(s)	4	(1.9)	3	(1.3)	7	(1.6)

13926A Final TLG_Patients ST_DI04_PRIM 18FEB2014:08:50:29 SADs No.: 195 TGML v.6

To understand the pattern of withdrawals better, a Kaplan-Meier analysis of time to withdrawal was performed (see Figure 28: Study 13926A (SOLUTION). Kaplan-meier analysis of time to withdrawal (APTS)), which indicated that patients on venlafaxine XR tended to withdraw earlier than those on vortioxetine.

Figure 27: Study 13926A (SOLUTION). Modified CONSORT flow diagram of patient disposition

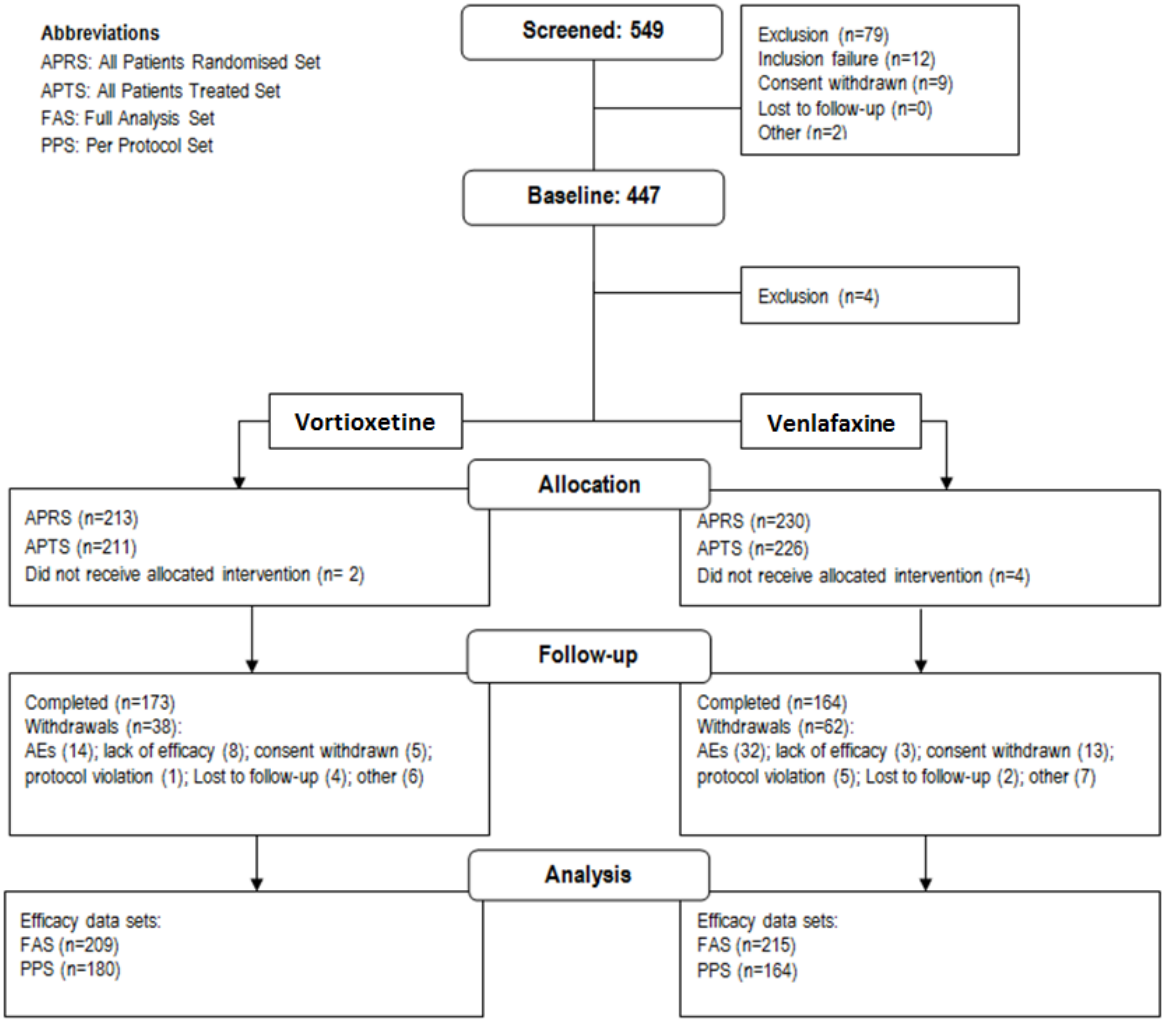
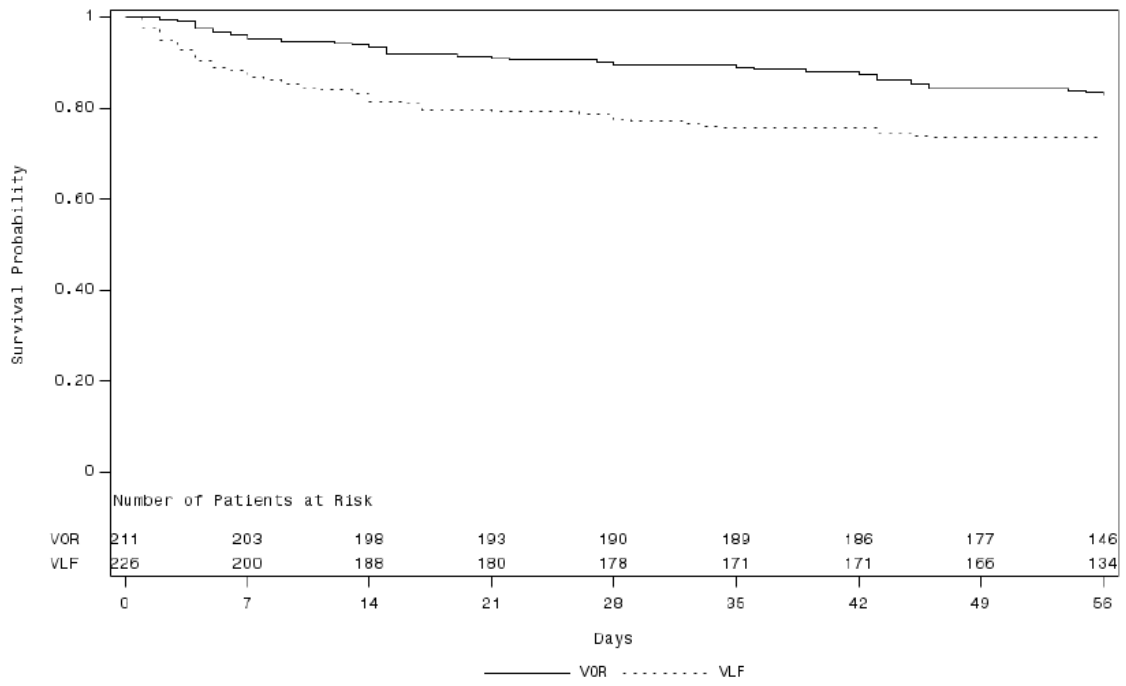


Figure 28: Study 13926A (SOLUTION). Kaplan-meier analysis of time to withdrawal (APTS)



6.3.7. Critical appraisal of relevant RCTs

6.3.7.1. Study 13926A (SOLUTION)

A critical appraisal of Study 13926A (SOLUTION) is made in Table 27.

Table 27: Critical appraisal of Study 13926A (SOLUTION)

Criteria	Methodology used[27]	Appraisal	Adequacy (Yes/No)
Was the method used to generate random allocations adequate?	At each site, sequentially enrolled patients were assigned the lowest randomisation number available in blocks of four using an interactive voice/web response system (IVRS). The IVRS randomly allocated each patient to a treatment group during the call and assigned the patient a randomisation number according to a randomisation list that was computer generated by H. Lundbeck A/S, the manufacturer of vortioxetine. All investigators, trial personnel and patients were blinded to treatment assignment for the duration of the study. The randomisation code was not broken for any patient.		Yes

Was the allocation adequately concealed?	Global Pharmacovigilance (GPV), H.Lundbeck A/S, and the investigator or pharmacist at the site had access to the details of the double-blind treatment for each patient. Access to these details was via IVRS. The randomisation code was to be broken by the investigator only in an emergency situation in order to give the patient optimal treatment. The randomisation code was not broken for any patient during the study.		Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Block randomisation (see above).	As Table 24 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?	Global Pharmacovigilance (GPV), H.Lundbeck A/S, and the investigator or pharmacist at the site had access to the details of the double-blind treatment for each patient. Access to thesedetails was via IVRS. The randomisation code was to be broken by the investigator only in an emergency situation in order to give the patient optimal treatment. The randomisation code was not broken for any patient during the study.		Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes. A post hoc sensitivity analysis was undertaken based on the APTS due to the high number of patients in the venlafaxine XR group who were excluded from the FAS. 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 imbalance in dropouts was adjusted for by re-conducting the analyses on the APTS.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no such evidence.	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. A post hoc sensitivity analysis was undertaken based on the APTS due to the high number of patients in the venlafaxine XR group who were excluded from the FAS. 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.		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.

6.3.8. Results Study 13926A (SOLUTION)

6.3.8.1. Efficacy

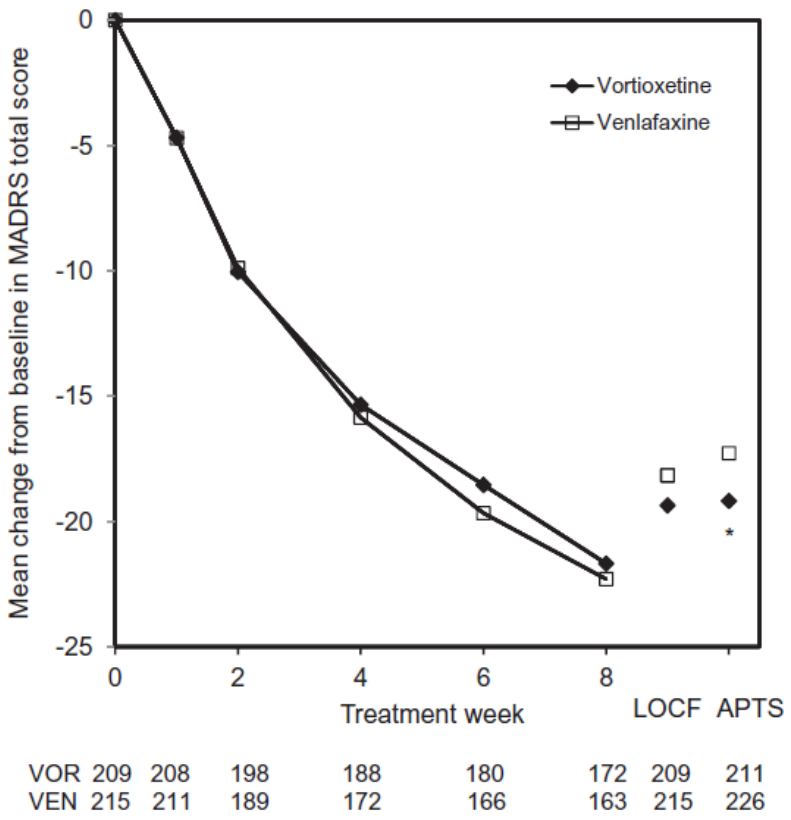
Primary efficacy endpoint

In the primary efficacy analysis, the mean change from baseline in MADRS total score at Week 8 (ANCOVA, FAS, LOCF) was -19.4 (vortioxetine) and -18.2 points (venlafaxine XR). The mean difference from venlafaxine XR for vortioxetine was -1.2 (95% CI: -3.0 to 0.6) in favour of vortioxetine. Non-

inferiority was established, as the upper bound of the 95% CI was 0.6 MADRS points, clearly below the non-inferiority margin of +2.5 MADRS points. To analyse the robustness of the results of the primary efficacy analysis, a pre-specified sensitivity analysis was performed: at Week 8, the difference to venlafaxine XR was 0.6 (95% CI: -0.9 to 2.2) points using ANCOVA (FAS, OC) which also showed non-inferiority to venlafaxine XR with a numerical advantage for venlafaxine XR.

As significantly (p=0.0160, chi-square) more patients treated with venlafaxine XR (11 patients) than vortioxetine (two patients) withdrew from the study and did not have a valid post-baseline MADRS assessment and were excluded from the FAS, a post-hoc efficacy analysis was made on the APTS, imputing a zero change from baseline for these non-FAS patients. The mean change from baseline in MADRS total score at Week 8 was -19.2 and -17.3 points in the vortioxetine and venlafaxine XR groups, respectively, giving a mean difference of -1.90 (95% CI: -3.76 to -0.04; p=0.0452) points in favour of vortioxetine (ANCOVA, APTS, LOCF), which is the full intention to treat analysis.

Figure 29: Study 13926A (SOLUTION). Estimated change from baseline in MADRS total scores from baseline to Week 8 (FAS, OC by visit) and LOCF (FAS, ANCOVA) at Week 8



Secondary efficacy endpoints

Clinician rated assessments

Vortioxetine showed a numerical advantage over venlafaxine XR in pre-defined secondary efficacy analyses (MADRS total score, HAM-A total score, CGI-S score, CGI-I score; FAS, LOCF) (Table 28), including response and remission based on the MADRS, the CGI-S and the CGI-I.

At Week 8, the mean MADRS total score decreased (improved) from 32.3±4.6 at baseline to 13.6±9.6 (vortioxetine) and from 32.3±4.5 to 14.8±10.4 (venlafaxine XR) (FAS, LOCF) (Figure 29). Time to response

was not analysed, but a reduction of approximately 50% from baseline in the mean MADRS total score was seen at 4–6 weeks. By Week 6, 54.5% of vortioxetine patients and 53.0% of venlafaxine XR patients had responded (≥50% decrease from baseline) (FAS, LOCF). At Week 8, 66.5% of the patients in the vortioxetine group were MADRS responders compared to 61.4% of the patients in the venlafaxine XR group and 43.1% of the patients in the vortioxetine group were MADRS remitters compared to 41.4% of the patients in the venlafaxine XR group (FAS, LOCF) (Table 2). The mean HAM-A total score decreased from 20.6±7.3 at baseline to 9.7±7.3 at Week 8 (vortioxetine) and from 21.1±7.0 at baseline to 10.8±7.7 at Week 8 (venlafaxine XR) (FAS, LOCF).

Mean CGI-I and CGI-S scores improved throughout the 8 week treatment period in both treatment groups. The mean CGI-S score decreased from 4.84±0.71 at baseline to 2.66±1.25 at Week 8 (vortioxetine) and from 4.87±0.69 at baseline to 2.80±1.35 at Week 8 (venlafaxine XR) (FAS, LOCF). The CGI-I score decreased from 3.38±0.77 at Week 1 to 2.05±1.10 at Week 8 (vortioxetine) and from 3.41±0.83 at Week 1 to 2.20±1.16 at Week 8 (venlafaxine XR) (FAS, LOCF). At Week 8, 74.2% of the patients in the vortioxetine group were CGI-I responders compared to 67.4% of the patients in the venlafaxine XR group and 49.8% of the patients in the vortioxetine group were CGI-S remitters compared to 47.0% of the patients in the venlafaxine XR group (FAS, LOCF).

Table 28: Study 13926A (SOLUTION). Primary, secondary and post-hoc efficacy outcomes: scale score differences

Efficacy Variable	Change from baseline		Difference	95% CI
	Vortioxetine ($n=209$)	Venlafaxine XR ($n=215$)		
Primary				
MADRS total score	−19.4 ± 0.7	−18.2 ± 0.7	−1.2 ± 0.9	(−3.03 to 0.63)
Secondary				
Clinician-rated assessments				
HAM-A total score	−11.4 ± 0.5	−10.6 ± 0.5	−0.8 ± 0.7	(−2.09 to 0.45)
CGI-S score	−2.26 ± 0.09	−2.12 ± 0.09	−0.15 ± 0.12	(−0.39 to 0.09)
CGI-I score[a]	1.99 ± 0.08	2.14 ± 0.08	−0.14 ± 0.11	(−0.35 to 0.06)
MADRS response (%)[a]	66.5	61.4	—	1.25 (0.84 to 1.86)
CGI-I ≤2 (response) (%)[a]	74.2	67.4	—	1.39 (0.91 to 2.11)
MADRS remission (%)[a]	43.1	41.4	—	1.07 (0.73 to 1.58)
CGI-S ≤2 (remission) (%)[a]	49.8	47.0	—	1.11 (0.76 to 1.63)
Patient reported outcomes				
SDS total score	−7.59 ± 0.61	−6.56 ± 0.60	−1.03 ± 0.79	(−2.58 to 0.53)
SDS family life subscale	−2.61 ± 0.21	−2.28 ± 0.21	−0.33 ± 0.27	(−0.87 to 0.21)
SDS work subscale	−2.48 ± 0.22	−2.20 ± 0.22	−0.28 ± 0.28	(−0.83 to 0.28)
SDS social life subscale	−2.74 ± 0.21	−2.52 ± 0.20	−0.22 ± 0.27	(−0.75 to 0.31)
Q-LES-Q total score	8.5 ± 0.6	8.6 ± 0.6	−0.1 ± 0.8	(−1.67 to 1.47)
Q-LES-Q item 15[b]	0.56 ± 0.18	0.77 ± 0.23	−0.21 ± 0.27	(−0.77 to 0.34)
Q-LES-Q item 16[c]	1.10 ± 0.07	1.02 ± 0.07	0.08 ± 0.09	(−0.09 to 0.26)
Post-hoc analysis	$n=211$	$n=226$		
MADRS total score[d]	−19.2 ± 0.7	−17.3 ± 0.7	−1.9 ± 0.9	(−3.76 to −0.04)

[a]Absolute value, 95% CI given with the odds ratio.
[b]Satisfaction with medication item.
[c]Overall life satisfaction and contentment item.
[d]Post-hoc ANCOVA, APTS, LOCF analysis.
APTS: all-patients-treated set, 95% CI: 95% confidence interval, CGI-I: Clinical Global Impression–Improvement, CGI-S: Clinical Global Impression–Severity, FAS: full-analysis set, HAM-A: Hamilton Rating Scale for Anxiety, LOCF: last observation carried forward, MADRS: Montgomery–Åsberg Depression Rating Scale, Q-LES-Q: Quality of Life, Enjoyment and Satisfaction Questionnaire, SDS: Sheehan Disability Scale.

6.3.8.2. Patient reported outcomes

For patient-reported outcomes relating to overall functioning, including the SDS total score and all three subscales (family, work and social life), there was a numerical advantage for vortioxetine. The mean SDS total score decreased (improved) from approximately 19 at baseline to approximately 11 (vortioxetine),

and approximately 12 (venlafaxine XR) at Week 8 (FAS, LOCF) (Table 28). Comparable reductions were observed in the vortioxetine and venlafaxine XR groups in mean SDS total and subscale scores (family, work and social) at Week 8 (FAS, LOCF). The number of underproductive or lost days per week decreased in both treatment groups from 5.3 (vortioxetine) and 5.2 days (venlafaxine XR) at baseline to 2.7 (vortioxetine) and 3.0 days (venlafaxine XR) at Week 8.

At Week 8, the mean Q-LES-Q total score increased (improved) in both treatment groups from approximately 34 at baseline (both groups) to 42.3 (vortioxetine) and 42.6 (venlafaxine XR), whereas the mean Q-LES-Q item 15 score (satisfaction with medication) increased from 2.6 (vortioxetine) and 2.9 points (venlafaxine XR) at baseline to 3.1 (vortioxetine) and 3.4 points (venlafaxine XR) at Week 8, and the mean Q-LES-Q item 16 score (overall life satisfaction and contentment) increased from 2.1 (both groups) at baseline to approximately 3.1 points at Week 8 in both groups.

6.3.8.3. Subgroup analyses

The study was not powered to draw conclusions on subgroups, and furthermore, some subgroups were small. No statistically significant differences were detected in any of the subgroup analyses but some differences were seen in the MADRS total score in terms of sex, age, and number of previous MDEs; women, older patients, and patients with ≥3 previous MDEs) were associated with greater improvements in MADRS total score in favour of vortioxetine.

Overall, the results from the subgroup analyses support the results from the covariate analyses, where no statistically significant interactions between treatment and the investigated covariates were found.

6.3.8.4. Safety and tolerability

During the 8 week treatment period, approximately three-fifths of the patients in each treatment group had one or more treatment-emergent adverse events (TEAEs). During this period, 45 patients withdrew due to TEAEs, 14 (6.6%) in the vortioxetine group and 31 (13.7%) in the venlafaxine XR group (p=0.0149, chi-square test). The only TEAEs leading to withdrawal of ≥3 patients in either treatment group were nausea (3.3%) in the vortioxetine group and nausea (4.9%), dizziness (2.7%), palpitations (1.8%), dry mouth (1.3%) and asthenia (1.3%) in the venlafaxine XR group. The most common TEAEs reported by at least 5% of patients for vortioxetine were nausea, dizziness, headache, and dry mouth (Table 29). For the venlafaxine XR group the most common TEAEs reported by at least 5% of patients included those reported for vortioxetine but in addition, accidental overdose, decreased appetite, constipation, insomnia were also reported. TEAEs led to withdrawal of 6.6% of vortioxetine patients and 13.7% of venlafaxine XR patients, mostly in the first 2 weeks of treatment. The most common TEAEs leading to withdrawal were nausea (vortioxetine 3.3%, venlafaxine XR 4.9%), dizziness (vortioxetine 0%, venlafaxine XR 2.7%) and erectile dysfunction (vortioxetine 0%, venlafaxine XR 2.3%). In the entire study period (including the 4 week safety follow-up period), the incidence of suicide-related TEAEs (intentional overdose, suicide attempt, suicidal ideation) was low and comparable between treatment groups (1.4% for vortioxetine and 1.8% for venlafaxine XR).

In the entire study period, serious AEs (SAEs) were reported by 10 patients, two patients in the vortioxetine group and eight patients in the venlafaxine XR group. The only SAE reported by more than one patient was suicide attempt, with one patient in the vortioxetine group and two patients in the venlafaxine XR group. An improvement from baseline in the scores for MADRS item 10 (suicidal thoughts) was seen in both treatment groups. No deaths occurred during this study.

No clinically relevant changes over time or differences between treatment groups were seen in clinical laboratory test results, vital signs, weight, or ECG parameters. At last assessment, patients in the

vortioxetine group had a mean weight gain of 0.2 kg and patients in the venlafaxine XR group had a mean weight loss of 0.5 kg compared to baseline.

Table 29: Treatment-emergent adverse events (TEAEs) with an incidence of ≥5% in either treatment group in the 8 week treatment period (APTS).

Preferred Term	Vortioxetine 10 mg *n* (%) (*n* = 211)	Venlafaxine XR 150 mg *n* (%) (*n* = 226)
Patients with TEAEs	125 (59.2)	153 (67.7)
Nausea	51 (24.2)	53 (23.5)
Dizziness	17 (8.1)	29 (12.8)
Headache	17 (8.1)	15 (6.6)
Dry mouth	12 (5.7)	24 (10.6)
Accidental overdose†	10 (4.7)	12 (5.3)
Decreased appetite	10 (4.7)	23 (10.2)*
Constipation	9 (4.3)	18 (8.0)
Insomnia	5 (2.4)	16 (7.1)*

APTS: all-patients-treated set.
†Defined as a dose of study medication that exceeds the dose prescribed.
*$p < 0.05$ (Fisher's exact test).

In conclusion Study 13926A (SOLUTION) showed vortioxetine to be better tolerated than venlafaxine XR. Fewer vortioxetine than venlafaxine XR patients withdrew for any reason (18.0% versus 27.4%) or for adverse events (6.6% versus 13.7%). The most common TEAEs leading to withdrawal were nausea (vortioxetine 3.3%, venlafaxine XR 4.9%), dizziness (vortioxetine 0%, venlafaxine XR 2.7%) and erectile dysfunction (vortioxetine 0%, venlafaxine XR 2.3%).

6.3.8.5. Conclusions

In conclusion, vortioxetine in a dose of 10 mg/day was at least as effective as venlafaxine XR 150 mg/day in treating MDD over 8 weeks, with a numerical advantage on the MADRS of 1.2 points. This advantage was statistically significant in the post-hoc analysis of the APTS population, and vortioxetine was better tolerated. The results of this study further support the established efficacy of vortioxetine and also confirm the safety and good tolerability of vortioxetine seen in the pivotal clinical studies.

6.3.8.6. Generalisability to the UK population

Lundbeck believe that although on the face of it SOLUTION may not look transferable to the population in England and Wales it provides relevant results which can help to inform the decision making process.

The population of SOLUTION was 100% Asian. This however should not affect the transferability of results to a non-Asian population for the following reasons. Vortioxetine is extensively metabolised in the liver, primarily through oxidation catalysed by CYP2D6 and to a minor extent CYP3A4/5 and CYP2C9 (Brintellix SmPC June 2015). *In vitro* and in vivo studies indicate that venlafaxine is biotransformed to its major active metabolite, ODV, by CYP2D6. *In vitro* and *in vivo* studies indicate that venlafaxine is metabolised to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4 (Effexor SmPC January 2015). Sistonen et al (2007) suggests that there is considerable variation of CYP2D6 within

populations, but not between populations. Bradford (2002) found that Asians have a higher prevalence of a reduced function CYP2D6 allele, however since both vortioxetine and venlafaxine are primarily metabolised via CYP2D6 this should affect both venlafaxine and vortioxetine groups equally. Similarly any geographic variation in the CYP3A4 gene, which plays a minor role in the metabolism of both vortioxetine and venlafaxine, should affect both groups equally. A study in Asians and Caucasians (Mizutani et al 2003) found that in both populations, the poor metaboliser frequencies of the CYP3A4 and CYP2C9 were low. Thus geographic location per se, should affect the metabolism of vortioxetine and venlafaxine equally and the relative efficacy should be comparable in studies carried out in European and East Asian populations. This rationale has also been tested and is supported by leading clinical experts (see Appendix 6.4).

6.4. Appendix 4: Clinical advisory board report

Meeting with UK Clinical Experts to discuss inputs and pathways in health economic model in Major Depressive Disorder

3rd July 2015

Advisers/ UK Clinical Experts

Prof Guy Goodwin - *Oxford University*

Prof Cornelius Katona - *University College London*

Dr Hamish McAllister-Williams - *Newcastle University*

Prof Allan Young - *King's College London*

A short advisory board was held in London on 3rd July 2015 sponsored by Lundbeck Ltd to seek advice in response to requests and questions received from the National Institute for Health and Care Excellence (NICE) in its appraisal of vortioxetine for treating major depressive episodes. The minutes below have been reviewed by the experts listed above to ensure the minutes are a clear and fair representation of the discussions held at the meeting.

The meeting started with general questions to understand how patients with Major Depressive Disorder (MDD) are treated.

GENERAL QUESTIONS

- ***Referral to a specialist***
  - ***How many antidepressants does a patient receive within primary care for the treatment of a single major depressive episode before they are referred to a specialist?***

Response from advisors

The advisors agreed that at least 2 anti-depressants (ADs) would be tried in primary care before referral to secondary care, but the more likely/average number would be 3-4 different. Some patients may never get referred to secondary care and would be treated entirely in primary care (possibly with informal advice from secondary care, without the specialist actually seeing the patient). Often a referral to secondary care may result in advice from secondary care such as trying alternative therapies but the patient would be referred back to primary care immediately. The main reason people would be kept in secondary care would be additional problems (such as high suicide risk, psychosis) or psychiatric or physical co-morbidities.

Question

- ***If a patient is referred to a specialist for the treatment of their depression, at what point will they be referred back out to primary care?***

The general consensus was that patients would be referred back to primary care as soon as possible, once there is evidence of some improvement.

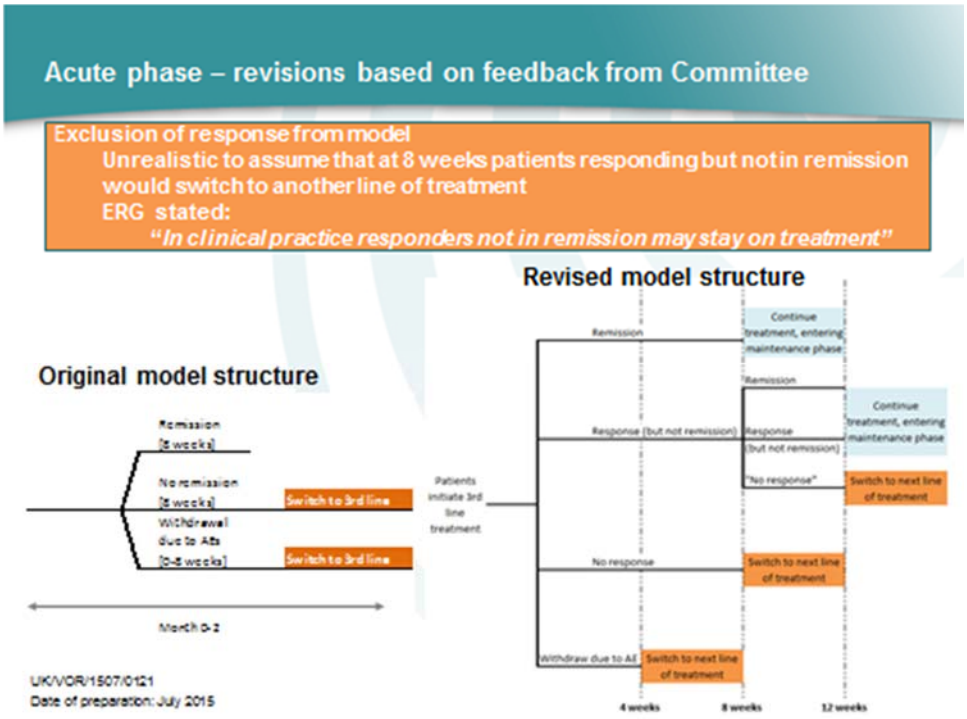
MODEL SPECIFIC QUESTIONS

The advisors were given an overview of the comments from the ERG and NICE on the health economic (HE) model submitted to NICE by Lundbeck and were shown an overview of the originally submitted versus the new model structure (comparison of treatment tree only; see Figure 30 below).

The advisers commented on the issue of modelling health states based on measures such as MADRS and HAM-D as these measures are not commonly used in primary care. The most commonly used measure in primary care was thought to be PHQ-9; however this may not be routinely used. Given this limitation the advisors discussed the different health states and pathways within the model.

The new structure was agreed as much more likely to reflect clinical practice. The advisors agreed with comments by NICE and the ERG that patients who had responded but not remitted would often stay on the same treatment and therefore the model should reflect this.

Figure 30 - Overview of original and revised model structure



Question 1 – non response at 8 weeks

- ***If a patient had not responded at 8 weeks would you switch their treatment?***
- ***Would it be at 8 weeks, earlier or later?***

Response from advisors

With respect to patients starting a third treatment after 2 treatment failures, it was agreed that 8 weeks would be reflective of clinical practice. The advisors commented that some patients are switched too early without being given sufficient time for the AD to take effect; this may happen more frequently when patients commence therapy (1st and 2nd line) as the patient and/or physician is eager for a response. It was agreed that 4 weeks for switching in the original model was too early and that 8 weeks is more reflective of clinical practice. The advisors therefore highlighted the need for an adequate trial period and dose titration during this period.

Question 2 - Response/No remission at 8 weeks

- ***The updated structure assumes that patients who have responded but not remitted at week 8 will continue treatment for another 4 weeks. Is this in line with the approach you would take in clinical practice?***

Response from advisors

It was agreed that most or all patients who had responded but not remitted would stay on treatment for at least a further 4 weeks. There was some discussion as to whether this might be longer than 4 weeks before the patient was re-assessed, so 4-8 weeks was thought to be a representative timeframe.

Question 3 - Response/No remission at 8 weeks

At 12 weeks patients are assessed again to determine if they are in the following health states:

- ***Remission 12 weeks***
- ***response/no remission 12 weeks or***
- ***no response 12 weeks***

A. ***Patients in remission at 12 weeks are assumed to continue on treatment – is this assumption OK?***

Response – Yes, this is also what guidelines recommend.

B. ***Patients in response at 12 weeks are assumed to continue on treatment – is this assumption OK?***

Response – Yes, although some patients would have treatment augmented.

C. ***Patients in "no response" at 12 weeks are assumed switch treatment – is this assumption OK?***

Response – Yes, patients with no response at 12 weeks would usually switch treatment.

D. **Would you consider these patients to be in "no response" or relapse?**

Response – These patients could not (by definition) be in the 'relapse' health state therefore they would have to be 'no response'.

Presentation of SOLUTION study to advisors and applicability of results to UK setting

The advisors were presented an overview of the SOLUTION study. This study was conducted to evaluate the efficacy, safety, and tolerability of vortioxetine 10 mg/day in patients from Asia with MDD, compared to an approved active comparator, venlafaxine XR 150 mg/day.

QUESTION

- ***Would you consider the results of this study relevant to the patients treated in UK clinical practice?***

In general the study was thought to be positive for vortioxetine and reflective of practice within the UK. The advisors commented that the dosage of both vortioxetine and venlafaxine may be low compared to doses used by psychiatrists in the UK but probably reflective of practice in primary care. The advisors commented that the higher number of drop-outs in the venlafaxine groups was not surprising. The only issue with transferability of the results would be that the study was carried out in Asian patients. The advisors suggested Lundbeck look into at CYP450 enzymes and metabolism of vortioxetine and venlafaxine in European and East Asian populations to establish whether there were clinically relevant differences.

Meeting Follow-Up

Following the meeting in response to the specific advice received regarding the SOLUTION study, further research was carried out into the transferability of these results into the European population. The following paragraph summarises the research and has been agreed by the advisers after the meeting.

Vortioxetine is extensively metabolised in the liver, primarily through oxidation catalysed by CYP2D6 and to a minor extent CYP3A4/5 and CYP2C9 (Brintellix SmPC June 2015). In vitro and in vivo studies indicate that venlafaxine is biotransformed to its major active metabolite O-desmethylvenlafaxine (ODV), by CYP2D6. In vitro and in vivo studies indicate that venlafaxine is metabolised to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4 (Efexor SmPC January 2015). Sistonen et al (2007) suggest that there is considerable variation of CYP2D6 within populations, but not between populations. Bradford (2002) found that Asians have a higher prevalence of a reduced function CYP2D6 allele, however since both vortioxetine and venlafaxine are primarily metabolised via CYP2D6 this should affect both venlafaxine and vortioxetine groups equally. Similarly any geographic variation in the CYP3A4 gene, which plays a minor role in the metabolism of both vortioxetine and venlafaxine, should affect both groups equally. A study in Asians and Caucasians (Mizutani et al 2003) found that in both populations, the poor metaboliser frequencies of the CYP3A4 and CYP2C9 were low. Thus in this context geographic location and ethnic grouping per se, should affect the metabolism of vortioxetine and venlafaxine equally and the relative efficacy should be comparable in studies carried out in European and East Asian populations.

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Advisor Profiles

Professor Guy Goodwin
Professor Guy Goodwin is Senior Research fellow at the University of Oxford, Oxford, UK, where he was previously WA Handley Professor of Psychiatry. He completed his medical degree and DPhil in Physiology at the University of Oxford and, following his training in psychiatry, became a Clinical Scientist and Consultant Psychiatrist at the Medical Research Council (MRC) Brain Metabolism Unit at the Royal Edinburgh Hospital, Edinburgh, UK.

Professor Goodwin's research interests are in the treatment of bipolar disorder and the application of neuroscience in understanding the neurobiology of mood disorders, with a focus on developing new treatments. He has been a lead investigator in clinical trials for bipolar affective disorder, including the BALANCE and CEQUEL studies. He works with industry in developing preclinical models of psychotropic drug action in humans.

Professor Goodwin has served as a member of the Wellcome Trust Neurosciences Panel, the Council of the British Association for Psychopharmacology, the Clinical Fellowships Panel and Advisory Board of the MRC, and INSERM's ANR panel. He was previously President of the British Association for Psychopharmacology and is a Fellow of the American College of Neuropsychopharmacology, Fellow and current President of the European College of Neuropsychopharmacology (ECNP) and a National Institute for Health Research Senior Investigator.

Professor Cornelius Katona
Cornelius Katona received his undergraduate education in Cambridge and at the London Hospital and his training in general and old age psychiatry at Fulbourn Hospital, Cambridge and St George's Hospital Medical School, London. He was Senior Lecturer in Psychiatry of the Elderly at University College London from 1986 till 1991 when he was appointed Foundation Professor of Psychiatry of the Elderly. Between 1998 and 2003 he served as Dean of the Royal College of Psychiatrists. Between 2003 and 2008 he was Dean of the Kent Institute of Medicine and Health Sciences and Professor of Psychiatry at the University of Kent. He is currently Hon. Professor of Psychiatry of the Elderly at University College London and works as a Consultant Psychiatrist in the charity and independent sectors.

Clinical Expertise
Cornelius is an old age psychiatrist with special interests in dementia and in mood disorders in old age. He also has research and clinical interests in the mental health needs of asylum seekers and refugees. He is the author of over 200 peer-reviewed articles and author / editor of 15 books.

Other Activities
Cornelius has been co-chair of the World Psychiatric Association section of affective disorders, Chair of the World federation of Societies of Biological Psychiatry Taskforce on Old Age and co-founder and vice-president of the International Society for Affective Disorders. He was editor in chief of the Journal of Affective Disorders between 1994 and 2015. He is Medical Director of the Helen Bamber Foundation, a human rights charity.

Dr Hamish McAllister-Williams
I qualified in medicine at University of Edinburgh, Scotland in 1987. Following house jobs in Medicine and Surgery, I was awarded a Wellcome Trust Clinical Training Fellowship in the Department of Pharmacology in Edinburgh gaining a PhD in Neuropharmacology for work studying serotonergic (5-HT)

responses in central neurons. I subsequently undertook clinical training in Psychiatry at the Royal Edinburgh Hospital and then moved to Newcastle University in 1995 as a Clinical Lecturer. In 1999 I was awarded a UK Medical Research Council Clinician Scientist Fellowship at Senior Lecturer level to investigate the pathophysiology of affective disorders, in particular the role of serotonin and cortisol. I completed a research MD degree in Psychopharmacology at Newcastle University describing a novel method of exploring 5-HT function in man that has been used to study corticosteroid-5-HT interactions and 5-HT abnormalities in depressed patients. In 2004 I was appointed a Reader in Clinical Psychopharmacology by Newcastle University.

Clinically, I am the lead clinician for the tertiary level Regional Affective Disorders Service based in Newcastle. This is the oldest and one of the largest such service in the UK aimed at patients with treatment refractory mood disorders.

I am a past General Secretary of the British Association for Psychopharmacology (BAP) and was appointed in 2012 as the BAP Director of Education. I am a major contributor to their CPD programme.

My current research is primarily related to investigations of the role of the pathophysiology and treatment of mood disorders and currently he is a Principle Investigator for two large multicentre studies investigating the use of a steroid synthesis inhibitor as an augmenter of antidepressants in patients with treatment refractory depression, and ketamine augmentation of ECT.

Professor Allan Young

Professor Allan Young is current head of The Centre for Affective Disorders (CfAD), King's College London Institute of Psychiatry, Psychology and neuroscience (IoPPN).

Professor Allan Young, MB, ChB, MPhil, PhD, FRCPsych, FRCP(C), was the former Chair of Psychiatry at Imperial College London where he was also Director of the Centre for Mental Health within the Division of Brain Sciences. His research interests focus on the cause and treatments for severe psychiatric illnesses, particularly mood disorders. He has held academic appointments at the Universities of Edinburgh, Oxford, Newcastle upon Tyne, (latterly holding the Chair of General Psychiatry at Newcastle) and UBC, Vancouver, Canada where he held the Leading Edge Endowment Fund Endowed Chair in Research in the Department of Psychiatry and was also the Director of the Institute of Mental Health. Professor Young is currently President of the International Society for Affective Disorders and Chair of the Psychopharmacology Group in the Royal College of Psychiatrists.

6.5. Appendix 5: Treatments associated with QTc prolongation

Table 30: Treatments known to prolong QT interval

Type of therapy	Treatment
Antiarrhythmics	Class 1: ajmaline*, cibenzoline*, dihydroquinidine*, disopyramide, encainide*, flecainide, mexiletine, pirmenol*, procainamide, propafenone quinidine* Class 3: almokalant*, amiodarone, azimilide*, bretylium, dofetilide*, dronedarone*, d-sotalol*, ersentilide*, ibutilide*, nifekalant*, sematilide*, sotalol, terikalant*
Anti-anginals/vasodilators	bepridil*, lidoflazine*, prenylamine*, ranolazine, terodiline*, vardenafil
Anti-hypertensives	indapamide, isradipine, moexipril/hydrochlorthiazide, nicardipine
Antihistamines	astemizole*, azelastine, diphenhydramine, ebastine*, hydroxyzine, terfenadine*
Serotonin agonists and antagonists	cisapride*, dolasetron, granisetron, ketanserin*, ondansetron
Antimicrobials	Macrolide antibiotics: azithromycin, clarithromycin, erythromycin, roxithromycin*, spiramycin, telithromycin Quinolone antibiotics: ciprofloxacin, gatifloxacin*, gemifloxacin*, grepafloxacin*, levofloxacin, moxifloxacin, ofloxacin, sparfloxacin* Antifungals: cotrimoxazole, fluconazole (caution with itraconazole), ketoconazole, voriconazole Others: pentamidine, trimethoprim sulfa (bactrim) Antiviral: foscarnet (HIV)
Antimalarials	amantidine, chloroquine, halofantrine*, quinine
Psychiatric drugs	Tricyclic antidepressants: amitriptyline, amoxapine*, clomipramine, desipramine*, doxepin, imipramine, nortriptyline, protriptyline*, trimipramine Phenothiazines: chlorpromazine, fluphenazine, prochlorperazine, thioridazine*, trifluoperazine Others: atomoxetine, citalopram, clozapine, droperidol*, fluoxetine, haloperidol, levomethadyl*, lithium, maprotiline, mesoridazine, methadone, paroxetine, pericycline, pimozide, quetiapine, risperidone, sertindole, sertraline, trazodone, venlafaxine, zimeldine*, ziprasidone
Anticonvulsant	felbamate*, fosphenytoin (prodrug of phenytoin)
Anti-migraine	naratriptan, sumatriptan, zolmitriptan
Anti-cancer	arsenic trioxide, geldanamycin*, sunitib, tacrolimus, tamoxifen
Others	alfuzosin, chloral hydrate, clobutinol*, domperidone, galantamine, octreotide, organophosphates*, perflutren lipid microspheres, probucol, solifenacin, tizanidine, tolterodine, vasopressin
Stimulant drugs	**Some cold remedies contain these drugs so it is important always to check the label.** adrenaline (epinephrine), amphetamine, cocaine, dexmethylphenidate, dobutamine, dopamine, ephedrine, fenfluramine, isoprenaline (isoproterenol), levalbuterol, metaproterenol, methylphenidate, midodrine, norepinephrine (noradrenaline), phentermine, phenylephrine, phenylpropanolamine, pseudoephidrine, ritodrine, salbutamol (albuterol), salmeterol, sibutramine, terbutaline

Source: www.SADS.co.uk Drugs to avoid http://www.sads.org.uk/drugs_to_avoid.htm
Please note: this list is not exhaustive.
● = Drugs which are unlicensed, withdrawn or suspended in the UK market.

6.6. Appendix 6: Additional clinical insight: guidelines and practice

6.6.1. Additional insight into clinical practice and the treatment pathway for depression in the UK

Additional insight into clinical guidelines and practice, especially with regards to when a patient would switch treatment, was required in order to inform the updated model structure. This section provides an overview of the clinical pathway from both NICE CG90 and the British Association of Psychopharmacology (BAP). In addition to this 3 local guidelines are presented (selected due to their availability online), along with the results of a brief questionnaire conducted by Lundbeck to inform the updated model structure, are reported.

6.6.2. National Guidelines

6.6.2.1. Initiating and switching treatment

NICE CG90 and the BAP guidelines were considered the most relevant guidelines covering England and Wales. The recommendations with regards to treatment switching is summarised in Table 31.

TABLE 31: SUMMARY OF RECOMMENDATIONS OF NATIONAL GUIDELINES ON TREATMENT SWITCHING IN PATIENTS STARTING ANTIDEPRESSANT THERAPY

Weeks after treatment initiation	Guideline	
	CG90 (NICE, 2009)	BAP (Cleare 2015)
1-2 weeks	For the first 4 weeks check dose and that the antidepressant has been taken regularly	Continue adequately dosed antidepressant for at least 4 weeks before changing treatment due to lack of efficacy
3-4 weeks	If **response is absent or minimal** add in extra support and consider: • increasing the dose in line with the SmPC if there are no side-effect concerns; • switch to another antidepressant if there are side-effect concerns or if the patient prefers If **a patient's depression is showing some improvement by week 4** continue for another 2-4 weeks.	At 4 weeks: if there is **some improvement continue for a further 2-4 weeks**. If **no trajectory of improvement consider next steps** (switch, combination, augmentation); however, **if a patient has failed a number of treatments consider longer trials** before treatment change
4-6 weeks	Nothing reported	Nothing reported
6-8 weeks	Consider **switching to another antidepressant if response is still not adequate**; side-effects are too great or if the patient prefers.	If there is **moderate or greater improvement continue the same treatment**; if minimal then follow next steps (combination, augmentation, switch)

SmPC: Summary of product characteristics

As can be seen in Table 31 both guidelines are in general agreement. At week 4 CG90 recommends increasing the dose if response is absent or minimal, switching only if there are side-effect concerns or if the patient prefers. The BAP stipulates that if there is some improvement seen in the patient then continue for another 2-4 weeks. If however, there is no improvement then "next steps", including switching, augmentation and combination should be considered. This though is caveated with a recommendation of longer trials of treatment in patients who have failed on multiple previous treatments – a point which is of relevance to the 3rd line population being considered within this document. Both state that a treatment switch at week 6-8 should occur if the efficacy outcome is still not adequate/is minimal.

6.6.2.2. Length of maintenance treatment

CG90 recommends that patients should continue maintenance treatment for at least 6 months. At 6 months a patient should be reassessed and a decision on whether further treatment is necessary should be made. When deciding whether to continue maintenance treatment beyond 2 years, re-evaluation of the person with depression, taking into account age, comorbid conditions and other risk factors should be conducted.

The BAP guidelines state that in patients who are responsive to treatment their medication should be continued at the acute treatment dose after remission, with the duration of maintenance treatment determined by risk of relapse. In patients at lower risk of relapse (e.g. first episode without risk factors) the duration should be at least 6-9 months. Duration in other instances should be tailored to the individual relapse risk, considering a duration of at least 1 year after full remission in patients with any increased risk of relapse. In higher-risk patients (e.g. more than five lifetime episodes and/or two episodes in the last few years) at least 2 years should be advised and for most "long-term" treatment should be considered.

6.6.2.3. Referrals to secondary care

NICE CG90 states referral to specialist mental health services should normally be reserved for people with depression who are at significant risk of self-harm, have psychotic symptoms, require complex multi-professional care, or where an expert opinion on treatment and management is needed. The guidelines split points to be considered into two baskets: those that favour referral and those that favour urgent referral.

Factors that favour referral to mental health professionals:

- inadequate or incomplete response to two or more interventions
- recurrent episode within 1 year of last episode
- history suggestive of bipolar disorder
- the person with depression or relatives request referral
- more persistent suicidal thoughts
- self-neglect

Factors that favour urgent referral to specialist mental health services

- actively suicidal ideas or plans

- psychotic symptoms
- severe agitation accompanying severe symptoms
- severe self-neglect

The BAP guideline provides little guidance on referral to specialist care, stating only the following:

"Summary: Criteria for psychiatric/specialist referral are based on risk and requirement for specialist expertise (IV)

Certain conditions – such as high suicide risk, psychotic major depression and major depression in bipolar patients – and certain groups – such as children and adolescents – have specific treatment implications (Goodwin, 2003; National Institute for Clinical Excellence, 2009) generally regarded as requiring specialist expertise. There are no controlled data related to indications for referral."

6.6.3. Local clinical guidelines

In addition to the National guidelines summarised above, Lundbeck have sourced online 3 publically available local guidelines to assess whether these are in line with national recommendations. These are as follows:

- Devon Partnership NHS: Pharmacological Treatment of Unipolar Depression
- Dorset Healthcare Foundation Trust, Bournemouth and Poole, and Dorset Primary Care Trusts: Primary Care Protocol for Depression
- Nottingham City PCT and Nottinghamshire County teaching PCT and Bassetlaw PCT: Primary Care Guidelines for Depression in Adults

6.6.3.1. Devon Partnership NHS: Pharmacological Treatment of Unipolar Depression

All recommendations are in line with NICE CG90.

6.6.3.2. Dorset Healthcare Foundation Trust, Bournemouth and Poole, and Dorset Primary Care Trusts: Primary Care Protocol for Depression

When switching, 6 weeks of antidepressant treatment should be prescribed. If patients are unable to tolerate this treatment then switch to a different better tolerated antidepressant or consider a brief period of concomitant benzodiazepine. If a patient achieves partial response within 6 weeks then increase the dose up to the maximum the patient can tolerate and continue for up to 12 weeks. If symptoms persist then consider dual action antidepressant (3rd line).

Patients should be continued on treatment for 6 months from resolution of symptoms. If a patient has had 2 or 3 previous episodes and significant impairment continue for minimum 2 years.

A patient should be referred to the Community Mental Health Team (CMHT) if a patient has not responded to 2-3 antidepressants.

The guideline does not provide information about when a patient should be referred back to be managed in primary care.

6.6.3.3. Nottingham City PCT and Nottinghamshire County teaching PCT and Bassetlaw PCT: Primary Care Guidelines for Depression in Adults

Considerations before switching are detailed within this guideline. If partial response is achieved wait up to 6 weeks (12 weeks in elderly patients) before considering changes to treatment (switch or increase dose). If no response, check the treatment is being taken regularly and at the required dose. If there is no response at 4 weeks the dose should be increased within the BNF recommended effective dose range. If there is still not response after a further 2-4 weeks then switch treatment (4-6 weeks in elderly).

Treatment should continue for at least 6 months. After 6 months the patient should be reviewed and an assessment of whether further treatment is necessary should be undertaken.

6.6.3.4. Summary of local guidelines

Generally, from this small sample it seems local guidelines broadly align with the recommendations in NICE CG90. The only discrepancy is that the Dorset guideline suggests that if a patient has had a partial response then switch should be considered at 6 weeks.

6.6.4. Questionnaire on treatment practices in the NHS

In order to gain insight into current clinical practice Lundbeck created a questionnaire to capture information on the treatment of depression in the NHS. A copy of the questionnaire distributed is included in Appendix 6.7. The primary aim of this questionnaire was to ensure that all changes to the cost-effectiveness model reflected both guideline recommendations and clinical practice.

An overview of the complete set of results is included in Appendix 6.7.

A total of 7 HCPs agreed to take part in the survey. They were not incentivised by Lundbeck in any way to take part or provide their responses. Six of the participants were psychiatrists and the seventh was a GP with special interest in mental health.

6.6.4.1. Results

Referral to a specialist

The majority of participants answered that patients usually receive between 2-3 antidepressants before being referred to a specialist. There was general agreement as soon as a patient was showing substantial signs of improvement (e.g. responding to treatment) they would be referred back out to primary care for the continued management of their depression.

Switching treatments

- **Non responders:** the group of clinicians generally fell into two groups – those who would switch a patient in non-response at 4 weeks and those who would at 8 weeks.
- **Responders:** the majority of feedback received indicated that patients in response would be continued on treatment into the maintenance phase, indicating that for some patients, response

(rather than remission) would be seen as an adequate clinical outcome. However, 3 of the 7 questionnaires completed indicated that patients would be switched at 8 weeks if they were in response but not remission after 8 weeks of treatment.

- **Remitters**: The questionnaire feedback indicated that patients who were in remission would be continued on treatment until the end of the maintenance phase.

Average treatment length

Only 6 of the 7 participants provided a response to the specific question around length of maintenance treatment. There were mixed responses in terms of how long a patient should be continued on maintenance treatment in order to consolidate the antidepressive response.

Half of the responses indicated that a patient would be kept on maintenance treatment for between 4-12 months. Two of the participants suggested that treatment length was dependant on number of previous episodes giving the following responses: 1st episode – 6 to 12 months: 2nd episode – 2-3 years: >3 episodes at least 3 -5 years. The final participant answered that all patients would be on treatment for the remainder of their life. The answers to this question were heavily influenced by the patient population each of the clinicians treated in general clinical practice.

In order to assess the average length of treatment overall, patients from IMS Heath's Longitudinal Patient Data set were analysed. The data shows that the average length of treatment for patients treated with an antidepressant, and who have a diagnosis of depression in their record, is 475.5 days – approximately 1 year and 3 months (IMS 2015).

6.6.5. Conclusions regarding consistency of clinical practice

The review of the clinical guidelines and responses to the questionnaire provide a good overview of the consistencies and inconsistencies associated with the treatment and management of depression between recommendation and clinical practice.

The national (CG90 and the BAP) and local guidelines are generally consistent. However the results of the questionnaires indicate that there is some variation between the approaches taken by individual clinicians as well as compared to clinical guidelines both locally and nationally. This may be due to the variation in patient population treated by each of the clinicians in addition to variation in clinician's treatment strategies.

A more focussed summary identifying the specific aspects of the guidelines and clinical data which relate to the model structure and assumptions are explicitly discussed in Section 3.6.2.

6.7. Appendix 7: Questionnaire regarding clinical practice to inform a cost-effectiveness model in MDD to be submitted to NICE

Thank you for agreeing to complete this short survey. We are mindful that the treatment of depression is tailored to each individual patient. However, for the purposes of this questionnaire please answer for the majority of patients. If there are large variations between different groups of patients then please provide us with the insight within your responses below.

Referral to specialists

10. How many antidepressants does a patient receive within primary care for the treatment of a single major depressive episode before they are referred to a specialist?

11. If a patient is referred to a specialist for the treatment of their depression, at what point will they be referred back out to primary care?

Treatment switching

Please think about a patient who has failed on 2 previous antidepressants (at a therapeutic dose for an adequate trial period) for the treatment of their current episode.

12. What would you consider an adequate "trial period" of an antidepressant (used as a third treatment) to determine efficacy (if the patient could tolerate the product)?
    a. And how would you define "efficacy"? E.g. response (>50% reduction in symptoms), remission, something else?

4 weeks of treatment

13. If a patient has shown no improvement/minimal improvement after 4 weeks of treatment on their 3rd antidepressant would you continue their treatment or stop/change it?

    a. If you would continue, how long would you continue for before reassessment and would you adjust the dose?
    a. If you would stop/change treatment, what approach would you take? E.g. switch treatment, augmentation, combination

14. Would your answers differ to the above if the patient had:

    a. Responded (50% reduction in symptom score)?

    b. Remitted?

8 weeks of treatment (similar questions to the above at 4 weeks)

15. If a patient has shown no improvement/minimal improvement after 8 weeks of treatment on their 3rd antidepressant would you continue their treatment or stop/change it?

    g. If you would continue, how long would you continue for before reassessment and would you adjust the dose?
    h. If you would stop/change treatment, what approach would you take? E.g. switch treatment, augmentation, combination

16. Would your answers differ to the above if the patient had:

    i. Responded (50% reduction in symptom score)?

    j. Remitted?

12 weeks of treatment

17. If a patient has shown no improvement/minimal after 12 weeks of treatment on their 3rd antidepressant would you continue their treatment or stop/change it?

c. If you would continue, how long would you continue for before reassessment and would you adjust the dose?
d. If you would stop/change treatment, what approach would you take? E.g. switch treatment, augmentation, combination

18. Would your answers differ to the above if the patient had:

k. Responded (50% reduction in symptom score)?

i. If you would continue this patient on treatment how long would they be continued for?

ii. In addition, if continued on treatment would you ever expect them to achieve remission and subsequent recovery?

1. If so, as an average how long would you expect (on average) each of these milestones to take?

l. Remitted?

General questions:

19. Would you expect a patient who does not achieve response at week 8 to achieve the following at week 12, if so, what proportion?
Remission:
Response:
No response:

20. How long is the average patient continued on treatment for once symptom resolution has been achieved?

Many thanks for your participation in this brief questionnaire. Your feedback is valued by the Lundbeck team.

6.8. Appendix 8: Model Parameters

Table 32: Model parameters - rates of side-effects (all analyses bar SOLUTION)

Short-term side-effects (acute phase)				
Side-effect	**Treatment**	**Probability**	**Distribution**	**Source**
Sexual dysfunction	Vortioxetine	0.40%	Beta(α: 1,β: 252)	14178A (REVIVE)
	Agomelatine	0.00%	Beta(α: 0,β: 242)	14178A (REVIVE)
	Sertraline	10.64%	Beta (α: 131; β: 1,100)	Cipriani 2010
	Venlafaxine	14.38%	Beta(α: 22,β: 131)	Pooled Cochrane reviews
	Citalopram	6.24%	Beta (α:57; β:856)	Cipriani 2012
	Escitalopram	6.69%	Beta(α: 48,β: 670)	Cipriani 2009
	Duloxetine	3.77%	Beta(α: 18,β: 460)	Cipriani 2012
Dry mouth	Vortioxetine	4.74%	Beta(α: 12,β: 241)	14178A (REVIVE)
	Agomelatine	3.31%	Beta(α: 8,β: 234)	14178A (REVIVE)
	Sertraline	14.45%	Beta (α:305; β:1,805)	Cipriani 2010
	Venlafaxine	23.02%	Beta(α: 148,β: 495)	Pooled Cochrane reviews
	Citalopram	6.68%	Beta (α:92; β:1,286)	Cipriani 2012
	Escitalopram	7.93%	Beta(α: 227,β: 2634)	Cipriani 2009
	Duloxetine	15.00%	Beta(α: 324,β: 1836)	Cipriani 2012
Nausea	Vortioxetine	16.21%	Beta(α: 41,β: 212)	14178A (REVIVE)
	Agomelatine	9.09%	Beta(α: 22,β: 220)	14178A (REVIVE)
	Sertraline	26.17%	Beta (α:693; β:1,955)	Cipriani 2010
	Venlafaxine	41.02%	Beta(α: 345,β: 496)	Pooled Cochrane reviews
	Citalopram	10.99%	Beta (α:172; β:1,393)	Cipriani 2012
	Escitalopram	15.28%	Beta(α: 464,β: 2572)	Cipriani 2009
	Duloxetine	30.27%	Beta(α: 702,β: 1617)	Cipriani 2012
Sweating	Vortioxetine	2.37%	Beta(α: 6,β: 247)	14178A (REVIVE)
	Agomelatine	2.07%	Beta(α: 5,β: 237)	14178A (REVIVE)
	Sertraline	13.34%	Beta (α:234; β:1,520)	Cipriani 2010
	Venlafaxine	12.87%	Beta(α: 105,β: 711)	Pooled Cochrane reviews
	Citalopram	6.50%	Beta (α:53; β:762)	Cipriani 2012
	Escitalopram	5.21%	Beta(α: 88,β: 1602)	Cipriani 2009
	Duloxetine	8.85%	Beta(α: 166,β: 1709)	Cipriani 2012

Somnolence	Vortioxetine	4.00%	Beta(α: 10,β: 243)	14178A (REVIVE)
	Agomelatine	7.85%	Beta(α: 19,β: 223)	14178A (REVIVE)
	Sertraline	9.15%	Beta (α:188; β:1,867)	Cipriani 2010
	Venlafaxine	8.58%	Beta(α: 70,β: 746)	Pooled Cochrane reviews
	Citalopram	6.85%	Beta (α:70; β:952)	Cipriani 2012
	Escitalopram	6.56%	Beta(α: 163,β: 2322)	Cipriani 2009
	Duloxetine	9.15%	Beta(α: 212,β: 2105)	Cipriani 2012
Headache	Vortioxetine	10.28%	Beta(α: 26,β: 227)	14178A (REVIVE)
	Agomelatine	13.22%	Beta(α: 32,β: 210)	14178A (REVIVE)
	Sertraline	26.08%	Beta (α:684; β:1,939)	Cipriani 2010
	Venlafaxine	21.62%	Beta(α: 221,β: 801)	Pooled Cochrane reviews
	Citalopram	10.85%	Beta (α:155; β:1,274)	Cipriani 2012
	Escitalopram	15.71%	Beta(α: 477,β: 2559)	Cipriani 2009
	Duloxetine	15.59%	Beta(α: 337,β: 1825)	Cipriani 2012
Diarrhoea	Vortioxetine	3.16%	Beta(α: 8,β: 245)	14178A (REVIVE)
	Agomelatine	3.31%	Beta(α: 8,β: 234)	14178A (REVIVE)
	Sertraline	20.14%	Beta (α:493; β:1,955)	Cipriani 2010
	Venlafaxine	8.95%	Beta(α: 80,β: 814)	Pooled Cochrane reviews
	Citalopram	6.74%	Beta (α:88; β:1,218)	Cipriani 2012
	Escitalopram	8.33%	Beta(α: 219,β: 2411)	Cipriani 2009
	Duloxetine	7.65%	Beta(α: 134,β: 1617)	Cipriani 2012
Insomnia	Vortioxetine	7.10%	Beta(α: 18,β: 235)	14178A (REVIVE)
	Agomelatine	2.89%	Beta(α: 7,β: 235)	14178A (REVIVE)
	Sertraline	18.10%	Beta (α:402; β:1,819)	Cipriani 2010
	Venlafaxine	17.96%	Beta(α: 144,β: 658)	Pooled Cochrane reviews
	Citalopram	7.46%	Beta (α:115; β:1,427)	Cipriani 2012
	Escitalopram	8.88%	Beta(α: 232,β: 2382)	Cipriani 2009
	Duloxetine	12.30%	Beta(α: 256,β: 1825)	Cipriani 2012
Dizziness	Vortioxetine	7.11%	Beta(α: 18,β: 235)	14178A (REVIVE)
	Agomelatine	11.57%	Beta(α: 28,β: 214)	14178A (REVIVE)
	Sertraline	10.40%	Beta (α:184; β:1,586)	Ciprianin 2010
	Venlafaxine	13.24%	Beta(α: 116,β: 760)	Pooled Cochrane reviews

	Citalopram	4.58%	Beta (α:39; β:812)	Ciprianin 2012
	Escitalopram	5.34%	Beta(α: 113,β: 2002)	Cipriani 2009
	Duloxetine	11.36%	Beta(α: 213,β: 1662)	Cipriani 2012
Long-term side-effects (maintenance phase)				
Side-effect	**Treatment**	**Probability**	**Distribution**	**Source**
Sexual dysfunction	Vortioxetine	1.56%	Beta (α:12; β:755)	Pooled long-term extension studies
	Agomelatine	0.00%	Beta (α:0; β:165)	Goodwin 2009
	Sertraline	23.00%	Beta (α:134; β:450)	Bet 2013
	Venlafaxine	31.00%	Beta (α:45; β:100)	Bet 2013
	Citalopram	23.00%	Beta (α:134; β:450)	Bet 2013
	Escitalopram	23.00%	Beta (α:134; β:450)	Bet 2013 (use pooled SSRI value)
	Duloxetine	31.00%	Beta (α:45; β:100)	Bet 2013 (assume same as venlafaxine)
Insomnia	Vortioxetine	3.50%	Beta (α:27; β:740)	Pooled long-term extension studies
	Agomelatine	1.80%	Beta (α:3; β:162)	Goodwin 2009
	Sertraline	7.00%	Beta (α:41; β:543)	Bet 2013
	Venlafaxine	10.00%	Beta (α:15; β:130)	Bet 2013
	Citalopram	7.00%	Beta (α:41; β:543)	Bet 2013
	Escitalopram	7.00%	Beta (α:41; β:543)	Bet 2013 (use pooled SSRI value)
	Duloxetine	10.00%	Beta (α:15; β:130)	Bet 2013 (assume same as venlafaxine)
Weight gain	Vortioxetine	2.90%	Beta (α:22; β:745)	Pooled long-term extension studies
	Agomelatine	0.00%	Beta (α:0; β:0)	Goodwin 2009
	Sertraline	19.00%	Beta (α:111; β:473)	Bet 2013
	Venlafaxine	17.00%	Beta (α:25; β:120)	Bet 2013
	Citalopram	19.00%	Beta (α:111; β:473)	Bet 2013
	Escitalopram	19.00%	Beta (α:111; β:473)	Bet 2013 (use pooled SSRI value)
	Duloxetine	17.00%	Beta (α:25; β:120)	Bet 2013 (assume same as venlafaxine)

Table 33: Disutilities associated with adverse events

Disutilities of side effect		Base-case	
		Value	Source
Short-term and long-term adverse events	Sexual dysfunction	0.049	Sullivan 2004
	Headache	0.115	Sullivan 2004
	Diarrhoea	0.044	Sullivan 2004
	Somnolence	0.085	Sullivan 2004
	Nausea	0.065	Sullivan 2004
	Insomnia	0.129	Sullivan 2004
	Dry mouth	0	
	Dizziness	0	
	Sweating	0	
	Weight gain	0.032	Dixon 2004, REVIVE CSR

Table 34: Resource use unit costs

Resource	Unit cost (£)
GP consultations	45
Psychiatrist consultations	125
Psychotherapy or counselling	145
Psychiatric ward admissions	342
General ward admissions	697
Accident & emergency visits	177

Table 35: Health care resource utilisation by health state

Healthcare resource utilization					
Resource		Base-case			Scenario +30% resource use for responders
		No. of visits	Patients with ≥1 visit (%)	Source	No. of visits
GP consultations	Remission 0-8 weeks	**2.50**	100.0%	PERFORM	
	No response 0-8 weeks	**2.80**	100.0%	PERFORM	

	Response 0-8 weeks	**2.50**	100.0%	Assumed equivalent to remission	*3.25*
	Remission 8-12 weeks	*1.25*	100.0%	Calculation	
	Response 8-12 weeks	*1.25*	100.0%	Assumed equivalent to remission	*1.63*
	No response 8-12 weeks	*1.40*	100.0%	Calculation; assumption	
	Remission after 12 weeks	**2.15**	100.0%	Byford 2011	
	Response after 12 weeks	**2.15**	100.0%	Assumed equivalent to remission	*2.80*
	Relapse after 12 weeks	**2.89**	100.0%	Byford 2011	
Psychiatrist consultations	Remission 0-8 weeks	**0.00**	0.0%	PERFORM	
	No response 0-8 weeks	**1.00**	1.3%	PERFORM	
	Response 0-8 weeks	**0.00**	0.0%	Assumed equivalent to remission	*0.00*
	Remission 8-12 weeks	*0.00*	0.0%	Calculation; assumption	
	Response 8-12 weeks	**0.00**	0.0%	Assumed equivalent to remission	*0.00*
	No response 8-12 weeks	*0.50*	1.3%	Calculation; assumption	
	Remission after 12 weeks	**0.23**	2.9%	Byford 2011	
	Response after 12 weeks	**0.23**	2.9%	Assumed equivalent to remission	0.30
	Relapse after 12 weeks	**0.23**	5.0%	Byford 2011	
Psychotherapy or counselling	Remission 0-8 weeks	**1.20**	12.7%	PERFORM	
	No response 0-8 weeks	**2.10**	18.8%	PERFORM	
	Response 0-8 weeks	**1.20**	12.7%	Assumed equivalent to remission	*1.56*
	Remission 8-12 weeks	*0.60*	12.7%	Calculation; assumption	
	Response 8-12 weeks	**0.60**	12.7%	Assumed equivalent to remission	*0.78*
	No response 8-12 weeks	*1.05*	18.8%	Calculation; assumption	
	Remission after 12 weeks	**0.00**	0.2%	Byford 2011	

	Response after 12 weeks	**0.00**	0.0%	Assumed equivalent to remission	0.00
	Relapse after 12 weeks	**0.00**	0.2%	Byford 2011	
		Mean number of days	**Patients with ≥1 visit by ward (%)**		
Psychiatric ward admissions	Remission 0-8 weeks	**0.00**	0.0%	PERFORM	
	No response 0-8 weeks	**0.00**	0.0%	PERFORM	
	Response 0-8 weeks	**0.00**	0.0%	Assumed equivalent to remission	*0.00*
	Remission 8-12 weeks	*0.00*	0.0%	Calculation; assumption	
	Response 8-12 weeks	**0.00**	0.0%	Assumed equivalent to remission	
	No response 8-12 weeks	**0.00**	0.0%	Calculation; assumption	
	Remission after 12 weeks	**0.22**	5.2%	Byford 2011	
	Response after 12 weeks	**0.22**	5.2%	Assumed equivalent to remission	0.29
	Relapse after 12 weeks	**0.23**	5.7%	Byford 2011	
General ward admissions	Remission 0-8 weeks	**0.00**	0.0%	PERFORM	
	No response 0-8 weeks	**0.00**	0.0%	PERFORM	
	Response 0-8 weeks	**0.00**	0.0%	Assumed equivalent to remission	*0.00*
	Remission 8-12 weeks	*0.00*	0.0%	Calculation; assumption	
	Response 8-12 weeks	**0.00**	0.0%	Assumed equivalent to remission	*0.00*
	No response 8-12 weeks	**0.00**	0.0%	Calculation; assumption	
	Remission after 12weeks	**0.00**	0.0%	Assumed equivalent to acute phase	
	Response after 12 weeks	**0.00**	0.0%	Assumed equivalent to remission	0.00
	Relapse after 12 weeks	**1.00**	0.5%	Assumed equivalent to acute phase	
Accident & Emergency visits	Remission 0-8 weeks	**0.00**	0.0%	PERFORM	
	No response 0-8 weeks	**0.00**	0.0%	PERFORM	

	Response 0-8 weeks	**0.00**	0.0%	Assumed equivalent to remission	*0.00*
	Remission 8-12 weeks	*0.00*	0.0%	Calculation; assumption	
	Response 8-12 weeks	**0.00**	0.0%	Assumed equivalent to remission	*0.00*
	No response 8-12 weeks	**0.00**	0.0%	Calculation; assumption	
	Remission after 12 weeks	**0.22**	3.1%	Byford 2011	
	Response after 12 weeks	**0.22**	3.1%	Assumed equivalent to remission	0.29
	Relapse after 12 weeks	**0.25**	3.3%	Byford 2011	

6.9. Appendix 9: cost-effectiveness acceptability curves

6.9.1. Switch network

Figure 31: Cost-effectiveness acceptability curve: switch network - vortioxetine vs. sertraline

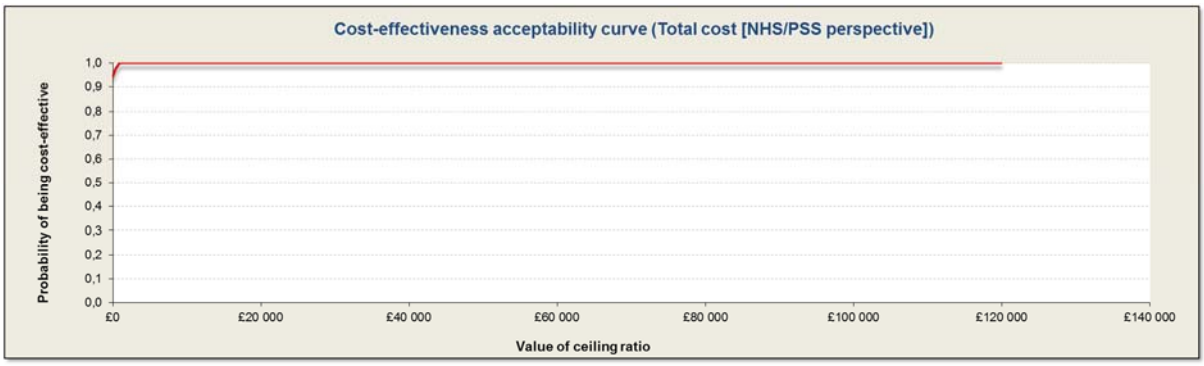


Figure 32: Cost-effectiveness acceptability curve: switch network - vortioxetine vs. venlafaxine

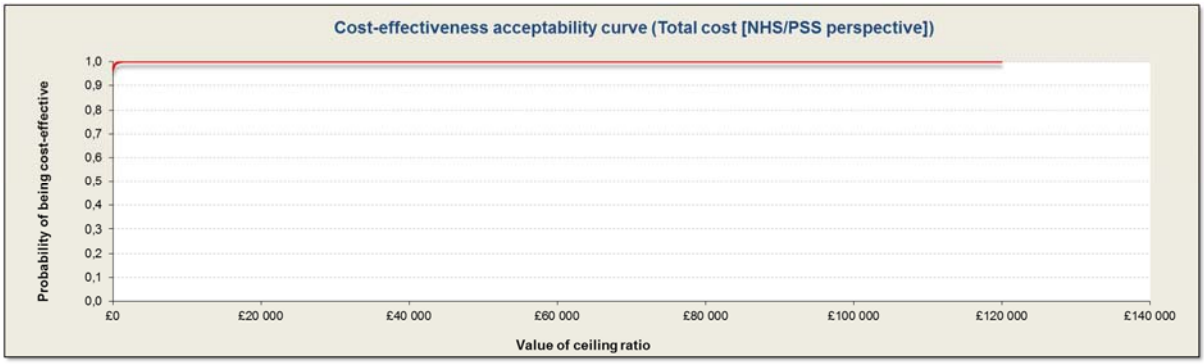
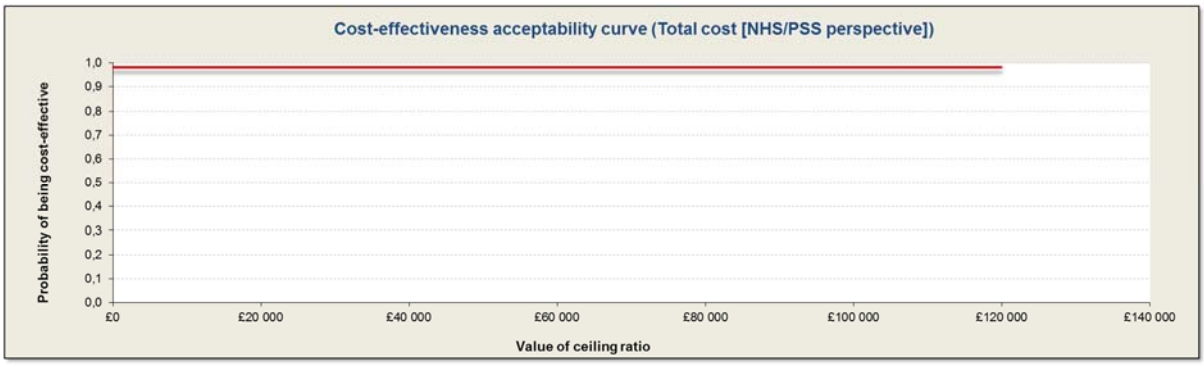


Figure 33: Cost-effectiveness acceptability curve: switch network - vortioxetine vs. agomelatine



6.9.2. Llorca (2014)

Figure 34: Cost-effectiveness acceptability curve: Llorca - vortioxetine vs. escitalopram

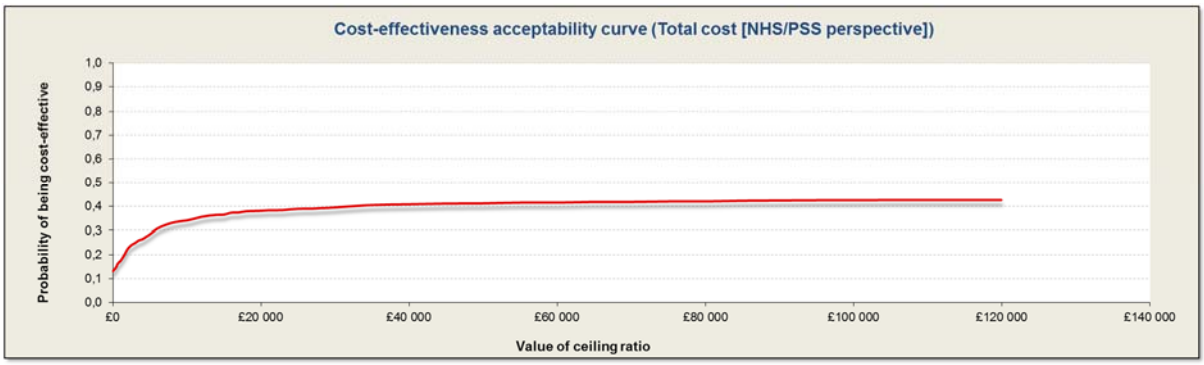


Figure 35: Cost-effectiveness acceptability curve: Llorca - vortioxetine vs. venlafaxine

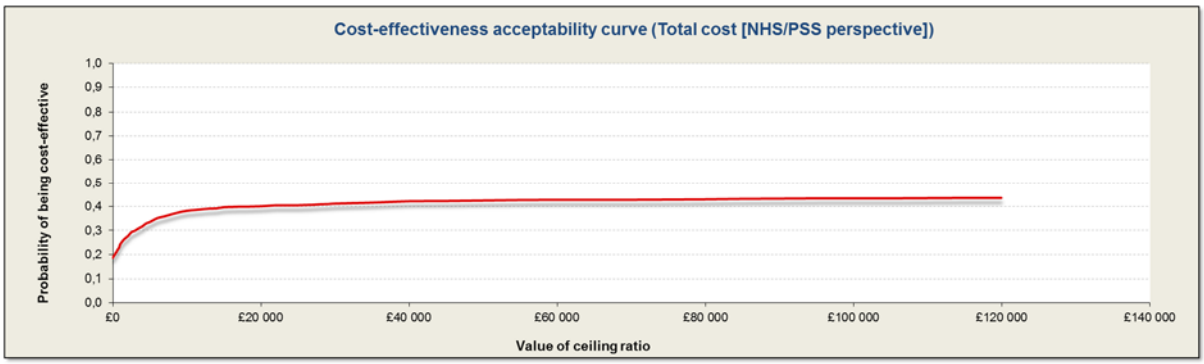


Figure 36: Cost-effectiveness acceptability curve: Llorca - vortioxetine vs. duloxetine

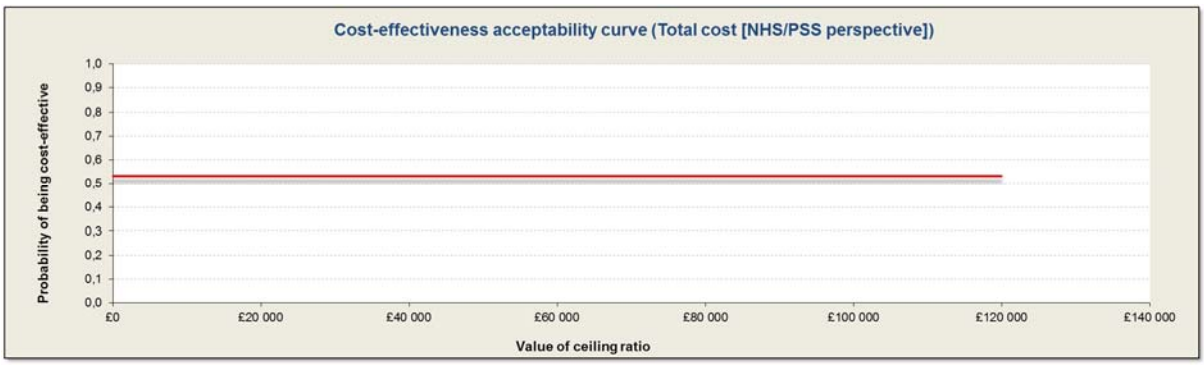
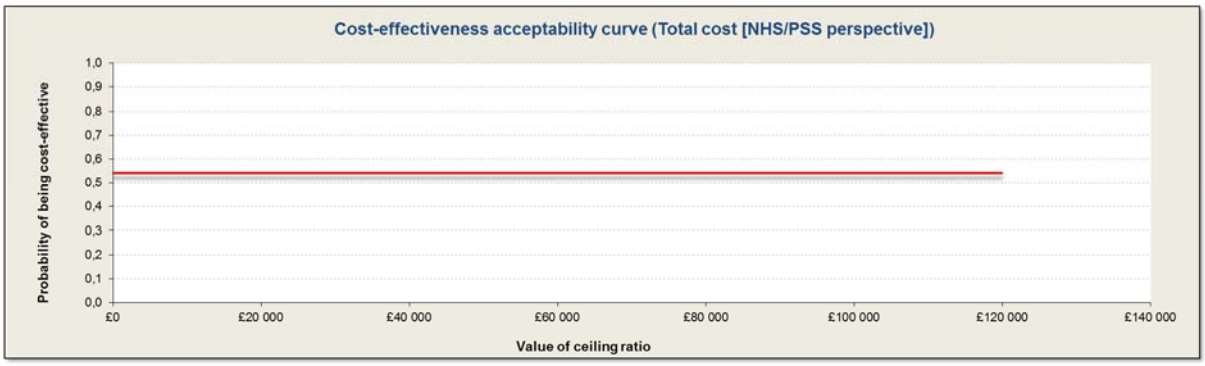


Figure 37: Cost-effectiveness acceptability curve: Llorca - vortioxetine vs. agomelatine



6.9.3. Pae (2014)

Figure 38: Cost-effectiveness acceptability curve: Pae- vortioxetine vs. duloxetine

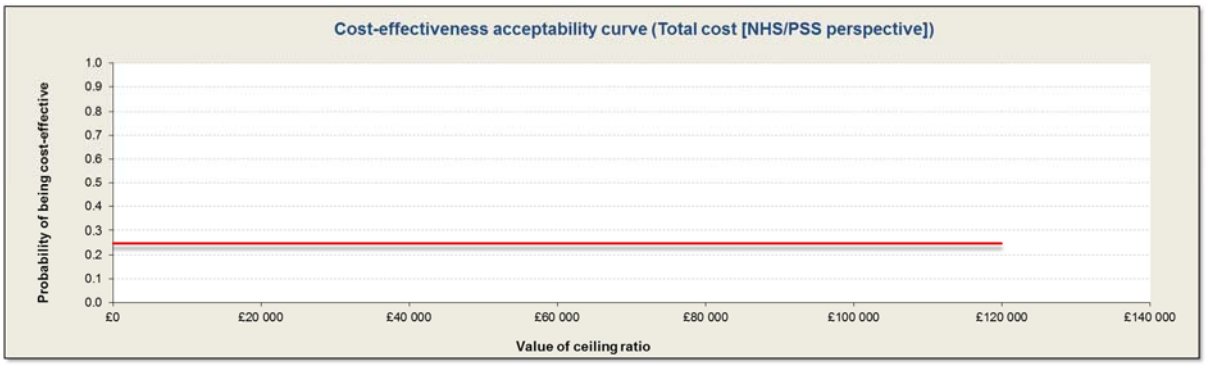


Figure 39: Cost-effectiveness acceptability curve: Pae - vortioxetine vs. venlafaxine

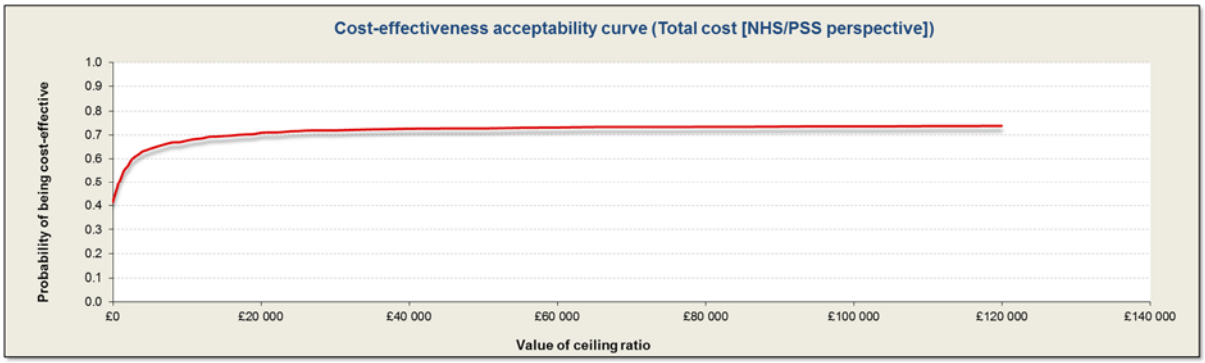
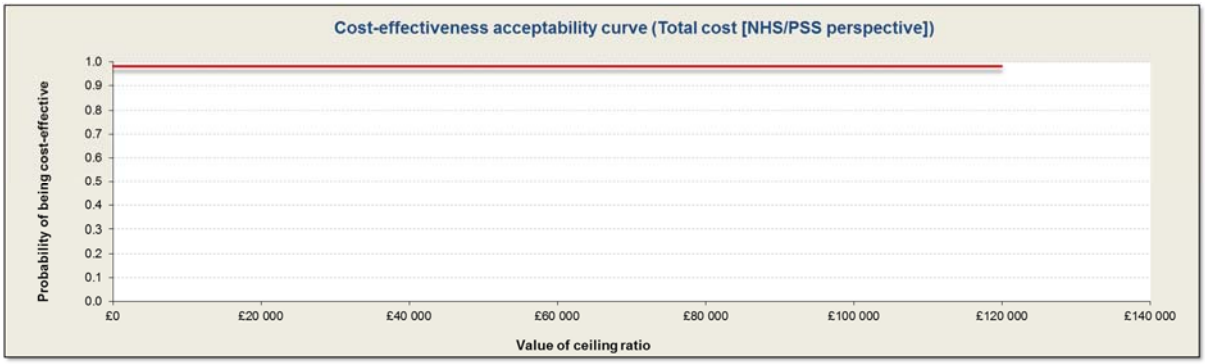
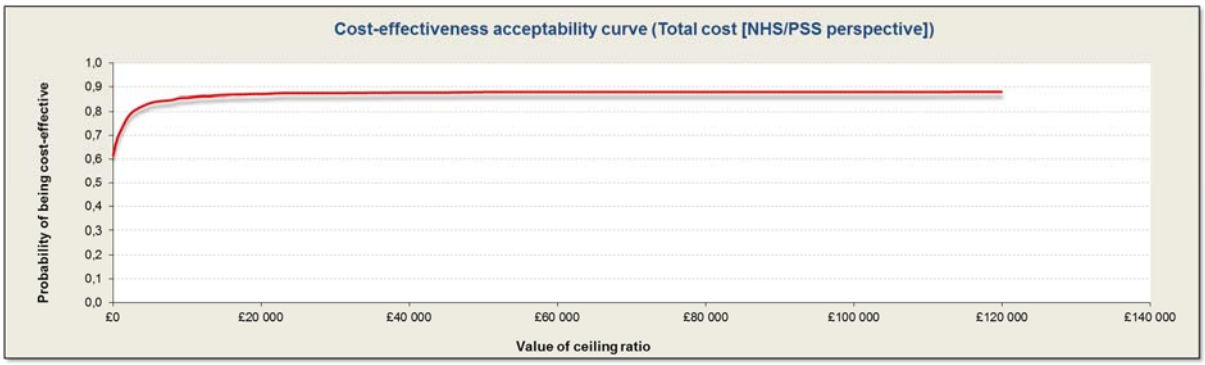


Figure 40: Cost-effectiveness acceptability curve: Pae - vortioxetine vs. agomelatine



6.9.4. SOLUTION (Wang 2015)

Figure 41: Cost-effectiveness acceptability curve: SOLUTION- vortioxetine vs. venlafaxine



6.9.5. Par/equivalent efficacy assumption

Figure 42: Cost-effectiveness acceptability curve: Par/equivalent efficacy- vortioxetine vs. citalopram

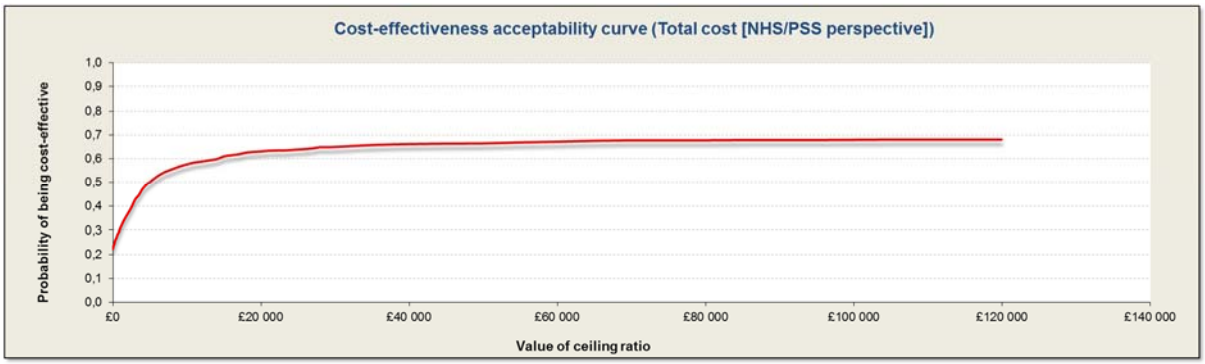


Figure 43: Cost-effectiveness acceptability curve: Par/equivalent efficacy- vortioxetine vs. escitalopram

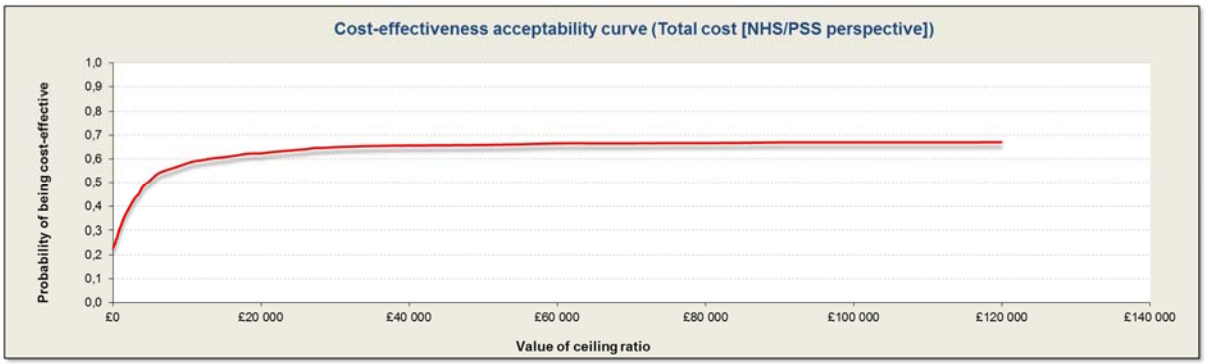


Figure 44: Cost-effectiveness acceptability curve: Par/equivalent efficacy- vortioxetine vs. sertraline

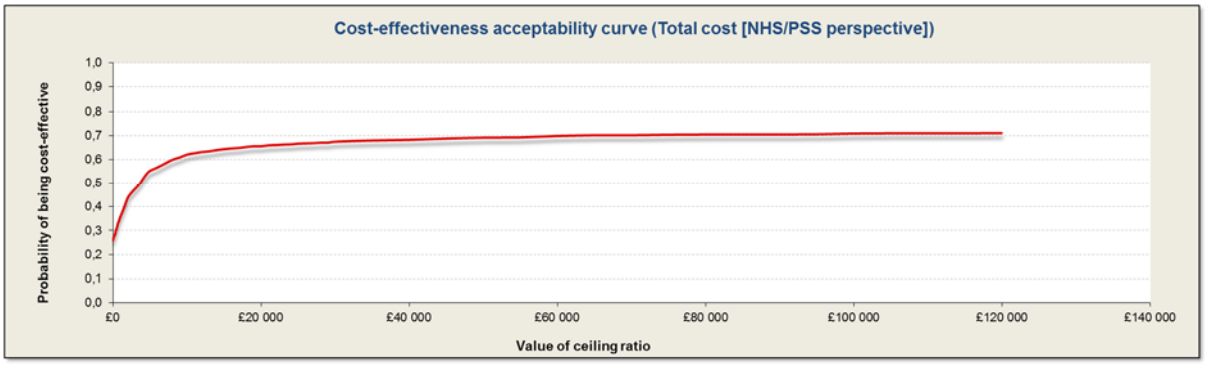


Figure 45: Cost-effectiveness acceptability curve: Par/equivalent efficacy- vortioxetine vs. venlafaxine

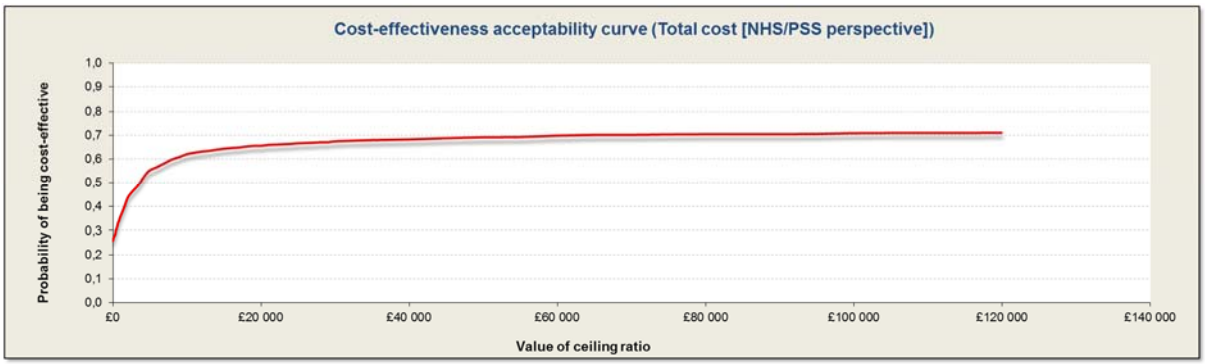


Figure 46: Cost-effectiveness acceptability curve: Par/equivalent efficacy- vortioxetine vs. duloxetine

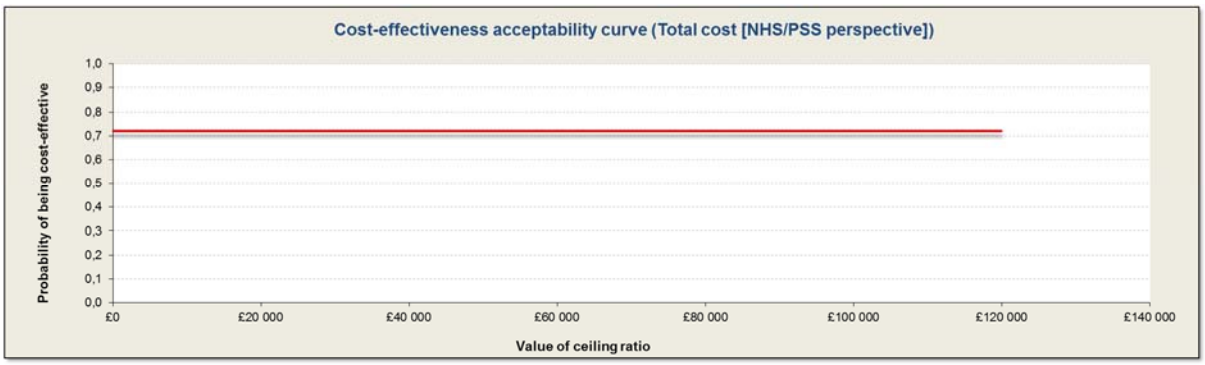
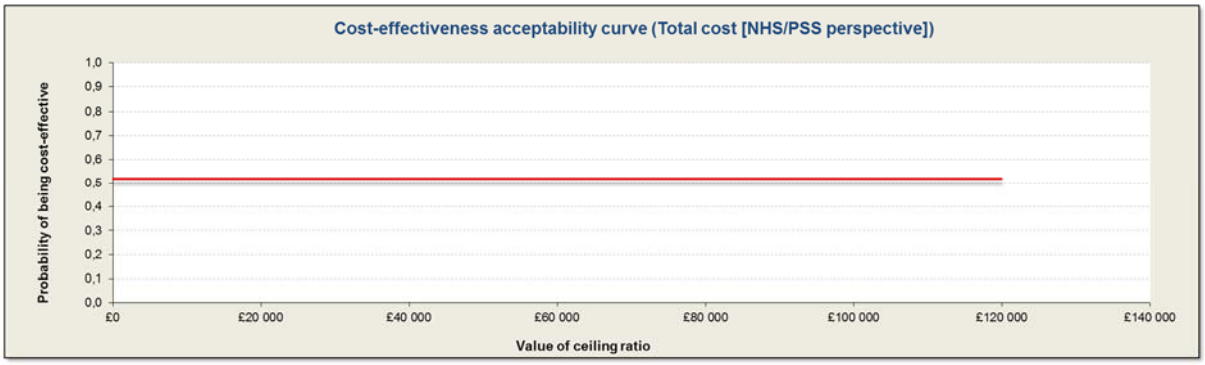


Figure 47: Cost-effectiveness acceptability curve: Par/equivalent efficacy- vortioxetine vs. agomelatine



6.10. Appendix 10: Results – remission only model

Table 36: Remission only model: Analysis set 4a: Up to 6 months maintenance & risk of recurrence in recovery – primary care

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Escitalopram	£989.32	1.447	£10,804.68	Ref	Ref	Ref	NA
Citalopram	£992.63	1.446	£4,678.59	£3.31	-0.001	Dominated	NA
Venlafaxine	£1,019.26	1.444	£4,678.59	£26.63	-0.002	Dominated	Ref
Vortioxetine	£1,054.45	1.452	NA	£35.19	0.008	£10,804.68	£4,678.59
Duloxetine	£1,089.97	1.446	Dominant	£35.52	-0.006	Dominated	Dominated
Sertraline	£1,090.54	1.445	Dominant	£0.57	-0.001	Dominated	Dominated
Agomelatine	£1,110.84	1.452	£467,272.00	£20.30	0.007	£467,272.00	£467,272.00
SOLUTION							
Venlafaxine	£1,010.69	1.446	£7,251.29	Ref	Ref	Ref	Ref
Vortioxetine	£1,054.77	1.452	NA	£44	0.006	£7,251.29	£7,251.29
SWITCH							
Citalopram	£985.38	1.448	£21,721.81	Ref	Ref	Ref	NA
Venlafaxine	£1,035.89	1.436	£1,221.33	£50.51	-0.012	Dominated	Ref
Vortioxetine	£1,054.45	1.452	NA	£18.56	0.015	£21,721.81	£1,221.33
Duloxetine	£1,089.17	1.447	Dominant	£34.72	-0.005	Dominated	Dominated
Agomelatine	£1,123.06	1.438	Dominant	£33.89	-0.009	Dominated	Dominated
LLORCA							
Escitalopram	£984.60	1.449	Dominated	Ref	Ref	Ref	NA
Venlafaxine	£992.06	1.457	-£11,663.69	£7.46	0.008	£916.94	Ref
Vortioxetine	£1,054.49	1.452	NA	£62.43	-0.005	Dominated	Dominated
Duloxetine	£1,085.50	1.450	Dominant	£31.01	-0.001	Dominated	Dominated
Agomelatine	£1,116.67	1.446	Dominant	£31.17	-0.004	Dominated	Dominated
PAE							
Venlafaxine	£1,013.41	1.447	£8,579.38	Ref	Ref	Ref	Ref
Vortioxetine	£1,054.45	1.452	NA	£41.04	0.005	£8,579.38	£8,579.38
Duloxetine	£1,076.10	1.459	£2,894.07	£21.65	0.007	£2,894.07	£2,894.07
Agomelatine	£1,125.98	1.435	Dominant	£49.87	-0.024	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

Table 37: Remission only model: Analysis set 4b: Up to 6 months maintenance & risk of recurrence in recovery – secondary care

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Escitalopram	£2,218.76	1.447	£7,773.40	Ref	Ref	Ref	NA
Citalopram	£2,228.91	1.446	£3,206.00	£10.15	-0.001	Dominated	NA
Venlafaxine	£2,249.28	1.444	£3,206.00	£20.37	-0.002	Dominated	Ref
Vortioxetine	£2,273.39	1.452	NA	£24.11	0.008	£7,773.40	£7,773.40
Duloxetine	£2,319.99	1.446	Dominant	£46.60	-0.006	Dominated	Dominated
Sertraline	£2,326.40	1.445	Dominant	£6.40	-0.001	Dominant	NA
Agomelatine	£2,331.79	1.452	£483,971.37	£5.40	0.007	£483,971.37	£483,971.37
SOLUTION							
Venlafaxine	£2,242.51	1.446	£5,210.87	Ref	Ref	Ref	Ref
Vortioxetine	£2,274.19	1.452	NA	£31.68	0.006	£5,210.87	£5,210.87
SWITCH							
Citalopram	£2,206.65	1.448	£20,983.76	Ref	Ref	Ref	NA
Vortioxetine	£2,273.37	1.452	NA	£66.72	0.003	£20,983.76	Ref
Venlafaxine	£2,287.37	1.436	Dominant	£14.00	-0.015	Dominated	Dominated
Duloxetine	£2,310.88	1.447	Dominant	£23.51	0.011	Dominated	Dominated
Agomelatine	£2,373.72	1.438	Dominant	£62.83	-0.009	Dominated	Dominated
LLORCA							
Venlafaxine	£2,192.90	1.457	Dominated	Ref	Ref	Ref	Ref
Escitalopram	£2,205.08	1.449	£24,692.86	£12.19	-0.008	Dominated	NA
Vortioxetine	£2,273.81	1.452	NA	£68.73	0.003	Dominated	Dominated
Duloxetine	£2,300.94	1.450	Dominant	£27.13	-0.001	Dominated	Dominated
Agomelatine	£2,347.51	1.446	Dominant	£46.57	-0.004	Dominated	Dominated
PAE							
Venlafaxine	£2,236.76	1.447	£7,653.60	Ref	Ref	Ref	Ref
Duloxetine	£2,270.83	1.459	Dominated	£34.07	0.012	£2,778.20	£2,778.20
Vortioxetine	£2,273.37	1.452	NA	£2.54	-0.007	Dominated	Dominated
Agomelatine	£2,383.71	1.435	Dominant	£110.34	-0.017	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

Table 38: Analysis Set 5a. Remission only model (up to 22 months maintenance): primary care initiation and maintenance

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Escitalopram	£1,854.70	1.421	£19,658.31	Ref	Ref	Ref	NA
Citalopram	£1,856.27	1.420	£25,339.39	£1.56	-0.001	Dominated	NA
Venlafaxine	£1,905.77	1.418	£10,039.91	£51.07	-0.003	Dominated	Dominated
Vortioxetine	£1,989.91	1.427	NA	£135.20	0.005	£19,658.31	£19,658.31
Sertraline	£2,068.89	1.419	Dominant	£78.99	-0.008	Dominated	NA
Duloxetine	£2,069.84	1.420	Dominant	£0.95	0.001	Dominated	Dominated
Agomelatine	£2,125.00	1.427	£1,566,398.15	£55.16	0.007	£1,566,398.15	£1,566,398.15
SOLUTION							
Venlafaxine	£1,897.35	1.420	£13,150.23	Ref	Ref	Ref	Ref
Vortioxetine	£1,990.12	1.427	NA	£92.77	0.007	£13,150.23	£13,150.23
SWITCH							
Citalopram	£1,852.50	1.423	£38,214.12	Ref	Ref	Ref	NA
Venlafaxine	£1,919.57	1.410	£4,091.83	£67.07	-0.014	Dominated	Ref
Vortioxetine	£1,989.91	1.427	NA	£70.34	0.017	£38,214.12	£4,091.83
Duloxetine	£2,070.81	1.422	Dominant	£80.90	-0.005	Dominated	Dominated
Agomelatine	£2,091.52	1.411	Dominant	£20.72	-0.010	Dominated	Dominated
LLORCA							
Escitalopram	£1,851.63	1.424	£44,055.07	Ref	Ref	Ref	Ref
Venlafaxine	£1,881.35	1.433	Dominated	£29.72	0.009	£3,196.04	NA
Vortioxetine	£1,989.86	1.427	NA	£108.51	-0.006	Dominated	Dominated
Duloxetine	£2,076.43	1.425	Dominant	£86.57	-0.001	Dominated	Dominated
Agomelatine	£2,111.05	1.421	Dominant	£34.62	-0.005	Dominated	Dominated
PAE							
Venlafaxine	£1,902.11	1.420	£12,772.47	Ref	Ref	Ref	Ref
Vortioxetine	£1,989.91	1.427	NA	£87.80	0.007	£12,772.47	£12,772.47
Agomelatine	£2,083.55	1.408	Dominant	£93.64	-0.019	Dominated	Dominated
Duloxetine	£2,090.65	1.435	£11,819.61	£7.11	0.028	£11,819.61	£11,819.61

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

Table 39: Analysis Set 5b. Remission only model (up to 22 months maintenance): Secondary care initiation and maintenance

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Escitalopram	£4,201.79	1.421	£19,488.13	Ref	Ref	Ref	NA
Citalopram	£4,208.66	1.420	£26,118.01	£6.87	-0.001	Dominated	NA
Venlafaxine	£4,251.04	1.418	£10,752.11	£42.38	-0.002	Dominated	Ref
Vortioxetine	£4,341.14	1.427	NA	£90.11	0.008	£19,488.13	£10,752.11
Sertraline	£4,418.72	1.419	Dominant	£73.97	-0.007	Dominated	Dominated
Duloxetine	£4,415.11	1.420	Dominant	£3.61	-0.001	Dominated	NA
Agomelatine	£4,479.78	1.427	£1,607,480.31	£61.06	0.008	£1,607,480.31	£1,607,480.31
SOLUTION							
Venlafaxine	£4,243.88	1.420	£13,867.82	Ref	Ref	Ref	Ref
Vortioxetine	£4,341.71	1.427	NA	£97.83	0.007	£13,867.82	£13,867.82
SWITCH							
Citalopram	£4,193.59	1.423	£41,033.67	Ref	Ref	Ref	NA
Venlafaxine	£4,280.38	1.410	£3,534.07	£86.79	-0.014	Dominated	Ref
Vortioxetine	£4,341.13	1.427	NA	£60.75	0.017	£41,033.67	£3,534.07
Duloxetine	£4,409.98	1.422	Dominant	£68.85	-0.005	Dominated	Dominated
Agomelatine	£4,462.17	1.411	Dominant	£52.20	-0.010	Dominated	Dominated
LLORCA							
Escitalopram	£4,192.17	1.424	£47,555.77	Ref	Ref	Ref	Ref
Venlafaxine	£4,205.63	1.433	Dominated	£13.46	0.009	£1,447.82	NA
Vortioxetine	£4,341.38	1.427	NA	£135.75	-0.006	Dominated	Dominated
Duloxetine	£4,411.11	1.425	Dominant	£69.73	-0.001	Dominated	Dominated
Agomelatine	£4,470.42	1.421	Dominant	£59.31	-0.005	Dominated	Dominated
PAE							
Venlafaxine	£4,248.07	1.420	£13,537.75	Ref	Ref	Ref	Ref
Vortioxetine	£4,341.13	1.427	NA	£93.06	0.007	£13,537.75	£13,537.75
Duloxetine	£4,410.43	1.435	£8,129.88	£69.30	0.009	£8,129.88	£8,129.88
Agomelatine	£4,457.98	1.408	Dominant	£47.56	-0.028	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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..

Table 40: Analysis Set 6a. Remission only model (up to 6 months maintenance & no risk of recurrence in recovery): primary care initiation and maintenance

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Escitalopram	£1,734.87	1.421	£2,020.37	Ref	Ref	Ref	NA
Citalopram	£1,736.71	1.420	£1,315.07	£1.84	-0.001	Dominated	NA
Vortioxetine	£1,745.65	1.427	NA	£8.94	0.007	£2,020.37	Ref
Venlafaxine	£1,765.66	1.418	Dominant	£20.01	-0.008	Dominated	Dominated
Sertraline	£1,835.69	1.419	Dominant	£70.03	0.000	Dominated	Dominated
Duloxetine	£1,836.37	1.420	Dominant	£0.68	0.001	Dominated	Dominated
Agomelatine	£1,852.11	1.427	£1,234,426.82 *	£15.74	0.007	£1,234,426.82	£1,234,426.82
SOLUTION							
Vortioxetine	£1,739.71	1.427	NA	Ref	Ref	Ref	Ref
Venlafaxine	£1,764.82	1.420	Dominant	£25.11	-0.007	Dominated	Dominated
SWITCH							
Citalopram	£1,732.66	1.423	£3,684.99	Ref	Ref	Ref	NA
Vortioxetine	£1,745.91	1.427	NA	£13.25	0.004	£3,684.99	Ref
Venlafaxine	£1,804.04	1.410	Dominant	£58.13	-0.017	Dominated	Dominated
Duloxetine	£1,837.34	1.422	Dominant	£33.30	0.012	Dominated	Dominated
Agomelatine	£1,911.51	1.411	Dominant	£74.17	-0.010	Dominated	Dominated
LLORCA							
Venlafaxine	£1,693.33	1.433	Dominated	Ref	Ref	Ref	Ref
Escitalopram	£1,730.80	1.424	£3,145.70	£37.47	-0.009	Dominated	NA
Vortioxetine	£1,740.67	1.427	NA	£9.87	0.003	Dominated	Dominated
Duloxetine	£1,820.68	1.425	Dominant	£80.01	-0.001	Dominated	Dominated
Agomelatine	£1,879.86	1.421	Dominant	£59.18	-0.005	Dominated	Dominated
PAE							
Vortioxetine	£1,745.91	1.427	NA	Ref	Ref	Ref	Ref
Venlafaxine	£1,750.71	1.422	Dominant	£4.80	-0.005	Dominated	Dominated
Duloxetine	£1,781.08	1.435	£4,125.82*	£30.37	0.014	£4,125.82	£4,125.82
Agomelatine	£1,925.65	1.408	Dominant	£144.57	-0.028	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

Table 41: Remission only model: Analysis set 6b: Maintenance treatment up to 6 months, no risk of recurrence in recovery – secondary care treatment setting

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Vortioxetine	£3,823.47	1.427	NA	Ref	Ref	Ref	Ref
Escitalopram	£3,890.69	1.421	Dominant	£67.22	-0.005	Dominated	NA
Citalopram	£3,897.56	1.420	Dominant	£6.87	-0.007	Dominated	NA
Venlafaxine	£3,923.12	1.418	Dominant	£25.56	-0.008	Dominated	Dominated
Duloxetine	£3,993.83	1.420	Dominant	£70.71	-0.007	Dominated	Dominated
Agomelatine	£3,994.16	1.427	£1,979,187.62	£0.33	0.000	£1,979,187.62	£1,979,187.62
Sertraline	£3,997.44	1.419	Dominant	£3.28	-0.008	Dominated	NA
SOLUTION							
Vortioxetine	£3,810.23	1.427	NA	Ref	Ref	Ref	Ref
Venlafaxine	£3,933.69	1.420	Dominant	£123.46	-0.007	Dominated	Dominated
SWITCH							
Vortioxetine	£3,824.04	1.427	NA	Ref	Ref	Ref	Ref
Escitalopram	£3,882.49	1.423	Dominant	£58.45	-0.004	Dominated	NA
Duloxetine	£3,988.70	1.422	Dominant	£106.21	-0.001	Dominated	Dominated
Venlafaxine	£4,009.98	1.410	Dominant	£21.28	-0.012	Dominated	Dominated
Agomelatine	£4,141.82	1.411	Dominant	£131.84	0.002	Dominated	Dominated
LLORCA							
Venlafaxine	£3,765.58	1.433	Dominated	Ref	Ref	Ref	Ref
Vortioxetine	£3,812.62	1.427	NA	£47.04	-0.006	Dominated	Dominated
Escitalopram	£3,878.50	1.424	Dominant	£65.88	-0.003	Dominated	NA
Duloxetine	£3,949.64	1.425	Dominant	£71.14	0.002	Dominated	Dominated
Agomelatine	£4,059.00	1.421	Dominant	£109.36	-0.005	Dominated	Dominated
PAE							
Vortioxetine	£3,824.04	1.427	NA	Ref	Ref	Ref	Ref
Duloxetine	£3,851.82	1.435	£3,259.20	-£27.78	-0.009	£3,259.20	£3,259.20
Venlafaxine	£3,890.21	1.422	Dominant	-£66.17	0.005	Dominated	Dominated
Agomelatine	£4,177.00	1.408	Dominant	-£352.96	0.019	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

6.11. Appendix 11: Response and remission model: Analysis Set 3a, 3b and 3c – 6 months maintenance & no recurrence in recovery phase

Table 42: Response and Remission Model Analysis 3a (6 months, no recurrence in the recovery phase): primary care initiation and maintenance

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Citalopram	£1,351.30	1.418	£4,440.10	Ref	Ref	Ref	NA
Escitalopram	£1,356.70	1.417	£3,821.75	£5.40	-0.001	Dominated	NA
Sertraline	£1,366.85	1.415	£2,642.80	£10.14	-0.002	Dominated	NA
Vortioxetine	£1,407.32	1.430	NA	£40.48	0.015	£4,440.10	Ref
Venlafaxine	£1,409.03	1.413	Dominant	£1.71	-0.018	Dominated	Dominated
Duloxetine	£1,558.29	1.414	Dominant	£149.25	0.002	Dominated	Dominated
Agomelatine	£1,576.38	1.431	£232,795.35	£18.09	0.017	£232,795.35	£232,795.35
SOLUTION							
Vortioxetine	£1,401.01	1.430	NA	Ref	Ref	Ref	Ref
Venlafaxine	£1,466.52	1.399	Dominant	£65.51	-0.032	Dominated	Dominated
SWITCH							
Vortioxetine	£1,407.59	1.430	NA	Ref	Ref	Ref	Ref
Sertraline	£1,667.24	1.332	Dominant	£259.65	-0.098	Dominated	NA
Venlafaxine	£1,668.02	1.339	Dominant	£0.78	0.006	Dominated	Dominated
Agomelatine	£1,704.45	1.382	Dominant	£36.43	0.044	Dominated	Dominated
LLORCA							
Escitalopram	£1,306.78	1.434	Dominated	Ref	Ref	Ref	NA
Venlafaxine	£1,338.36	1.435	Dominated	£31.58	0.001	£32,992.84	Ref
Vortioxetine	£1,402.26	1.430	NA	£63.90	-0.005	Dominated	Dominated
Duloxetine	£1,534.53	1.427	Dominant	£132.27	-0.003	Dominated	Dominated
Agomelatine	£1,591.30	1.427	Dominant	£56.77	0.000	Dominated	Dominated
PAE							
Vortioxetine	£1,407.32	1.430	NA	Ref	Ref	Ref	Ref
Venlafaxine	£1,413.47	1.413	Dominant	£6.15	-0.017	Dominated	Dominated
Duloxetine	£1,475.17	1.449	£3,672.12	£61.70	0.035	£3,672.12	£3,672.12
Agomelatine	£1,710.60	1.380	Dominant	£235.43	-0.069	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.

Table 43: Response and Remission Model Analysis 3b (6 months, no recurrence in the recovery phase): secondary care initiation and maintenance

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Vortioxetine	£3,031.81	1.430	NA	Ref	Ref	Ref	Ref
Citalopram	£3,073.33	1.418	Dominant	£41.51	-0.013	Dominated	NA
Escitalopram	£3,078.73	1.417	Dominant	£5.40	-0.001	Dominated	NA
Sertraline	£3,088.23	1.415	Dominant	£9.50	-0.002	Dominated	NA
Venlafaxine	£3,135.33	1.413	Dominant	£47.10	-0.002	Dominated	Dominated
Agomelatine	£3,262.57	1.431	£317,766.44	£127.24	0.018	£317,766.44	£317,766.44
Duloxetine	£3,284.58	1.414	Dominant	£22.01	-0.017	Dominated	Dominated
SOLUTION							
Vortioxetine	£3,018.20	1.430	NA	NA	NA	Ref	Ref
Venlafaxine	£3,253.21	1.399	Dominant	£277.40	-0.032	Dominated	Dominated
SWITCH							
Vortioxetine	£3,031.81	1.430	NA	Ref	Ref	Ref	Ref
Agomelatine	£3,579.82	1.382	Dominant	£610.08	-0.048	Dominated	Dominated
Venlafaxine	£3,688.52	1.339	Dominant	£145.03	-0.044	Dominated	Dominated
Sertraline	£3,715.43	1.332	Dominant	£33.83	-0.006	Dominated	NA
LLORCA							
Escitalopram	£2,968.02	1.434	Dominated	Ref	Ref	Ref	NA
Venlafaxine	£2,979.73	1.435	Dominated	£11.71	0.001	£12,240.94	Ref
Vortioxetine	£3,020.89	1.430	NA	£41.15	-0.005	Dominated	Dominated
Duloxetine	£3,215.17	1.427	Dominant	£194.28	-0.003	Dominated	Dominated
Agomelatine	£3,294.04	1.427	Dominant	£78.87	0.000	Dominated	Dominated
PAE							
Vortioxetine	£3,031.81	1.430	NA	Ref	Ref	Ref	Ref
Duloxetine	£3,070.89	1.449	£2,114.96	£39.08	0.018	£2,114.96	£2,114.96
Venlafaxine	£3,140.66	1.413	Dominant	£69.77	-0.035	Dominated	Dominated
Agomelatine	£3,594.32	1.380	Dominant	£453.66	-0.033	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * 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.

Table 44: Response and Remission Model Analysis 3c (6 months, no recurrence in the recovery phase): primary care initiation and maintenance + 30% increase in resource use for responders

Technologies	Total costs	Total QALYs	Pairwise ICER	Incremental analyses		All txs	w/o SSRI
			ICER Vortioxetine vs. comparator	Incremental costs	Incremental QALYs	ICER incremental (QALYs)	ICER incremental (QALYs)
BASE-CASE: PAR EFFICACY							
Citalopram	£1,360.06	1.418	£4,584.64	Ref	Ref	Ref	NA
Escitalopram	£1,365.46	1.417	£3,959.43	£5.40	-0.001	Dominated	NA
Sertraline	£1,375.59	1.415	£2,762.47	£10.13	-0.002	Dominated	NA
Venlafaxine	£1,417.57	1.413	£18.99	£41.98	-0.002	Dominated	Ref
Vortioxetine	£1,417.90	1.430	NA	£0.33	0.018	£4,584.64	£18.99
Duloxetine	£1,566.82	1.414	Dominant	£148.92	-0.016	Dominated	Dominated
Agomelatine	£1,586.36	1.431	£231,977.08	£19.54	0.017	£231,977.08	£231,977.08
SOLUTION							
Vortioxetine	£1,427.76	1.430	NA	Ref	Ref	Ref	Ref
Venlafaxine	£1,489.11	1.399	Dominant	£61.35	-0.032	Dominated	Dominated
SWITCH							
Vortioxetine	£1,418.17	1.430	NA	Ref	Ref	Ref	Ref
Venlafaxine	£1,655.41	1.339	Dominant	£237.24	-0.098	Dominated	Dominated
Sertraline	£1,656.18	1.332	Dominant	£0.78	0.006	Dominated	NA
Agomelatine	£1,704.57	1.382	Dominant	£36.43	0.044	Dominated	Dominated
LLORCA							
Escitalopram	£1,335.53	1.434	Dominated	Ref	Ref	Ref	NA
Venlafaxine	£1,363.84	1.435	Dominated	£28.31	0.001	£29,581.15	Ref
Vortioxetine	£1,429.00	1.430	NA	£65.17	-0.005	Dominated	Dominated
Duloxetine	£1,561.04	1.427	Dominant	£132.03	-0.003	Dominated	Dominated
Agomelatine	£1,619.40	1.427	Dominant	£58.37	0.000	Dominated	Dominated
PAE							
Vortioxetine	£1,434.07	1.430	NA	Ref	Ref	Ref	Ref
Venlafaxine	£1,437.84	1.413	Dominant	£3.77	-0.017	Dominated	Dominated
Duloxetine	£1,503.26	1.449	£3,744.58	£65.41	0.035	£3,744.58	£3,744.58
Agomelatine	£1,732.29	1.380	Dominant	£229.04	-0.069	Dominated	Dominated

CE, Cost-effective; ICER, Incremental cost-effectiveness ratio; k=threshold Pr, Probability; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; SSRI, Selective serotonin reuptake inhibitor Tx, treatment; w/o, without. * ICERs 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.