Vortioxetine for the treatment of major depressive disorder [ID583]

NICE Single Technology Appraisal

Responses to request for clarification of manufacturer submission

Submitted: 11 March 2015

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A1. Section D, Appendix Table D13: Please provide a rationale for lines 64 to 79 of the search strategy. 7

A2. Section D, Appendix Tables D33 and D34: Please provide an explanation for the term "2501" in line 13 of these strategies. 7

A3. Section D, Appendix Table D14: The typographical error in line 44 will have resulted in some records not been identified. Please check whether correcting the typographical error may have led to relevant records being missed. 7

A4. Patients were enrolled into the REVIVE trial if they received treatment with citalopram, escitalopram, paroxetine, sertraline, duloxetine or venlafaxine monotherapy. Please clarify why patients who received prior treatment with other serotonin reuptake inhibitors [SRIs], such as fluoxetine, were not included. 7

A5. Please clarify whether patients were allowed to receive additional support (such as GP care or counselling) during the course of the study. 7

A6. The REVIVE trial is described as being blinded, yet the dose of agomelatine was fixed at 25 mg per day for the first 2 weeks of treatment, whereas the dose of vortioxetine could be changed at week 1. Please clarify further how blinding was retained given this difference in the dose-modification pattern across treatment arms. 8

A7. Patients were eligible to be enrolled into the REVIVE trial if they were either an inpatient in a psychiatric hospital or an outpatient at a psychiatric setting at the time of the study entry. Please provide the proportion of patients who were inpatients and the proportion who were outpatients at the time they were recruited to the trial. 8

A8. The REVIVE trial included patients who had depressive symptoms considered as non or partially responsive to no more than one adequate course of SRI monotherapy, and who were candidates for a switch in the investigator's opinion and wished to change antidepressant treatment. Please clarify whether there were any specific criteria used to define patients as non-responsive or partially responsive. 8

A9. Please provide details of the recruitment setting for the TAK318 trial (that is, primary care, secondary care). 10

A10. Patients in the TAK318 trial received treatment with citalopram, paroxetine or sertraline. Please clarify why patients who received prior treatment with other selective serotonin reuptake inhibitors [SSRIs], such as fluoxetine, were not included. 10

A11. Figure B14 (page of 98 of the company's submission) presents a plot of changes in MADRS and CGI-I scores in the TAK318 trial. Please provide tabulated data on changes in scores used to produce these figures, with mean differences between arms, standard errors and 95% confidence intervals. Please provide similar data for all depression rating scales measured in the TAK318 trial. 10

A12. **Priority question**: The final scope issued by NICE lists several outcomes that are not presented in the results section (section 6.5 of the company's submission). Where possible, please provide summary tables and/or figures of results for the following outcomes, or clarify where data were not collected: 14

A13. For each depression rating scale used (for example, Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Depression Rating Scale [HAM-D], Clinical

Global Impression - Severity Scale [CGI-S]) please explain what is considered a clinically meaningful change or difference in these scales. 18

A14. **Priority question**: In section 6.1 of the company's submission, it is stated that the relative efficacy of anti-depressants cannot be assumed to be constant between initial and switch usage. Please provide any further supporting evidence for this statement beyond the quoted meta-analysis (Papakostas et al 2008). In particular, please provide any evidence that the relative efficacy of non-selective serotonin reuptake inhibitors (non-SSRIs) will differ between initial and switch usage. 20

A15. **Priority question**: Please provide results from meta-analyses or other forms of evidence syntheses based on all randomised controlled trials comparing vortioxetine with an active comparator and/or placebo in initial-use or mixed initial and switching use. Please provide results on the following outcomes, if available: 23

A16. For the indirect treatment comparison (ITC) analysis, the company assumed that the different definitions of remission across trials (using different depression rating scales) were equivalent and could be pooled in the analysis. Please provide justification for this assumption. 61

A17. **Priority question**: In the company's submission, the results of its ITC analysis were presented in terms of risk differences. Please present results from the ITC analysis in terms of relative risks. 61

A18. **Priority question**: Results for the company's ITC are provided for remission and withdrawal rates because of adverse events only. 64

A19. Please explain why the TAK318 trial was excluded from the ITC analysis. 75

A20. Table B39, last line (page 124 of the company's submission): please clarify how the adjusted indirect comparison estimated rate of withdrawals because of AEs was 18.0% for citalopram, compared with 5.3% in the original publication (Lenox-Smith et al. 2008). 75

A21. Please provide details of the recruitment setting for trials included in the ITC (that is, primary care, secondary care). 76

A22. Table B44 (page 133 of the company's submission), please provide the number and percentage of patients with a severe adverse event, and the number of discontinuations because of an adverse event per dosage (2.5-10.0 mg; 15-20 mg). 78

A23. **Priority question**: The scope of the literature search for adverse event studies was expanded to include 'non-switch populations' (see Section 6.9.1.2 of the company's submission). Given this, please clarify why most vortioxetine trials listed in Table B4, (page 64 of the company's submission), were not included in this review. If available, please provide summary adverse event data, including severe adverse events and discontinuation because of an adverse event, for all trials of vortioxetine and for all comparator treatment arms (including placebo). For example, by providing relative risks or risk differences between treatments, and results from meta-analyses, if these have been performed. 78

B1. It is noted that the recovery period in the company's economic model denotes a period of 4 months where the patient is not at-risk. Please carry out exploratory analyses around the time horizon, and present the cost-effectiveness results for time horizons of 2 and 8 months. 79

B2. According to NICE's guidance on depression in adults (see NICE Clinical Guideline 90), patients at risk of relapse should be treated with anti-depressants for at least 2 years. Please incorporate an additional scenario in the economic model where this is included and present the revised cost-effectiveness results for vortioxetine compared with each of the comparators. 80

B3. **Priority question**: Using results from the REVIVE trial, please provide average baseline and week 8 EQ-5D scores (and associated standard errors) for 'remitters' and 'non-remitters' separately. Please do this separately for those treated with vortioxetine and for those treated with agomelatine, as well as, a combined analysis. Please present the results according to the observed cases [OC], last observation carried forward [LOCF] and mixed model for repeated measures [MMRM] methods (that is, an expanded version of Table B15, page 91 of the company's submission). 82

B4. **Priority question**: Using results from the REVIVE trial, please provide average change in EQ-5D scores from baseline at week 8 (and associated standard errors) for remitters and non-remitters separately. Please do this separately for those treated with vortioxetine and for those treated with agomelatine, as well as, a combined analysis. Please present the results according to the OC, LOCF and MMRM methods..... 84

B5. It is noted that there is a 'switch cost' associated with changing therapy in the company's economic model. Please justify why this is additional to GP/specialist care visits, and whether switching would take place in primary or secondary care. 87

B6. **Priority question**: Please clarify how distributions have been assigned to the model parameter inputs in tables B59 and B60, pages 168 and 171 of the company's submission. Please present the data that underpins them, for example, standard deviation, standard error, number of observations etc. 88

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Section A: Clarification on effectiveness data

Literature searches

A1. Section D, Appendix Table D13: Please provide a rationale for lines 64 to 79 of the search strategy.

The systematic literature review in switch was an adaptation of a review previously undertaken by the 'Agency for Healthcare Research and Quality' (AHRQ), published in April 2012, assessing 'Treatment for Depression After Unsatisfactory Response to SSRIs[1;2]. The only change from AHRQ search was additional search string for monotherapy and deletion of search terms corresponding to adjunctive/combination therapy considering the objective of the Lundbeck review was to focus on antidepressant monotherapies only.

In terms of the rationale for lines 65 to 79 were introduced to remove editorial, notes, and general review from overall search hits (#64), while including meta-analysis, pooled studies, or systematic reviews, along with clinical data.

A2. Section D, Appendix Tables D33 and D34: Please provide an explanation for the term "2501" in line 13 of these strategies.

This is an error in the write-up of the search string. The original search strings have been revisited and the search term was as follows "CEA.mp." rather than "2501" as recorded in Tables D33 and D34 within Section D of the submission.

A3. Section D, Appendix Table D14: The typographical error in line 44 will have resulted in some records not been identified. Please check whether correcting the typographical error may have led to relevant records being missed.

44	"light thearpy" ;ti,ab,kw	0

Correcting the typographical error "light thearpy":ti,ab,kw" to "light therapy":ti,ab,kw" led to the addition of one record. This additional record evaluated combination therapy and hence does not meet the eligibility criteria of the review (monotherapies only). Hence, no relevant records have been missed as a consequence of the typographical error.

REVIVE trial

A4. Patients were enrolled into the REVIVE trial if they received treatment with citalopram, escitalopram, paroxetine, sertraline, duloxetine or venlafaxine monotherapy. Please clarify why patients who received prior treatment with other serotonin reuptake inhibitors [SRIs], such as fluoxetine, were not included.

The REVIVE study design included a screening period of 4–10 days, from which eligible patients were directly switched from their previous treatment to vortioxetine or agomelatine. Fluoxetine, the only other SSRI widely used in the UK (see Figure A10 of the main submission), was not permitted as a previous treatment due to its long half-life, in order to minimise potential carry-over effect, which could have interfered with the study results.

A5. Please clarify whether patients were allowed to receive additional support (such as GP care or counselling) during the course of the study.

Additional support was not allowed in order to avoid interference with the evaluation of the study drugs. Patients were excluded from the study if they were receiving formal cognitive or behavioral therapy or systematic, psychotherapy, or plans to start such therapy during the study (exclusion criterion n°17).

A6. The REVIVE trial is described as being blinded, yet the dose of agomelatine was fixed at 25 mg per day for the first 2 weeks of treatment, whereas the dose of vortioxetine could be changed at week 1. Please clarify further how blinding was retained given this difference in the dose-modification pattern across treatment arms.

All patients in REVIVE were started on the lower dose of either vortioxetine or agomelatine (10mg and 25mg respectively). In REVIVE, at week 1 the investigator had the opportunity to adjust (increase) the dose if initial response was unsatisfactory. As the allocated treatment was blinded, the investigator did not know whether the dose of vortioxetine or agomelatine was actually modified if the dose was adjusted at week 1. The study medication was packed in a way that the investigator chose between high or low dose. At week 1, both high and low dose in the agomelatine arm contained 25mg agomelatine.

A7. Patients were eligible to be enrolled into the REVIVE trial if they were either an inpatient in a psychiatric hospital or an outpatient at a psychiatric setting at the time of the study entry. Please provide the proportion of patients who were inpatients and the proportion who were outpatients at the time they were recruited to the trial.

The overwhelming majority (97.2%) patients recruited to REVIVE were outpatients; only the remaining 2.8% were inpatients at the time of recruitment.

A8. The REVIVE trial included patients who had depressive symptoms considered as non or partially responsive to no more than one adequate course of SRI monotherapy, and who were candidates for a switch in the investigator's opinion and wished to change antidepressant treatment. Please clarify whether there were any specific criteria used to define patients as non-responsive or partially responsive.

In REVIVE, both non-responders and partial-responders to previous SRI treatment were included, because both patient categories are eligible for a switch therapy. Together, these patients are termed "inadequate responders".

The patient population of inadequate responders was ensured by including patients who were considered by the investigators still symptomatic to a clinically significant extent following previous adequate antidepressant treatment and who were candidates for a switch in antidepressant treatment. The patients also had to be willing to change their current treatment due to inadequate response. Both the clinicians' and patients' perspectives of the limited effect of the previous antidepressant were considered, reflecting clinical practice. Inadequate responders were defined as non or partial responders to an adequate course (licensed dose for at least 6 weeks) of an SSRI/SNRI monotherapy, that is patients that fail to achieve an adequate improvement of depressive symptoms (even after a dose increase) were selected for enrolment based on the clinical criteria (investigator's judgment), which also included a cut-off of the MADRS total score ≥22 points and an item 1 score ≥3 points (apparent sadness) to ensure that patients still had a substantial level of depressive symptoms.

In summary, the evaluation of inadequate response to the prior antidepressant followed a process that reflects routine outcome monitoring in real-life practice, taking into account the investigators' assessments of clinically meaningful response and review of treatment compliance.

Lundbeck notes that a possible interpretation of question A8 is whether non- and partial responders were defined as distinct subgroups for analysis; these data were not collected and therefore no such subgroups could be identified.

TAK318 trial

A9. Please provide details of the recruitment setting for the TAK318 trial (that is, primary care, secondary care).

TAK318 was conducted in psychiatry outpatient settings only. All study sites were selected based on their prior experience conducting clinical trials in patients with major depressive disorder (MDD).

A10. Patients in the TAK318 trial received treatment with citalopram, paroxetine or sertraline. Please clarify why patients who received prior treatment with other selective serotonin reuptake inhibitors [SSRIs], such as fluoxetine, were not included.

Patients with a diagnosis of a Major Depressive Episode (MDE) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) receiving SSRI monotherapy (citalopram, paroxetine, or sertraline), for at least 8 weeks prior to the Screening Visit, and who were experiencing sexual dysfunction, were eligible. The study was conducted in US and Canada. An immediate switch from the previous antidepressant causing sexual dysfunction was chosen as it more clearly reflects clinical practice.

Due to this immediate switch and in order to minimise potential interactions, fluoxetine was excluded for the same reasons as described in answer to question A4.

A11. Figure B14 (page of 98 of the company's submission) presents a plot of changes in MADRS and CGI-I scores in the TAK318 trial. Please provide tabulated data on changes in scores used to produce these figures, with mean differences between arms, standard errors and 95% confidence intervals. Please provide similar data for all depression rating scales measured in the TAK318 trial.

Tables 1-3 below provide the tabulated data of change from baseline by study visit for the following symptom scores:

- MADRS total score
- CGI-I
- CGI-S

Table 1. Analysis of change from baseline in MADRS total score by study visit (MMRM) Repeated measures analysis. Full Analysis Set.

Study visit	Escitalopram (n=207)	Vortioxetine (n=217)
Baseline value		
N	203	211
LS mean (SE)	8.5 (0.38)	8.2 (0.37)
P-value, vortioxetine vs. escitalopram		0.574
Change from baseline visit at Week 2		
N	203	211
[redacted]	[redacted]	[redacted]

[redacted]		[redacted]
Change from baseline visit at Week 4		
N	188	187
[redacted]	[redacted]	[redacted]
Change from baseline visit at Week 6		
N	176	175
[redacted]	[redacted]	[redacted]
Change from baseline visit at Week 8		
N	174	165
LS mean (SE)	-1.7 (0.46)	-1.2 (0.47)
P-value, vortioxetine vs. escitalopram		0.520
LS mean differences (SE) from escitalopram		0.4 (0.65)
95% CI for differences		(-0.86, -1.71)

Notes: Baseline value is defined as the last observation prior to the first dose of double-blind medication. Baseline LS means and P-values were from an ANOVA model with terms for treatment and pooled center. Post-baseline LS means and P-values were from an MMRM model with baseline*week, pooled center, week, treatment and week*treatment as factors in the analysis.

Table 2. Analysis of change from baseline in CGI-I score by study visit (MMRM) Repeated measures analysis. Full Analysis Set.

Study visit	Escitalopram (n=207)	Vortioxetine (n=217)
Baseline CGI-S value		
N	207	217
LS mean (SE)	2.1 (0.05)	2.1 (0.05)
P-value, vortioxetine vs. escitalopram		0.938
CGI-I Week 1 Score		
N	206	212
[redacted]	[redacted]	[redacted]
CGI-I Week 2 Score		
N	200	202
[redacted]	[redacted]	[redacted]
CGI-I Week 4 Score		

N	188	187
[redacted]	[redacted]	[redacted]
CGI-I Week 6 Score		
N	176	175
[redacted]	[redacted]	[redacted]
CGI-I Week 8 Score		
N	174	165
LS mean (SE)	3.4 (0.08)	3.2 (0.08)
P-value, vortioxetine vs. escitalopram		0.342
LS mean differences (SE) from escitalopram		-0.1 (0.11)
95% CI for differences		(-0.33, -0.11)

Notes: Baseline value is defined as the last observation prior to the first dose of double-blind medication. Baseline LS means and P-values were from an ANOVA model with terms for treatment and pooled center. Post-baseline LS means and P-values were from an MMRM model with baseline*week, pooled center, week, treatment and week*treatment as factors in the analysis.

Table 3. Analysis of change from baseline in CGI-S score by study visit (MMRM) Repeated measures analysis. Full Analysis Set.

Study visit	Escitalopram (n=207)	Vortioxetine (n=217)
Baseline CGI-S value		
N	207	217
LS mean (SE)	2.1 (0.05)	2.1 (0.05)
P-value, vortioxetine vs. escitalopram		0.938
Change from baseline at Week 1		
N	206	212
[redacted]	[redacted]	[redacted]
Change from baseline at Week 2		
N	200	202
[redacted]	[redacted]	[redacted]
Change from baseline at Week 4		
N	188	187

[redacted]	[redacted]	[redacted]
Change from baseline at Week 6		
N	176	175
[redacted]	[redacted]	[redacted]
Change from baseline at Week 8		
N	174	165
LS mean (SE)	-0.2 (0.06)	-0.2 (0.06)
P-value, vortioxetine vs. escitalopram		0.400
LS mean differences (SE) from escitalopram		-0.1 (0.08)
95% CI for differences		(-0.23, -0.09)

Notes: Baseline value is defined as the last observation prior to the first dose of double-blind medication. Baseline LS means and P-values were from an ANOVA model with terms for treatment and pooled center. Post-baseline LS means and P-values were from an MMRM model with baseline*week, pooled center, week, treatment and week*treatment as factors in the analysis.

Outcomes

A12. ***Priority question****: The final scope issued by NICE lists several outcomes that are not presented in the results section (section 6.5 of the company's submission). Where possible, please provide summary tables and/or figures of results for the following outcomes, or clarify where data were not collected:*

As the population of interest given the decision problem was switch patients data only data which is relevant and applicable to this population has been reported. This either consists of direct evidence collected in the switch population or, based on clinical advice and opinion, from the full MDD population if deemed transferable.

a. relapse (including relapse rate and time from remission to relapse)

There is one relapse prevention study (NCT00596817), as reported in Table B4 of the main submission, which was excluded based on the population (i.e. it did not include a switch population). Therefore no long-term relapse data are available in the population of interest.

As a post hoc analysis in response to NICE's question A12a, relapse data are provided for Study TAK318, the study of treatment-emergent sexual dysfunction in otherwise well-controlled patients. MADRS score was a secondary endpoint in this study, which enabled calculation of relapse rates according to the criterion of a MADRS total score of ≥22. [redacted]

Figure 1 [redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 2 [redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b. sleep quality (in addition to sleep related adverse events)

Sleep quality data (other than those associated with sleep-related AEs e.g. insomnia) were not collected in any of the vortioxetine clinical trials in adults with MDD and hence are not available. Sleep related AE data are reported in the main submission for REVIVE and 318 and also for the short- and long-term MDD pools in response to QA15.

c. cognitive dysfunction

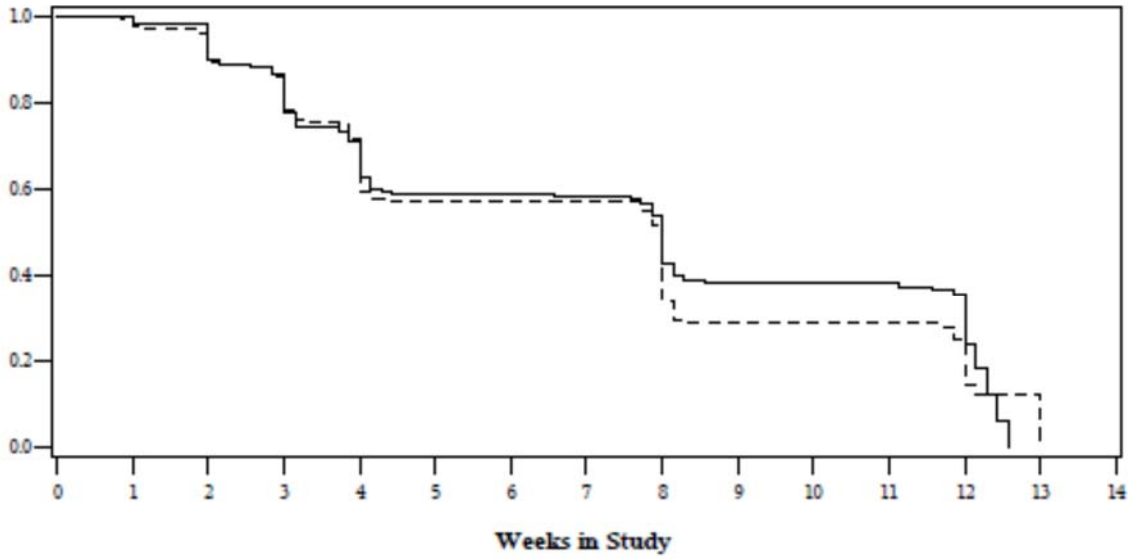
No data are currently available in the population of interest given the decision problem and therefore results have not been presented. As stated in Section 4.1.2 of the submission there is a growing body of evidence supporting the effects of vortioxetine on cognitive dysfunction. As part of this development programme Lundbeck are conducting a study specifically in the switch population (NCT02272517). This study is currently at the participant recruitment stage.

d. time to response

Below is a time-to-event analysis of first response in Study 14178A (REVIVE), in which response is defined as a ≥50% reduction in MADRS score. This is a post hoc analysis conducted only for the purpose of responding to the above specific question: it was not pre-planned or pre-specified in the study protocol or the statistical analysis plan. Rather, response rates were reported at each clinical assessment. By visual inspection of the Kaplan-Meier plot in Figure 3 separation between groups in favour of vortioxetine is apparent from 8 weeks. This finding is in line with the separation in response rates assessed at each

visit. That being said, the values differ slightly from the response rates obtained at each clinical assessment in the protocol-defined OC/LOCF analysis, since there are a few patients who respond at early assessments but do not maintain response until the end of the study. Hence, this time-to-event analysis reports time to *first* response, regardless of whether it is sustained to the end of study.

Figure 3: Study 14178A (REVIVE): Kaplan-Meier plot of time to first 50% response



Treatment	N	No. of events	% events	Cox hazard ratio	P-value
Agomelatine	241	152	63.1	1.22	0.075
Vortioxetine	252	187	74.2	.	.
Total	493	339	68.8	.	.

Treatment —— PBO - - - - VOR

HTA UK ET_R50_178A Date and Time: 06MAR15 12:57

e. adverse effects of treatment discontinuation

Adverse event data specifically associated with treatment discontinuation data are not available in the trials in switch populations (REVIVE, TAK318). However, the question of AEs following treatment discontinuation can be answered by reference to studies in general MDD populations.

On review of the evidence base available, the European Medicines Agency accepted that there was no evidence of clinically relevant discontinuation symptoms that warranted a dose tapering of vortioxetine. Due to the long plasma elimination half-life of 66 hours and the gradual elimination from the central 5-HT transporter, there is a relatively long natural down-taper. At this time, discontinuation symptoms are referred to in the SmPC as not relevant for vortioxetine and subsequently, there seems to be no need for gradual dose reduction of the substance.

In contrast, as stated in Section 4.1.3. of the main submission through a review of all antidepressants, Haddad and Anderson[3] concluded that discontinuation symptoms are associated with 25 of the available antidepressants including those most widely used in the UK (citalopram, sertraline, fluoxetine, mirtazapine, venlafaxine), with common symptoms including dizziness, headache, nausea and lethargy.

A13. For each depression rating scale used (for example, Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Depression Rating Scale [HAM-D], Clinical Global Impression - Severity Scale [CGI-S]) please explain what is considered a clinically meaningful change or difference in these scales.

Table 4 details what is considered a clinically meaningful change in symptom scores for the relevant scales. These clinically relevant differences are however in the context of assessing pharmacological compounds versus placebo. As discussed by Montgomery (2011)[4], this clinically relevant difference versus placebo is not to be generalised for comparisons between two active drugs, and one rule that can be applied for the translation from placebo-control to active-control comparison is 50% of the difference judged as clinically relevant in placebo-controlled studies:

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

The London New Drugs Group (LNDG) has accepted this criterion when assessing evidence to inform local decision-making[5]. This is demonstrated in their discussion of agomelatine and what should be considered a clinically relevant change in HAM-D17 score:

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

Table 4. Clinical relevance of changes in symptom scores on depression rating scales

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

Switching and initial-use trials

A14. ***Priority question****: In section 6.1 of the company's submission, it is stated that the relative efficacy of anti-depressants cannot be assumed to be constant between initial and switch usage. Please provide any further supporting evidence for this statement beyond the quoted meta-analysis (Papakostas et al 2008). In particular, please provide any evidence that the relative efficacy of non-selective serotonin reuptake inhibitors (non-SSRIs) will differ between initial and switch usage.*

To respond to this question, Lundbeck has conducted a basic structured literature review to identify publications which may provide additional information to the evidence identified by UK clinical experts in the submission regarding the difference in relative treatment effects at different treatment lines.

Results

The articles which were identified as relevant to this question are reported in Table 5.

Table 5: Publications of interest identified in the searches

Author (year)	Citation	Summary and evidence
Bauer 2009	The effect of venlafaxine compared with other antidepressants and placebo in the treatment of major depression: A meta-analysis. *European Archives of Psychiatry and Clinical Neuroscience* 259:172–185	Meta-analysis comparing venlafaxine (non-SSRI) with other antidepressants. Data is reported in before switch populations and after switch (TRD) populations. Odds ratios (OR) are a measure of relative efficacy. These data suggest that the relative efficacy of venlafaxine (a non-SSRI) compared with other antidepressants is greater in switch usage than in before switch usage. The differences may not be significant. Outcome Venlafaxine versus — Odds ratio [95% CI]: Trials of Initial treatment / Trials of switch treatment Response SSRIs: 1.15 [1.02–1.29] / - TCAs: 1.22 [0.96–1.54] / - Any AD: - / 1.38 [0.67–3.38] Remission SSRIs: 1.19 [1.06–1.34] / - TCAs: 1.06 [0.74–1.63] / - Any AD: - / 1.36 [0.99–2.10]
Souery 2011	Citalopram versus desipramine in treatment resistant depression: Effect of continuation or switching strategies. A randomized open study. *The World Journal of Biological Psychiatry*. 12: 364–375	Crossover study of citalopram (SSRI) and desipramine* (non-SSRI). No direct analysis of relative efficacy of the interventions before and after crossover is reported, but data in Table III may be able to be used to calculate a demonstrable difference: Response rate differences (calculated) (%): Before switch: Citalopram (cit) 54.12% vs desipramine (des) 55.22% = 1.1% After switch: Cit→des 50.00% vs. des→cit 37.50% = 12.5% Remission rate difference (calculated) (%): Before switch: Citalopram 18.82% vs desipramine 31.34% = 12.52% After switch: Cit→des 40.00% vs des→cit 37.5% = 2.5% The differences may not be significant. The publication focuses on whether, after inadequate response to 4 weeks of treatment, a treatment switch is an effective option. This treatment duration is unlikely to affect conclusions that relative treatment effects may differ but the magnitude of this difference in relative effect may change if an adequate treatment length of roughly 8 weeks is given (in line with NICE guidance). *not licensed in the UK
Keller 1998 and Thase 2002	The treatment of chronic depression, Part 2: A double blind, randomized trial of sertraline and imipramine. *Journal of Clinical Psychiatry* 59:11 598-607. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. *Archives of General Psychiatry.* 59: 233-239	Initial and subsequent crossover trial of sertraline (SSRI) and imipramine (non-SSRI). Calculation of the differences in change from baseline for each intervention (taken from Table 4 of Keller 1998 and Table 3 of Thase 2002) may indicate a small difference in relative efficacy of the two therapy classes in the before switch (Keller 1998) and post-switch (Thase 2002) populations. The differences may not be significant. Difference in mean change from baseline between sertraline and imipramine (calculated): HAM-D Before switch (Keller 1998): 0.1; After switch (Thase 2002): 2.8 MADRS Before switch (Keller 1998): 0.4; After switch (Thase 2002): 2.9

Abbreviations: OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; TRD, treatment resistant depression

Discussion

No studies were identified that aimed to specifically answer the question in the objective of this search. However, three studies were identified that do provide evidence in support of differences in relative treatment effects at different treatment lines.

The Bauer 2009 study[12] was a large meta-analysis, including over ten thousand patients. It compared venlafaxine with other antidepressants in initial vs. switch usage. The particular benefit of this meta-analysis, in addition to being large and comprehensive, is that it compares venlafaxine with four other groups of antidepressants or populations, allowing further comparisons to be made. Odds ratios for remission and treatment response are calculated, allowing comparison of the relative efficacy of venlafaxine (a non-SSRI) in the initial usage populations and the switch usage. The difference between the remission odds ratios for venlafaxine versus other antidepressants before switch (1.06 and 1.19) and after switch (1.36) is quite large, which suggests that the relative efficacy does differ between initial and switch usage, although it is not known whether it is statistically significant. Similar results are seen for the treatment response odds ratios.

Importantly, no studies were identified explicitly showing that the relative efficacy of SSRIs and non-SSRIs does not differ between initial and switch populations. A study by Wohlreich (2005)[13] identified through the search showed that the absolute rate of efficacy of duloxetine did not differ between initial usage and following switch from a SSRI. However, this is not clear evidence of the difference in relative efficacy between SSRIs and non-SSRIs between initial and switch usage as there is no comparison of duloxetine to an SSRI in the first line setting.

In addition, internally the study GSK AK1102365[14;15] was highlighted as providing supportive of this difference in relative treatment effects at different treatment lines. The study results indicate that, when used in switch patients, bupropion is only as effective as placebo. Although not licensed in the UK for the treatment of MDD, this result is not in line with the placebo-controlled data which would have been presented to regulatory agencies internationally to gain approval in countries in which it is now marketed for the treatment of MDD.

The results of the search demonstrate that there is a paucity of data specifically examining the relative efficacy of treatments before and after switching antidepressants. This is unsurprising given the limited totality of evidence currently available for antidepressants in the switch setting as supported by the systematic review in switch, presented in the main dossier; the NICE switch review and the AHRQ review.

However, on reflection of the data reported here, Lundbeck's contention that the relative efficacy of anti-depressants cannot be assumed to be constant between initial and switch usage is supported by the findings of all studies identified, including two large meta-analyses concerning two major antidepressant classes (Papakostas and Bauer). This is a difficult question to research as the few available studies are heterogeneous and potentially confounding factors cannot be eliminated in meta-analysing them. Nevertheless, Lundbeck contends that on the basis of the available evidence it would be inappropriate to assume that the efficacy of vortioxetine relative to comparators in initial use is transferable to the switch setting and this is supported by UK clinical expert opinion.

A15. ***Priority question****: Please provide results from meta-analyses or other forms of evidence syntheses based on all randomised controlled trials comparing vortioxetine with an active comparator and/or placebo in initial-use or mixed initial and switching use. Please provide results on the following outcomes, if available:*

a. Differences in mean change from baseline in depression rating scales (MADRS, HAM-D, CGI-S etc.) between treatments
b. Relative risks or risk differences in response, remission and withdrawal rates
c. Adverse events (AEs):
    i. Number of discontinuation as a result of AEs
    ii. Number and types of severe adverse events

Meta-analyses and evidence syntheses in switch

The population of interest given the decision problem is switch patients. At present the only evidence synthesis undertaken in the switch population is the indirect treatment comparison presented in the submission (Section 6.7). As stated in Section 6.1 of the submission *"the relative efficacy of antidepressants cannot be assumed to be constant between initial and switch usage"* whereas clinical opinion suggests that tolerability is likely to be. Therefore it is appropriate to use only relative efficacy rates from said switch ITC, but relative tolerability can be inferred from the full data packages available for antidepressants.

In spite of this, all evidence syntheses known to Lundbeck regardless of treatment line are presented below. These are as follows:

1. Meta-analyses (Lundbeck)
    a. Efficacy: vortioxetine short-term placebo-controlled pool
2. Pooled analyses (Lundbeck))
    a. Vortioxetine short-term safety and tolerability
    b. Vortioxetine long-term safety
3. Meta-analyses (external) including discussion on methodological inaccuracies
    a. Pae (2014)[16]
    b. Berhan and Barker (2014)[17]
    c. Citrome (2014)[18]
4. Indirect treatment comparisons/meta-regressions
    a. Llorca (2015)[19]
5. Analyses included in reimbursement submissions to authorities

Meta-analyses and pooled analyses of vortioxetine

Vortioxetine vs. placebo: Lundbeck meta-analysis

Data supporting comparisons of vortioxetine vs placebo are available from 14 placebo-controlled studies, of which data from 11 can be pooled for reasons detailed below. The 14 short-term studies (including the dedicated study in the elderly) were all designed in accordance with the guidelines in depression[20;21]. Seven of the 14 short-term, placebo-controlled studies (including the dedicated study in the elderly) included an active reference for evaluation of the internal validity of the studies[20].

Comparative efficacy between vortioxetine and 3 other marketed antidepressants are available from 3 active-comparator studies. Due to the differences in comparators and populations the studies cannot be pooled.

- Study 14178A (REVIVE): comparative evidence of vortioxetine *versus* agomelatine in patients with inadequate response after treatment with an SSRI or SNRI.
- Study 13926A (SOLUTION): comparative evidence of vortioxetine *versus* venlafaxine for the treatment of MDD in Asian patients.
- Study TAK318: comparative evidence of vortioxetine *versus* escitalopram on sexual functioning in patients with well-treated MDD who were experiencing SSRI-induced sexual dysfunction

These active comparator studies should not be confused with studies that include an active reference. Active references cannot be used to provide valid, unbiased comparisons with the study drug; the purpose of their inclusion in studies is to confirm assay sensitivity only. Active references were included in 7 of the 14 placebo-controlled studies: duloxetine was the active reference in 6 studies and venlafaxine in one study. All patients assigned to these active references were known responders. As stated in Section 1.4.1 of the submission, the EPAR noted: *"although no formal comparison was conducted, numerically larger effect sizes were observed for the active reference than for vortioxetine, except in studies 11492A and 11984A. The exclusion of non-responders and the inclusion of previous responders in the active reference arm could have introduced a bias in favour of the efficacy of the active reference, so differences in the efficacy of vortioxetine versus the active reference cannot be inferred on the basis of these studies."* For these reasons, results for the active references in trials (used only for internal control) have not been reported here on an individual study basis, but are available on request. A fuller rationale for the use of active references in trials of antidepressants can be found in Section 2.8.2 of the submission.

Meta-analyses for the evaluation of efficacy of vortioxetine from the short-term placebo-controlled pool

For comparisons across studies, a meta-analysis rather than a pooled analysis was considered the statistical methodology that would provide the most reliable estimates of treatment effect. Since not all doses of vortioxetine were included in all the studies, the comparison to an overall placebo group in a pooled analysis could be misleading. The meta-analyses were stratified geographically by all studies and all non-US studies for reasons explained in the Appendix.

Table 6. Overview of meta-analyses Included in the clinical efficacy data package

Meta-analysis	No. of studies included	Study IDs
All short-term placebo-controlled studies in adults	11	11492A , 11984A, 305, 13267A, 315, 316, 14122A, CCT-002, 303, 304, and 317
Non-US short-term placebo-controlled studies in adults	6	11492A , 11984A, 305, 13267A, 14122A, and CCT-002

Rationale for studies excluded from the meta-analysis:
Study 12541A: dedicated study in the elderly, and was therefore not included in the meta-analysis of short-term placebo-controlled studies in adult patients.
Study 202: the only short-term placebo-controlled study with flexible dosing (10 to 20mg/day)
Study CCT-003: exclusively conducted in Japanese patients

Placebo-controlled studies do not provide a proxy subgroup for switch population

With respect to prior treatment of patients recruited into the short-term, placebo-controlled trials, information was collected on the treatment of the current episode on the concomitant medication form. Medication used up to 3 months prior to screening was recorded, including the name of drug, dose, start and stop date, but no information on whether the patient responded or tolerated the drug. The trials mandated a washout period of at least 14 days prior to screening, which eliminated the possibility of a direct switch as required in the dedicated switch studies.

While it is possible, therefore, to identify patients who had received a previous antidepressant, such patients do not comprise a valid proxy subgroup for a switch population as defined in the decision problem.

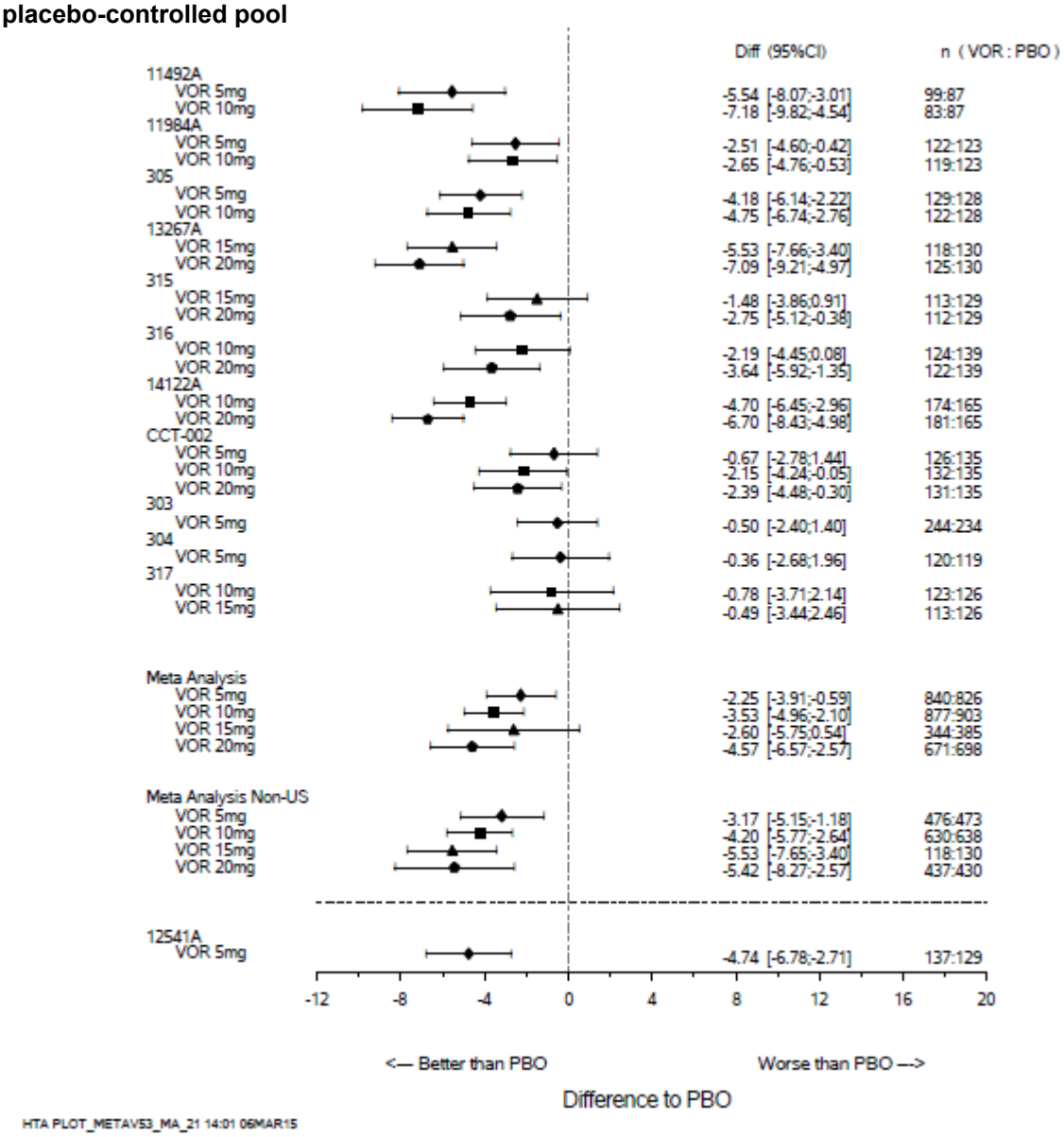
Endpoints: MADRS score change from baseline

The magnitude of the drug-placebo difference (effect size) in the mean change from baseline to endpoint on the pivotal efficacy assessment tool has been used to make a judgement of the clinical relevance of the efficacy. In the short-term, placebo-controlled studies in adults with vortioxetine, the effect sizes on the MADRS increase with increasing dose of vortioxetine (Figure 4).

The meta-analysis of all the short-term, placebo-controlled studies in adults supported the results of the individual studies, with a statistically significant effect size across studies of -2.3 points ($p < 0.007$), -3.6 points ($p < 0.001$), and -4.6 points ($P < 0.001$) at Week 6/8 for the 5mg, 10mg, and 20mg/day doses, respectively. The 15mg/day dose was not statistically significantly different from placebo in the meta-analysis, but the effect size was -2.6 points. Thus, the effect size for each of the therapeutic doses of vortioxetine was greater than the usual 2-point difference from placebo at endpoint that is frequently used in short-term, placebo-controlled studies to establish the clinical relevance of antidepressant efficacy[6;8].

In the meta-analysis of all the short-term, placebo-controlled, non-US studies in adults, the effect sizes and the increased effect with increasing dose were more pronounced. The effect sizes were -3.2, -4.2, -5.5, and -5.4 points at Week 6/8 for the 5mg, 10mg, 15mg, and 20mg/day doses, respectively.

Figure 4. Change from baseline in MADRS total score at week 6/8 (FAS, MMRM) – short-term, placebo-controlled pool

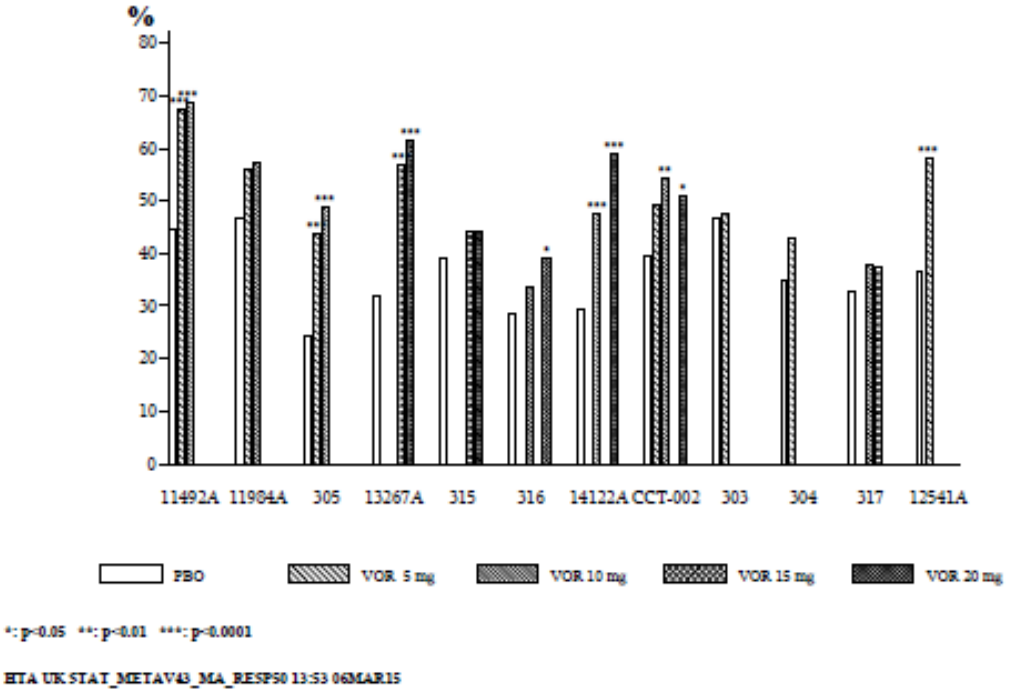


Endpoints: Response, remission and CGI-I score

The clinical relevance of the effect of vortioxetine in MDD was corroborated in the analyses of responders and remitters and in the analysis of the CGI-I score.

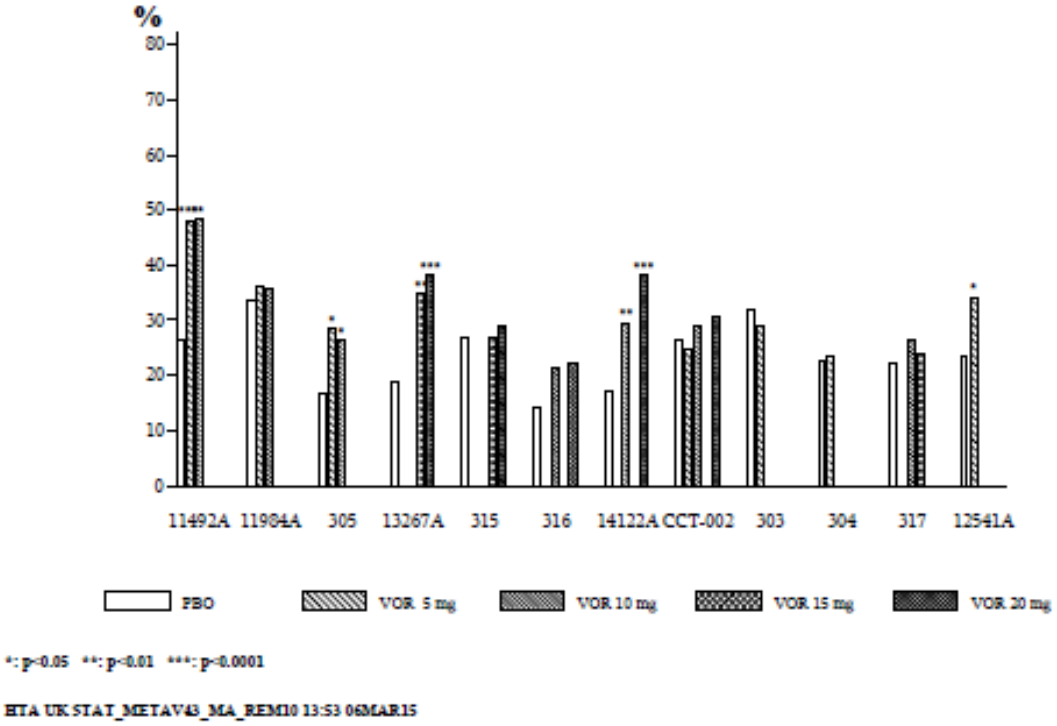
In the responder analysis (Figure 5) vortioxetine separated from placebo (P <0.05) at Week 6/8 in 6 of the 11 short-term, placebo-controlled studies in adults. In 4 of these studies (all non-US), the difference was >16 percentage points, which is regarded as sufficient to establish the clinical relevance of investigational treatments in studies submitted for licensing approval[2;7;10].

Figure 5. MADRS 50% response at week 6/8 (FAS, LOCF): short-term, placebo-controlled pool



Vortioxetine also separated from placebo (P <0.05) at Week 6/8 in the remitter analysis in 4 of the 11 short-term, placebo-controlled studies in adults (all non-US studies) (Figure 6).

Figure 6. Remission (MADRS ≤10) week 6/8 (FAS, LOCF): short-term, placebo-controlled pool



The meta-analysed results for response and remission rates vs. placebo are shown in Figure 7 and Figure 8, respectively.

Figure 7: Response rates at Week 6/8 - short-term placebo-controlled pool

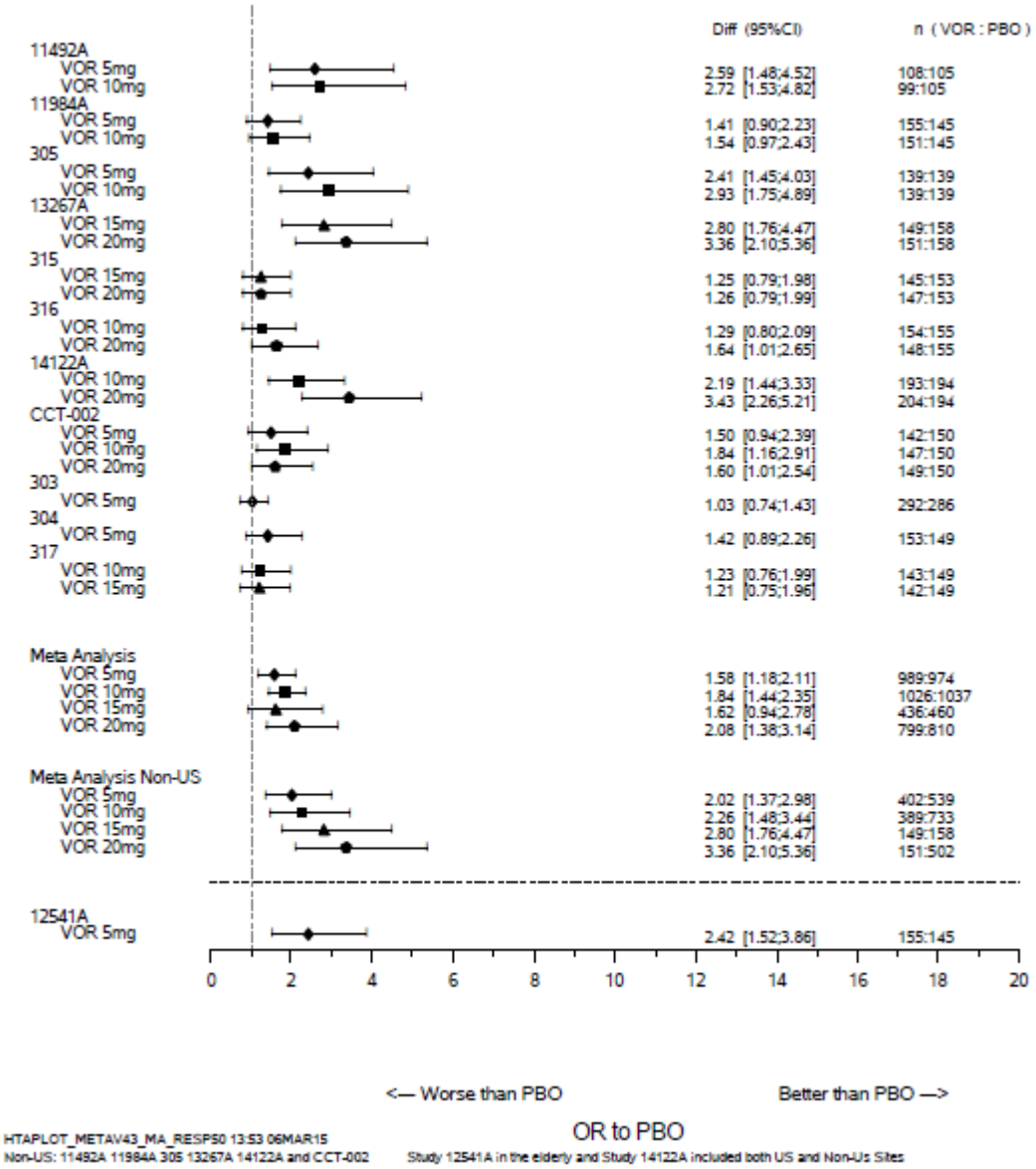
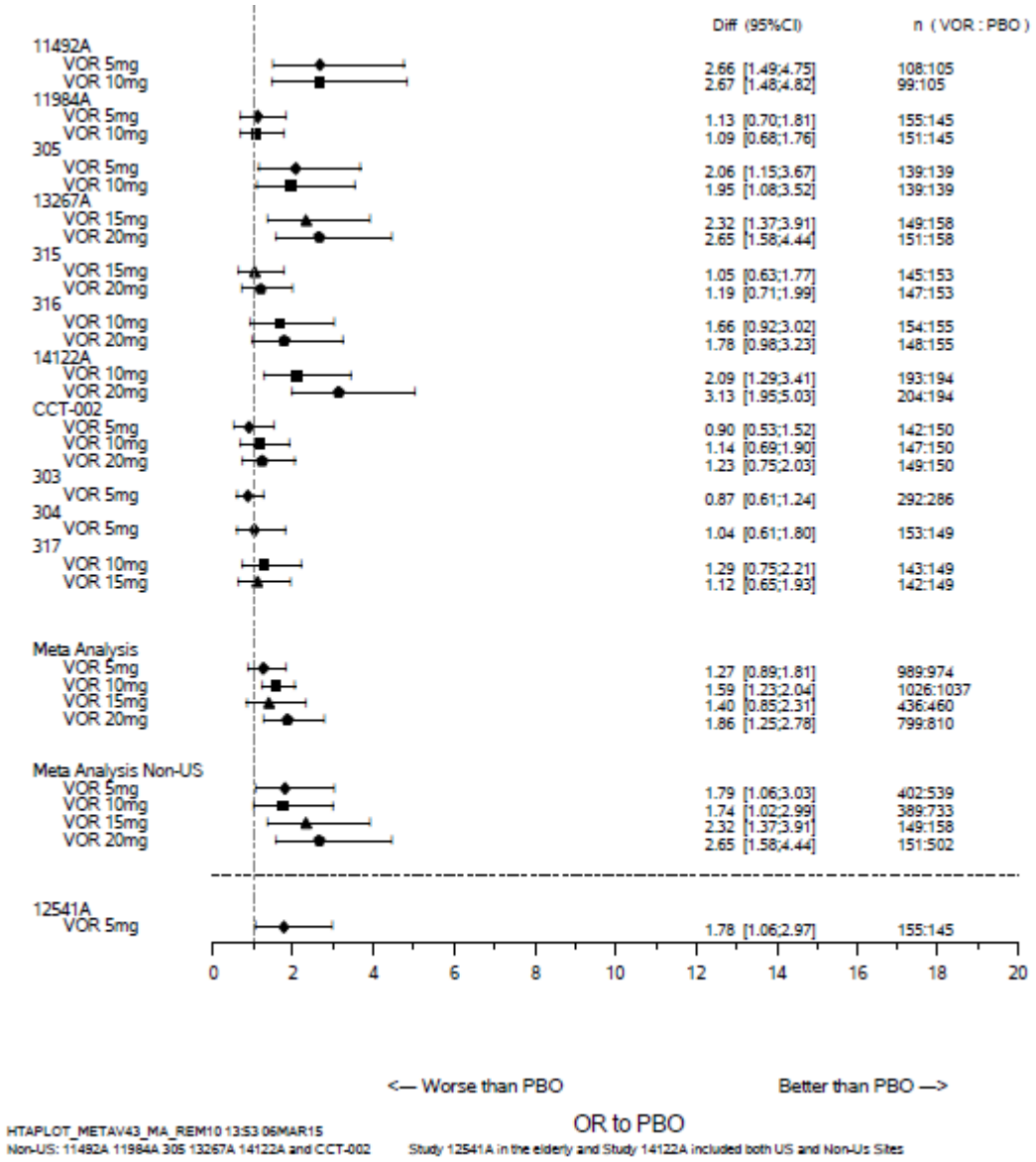


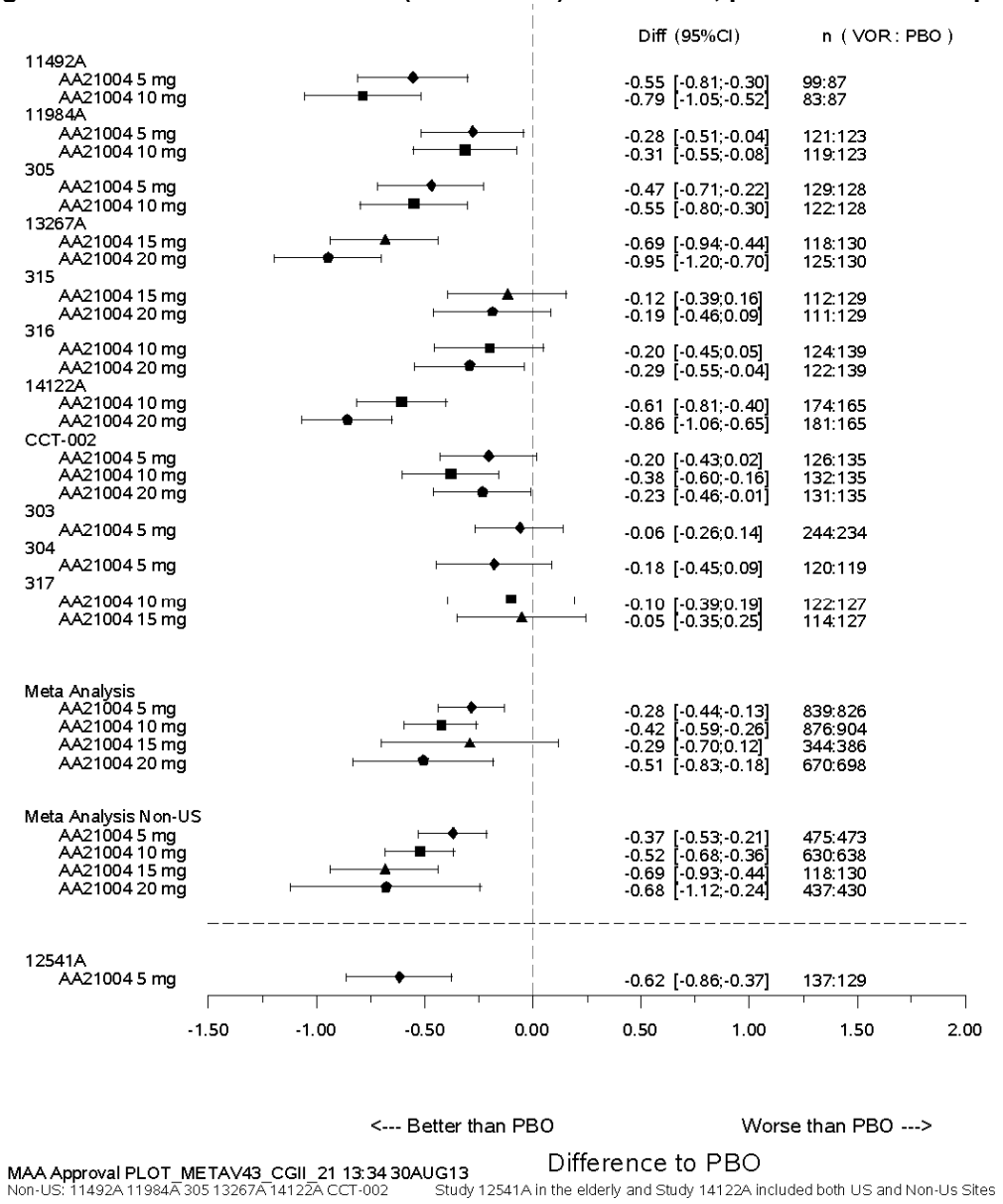
Figure 8: Remission rates at Week 6/8 - short-term placebo-controlled pool



The improvement in the CGI-I score at week 6/8 was greater (P <0.05) in the vortioxetine group than in the placebo group in 7 (in all 6 non-US studies and in one US study) of the 11 short-term, placebo-controlled studies in adults. The meta-analysis of all the short-term, placebo-controlled studies in adults supported the results of the individual studies, and showed an increased effect with increasing dose of vortioxetine (Figure 5).

In the dedicated study in the elderly, the clinical relevance of the effect on the MADRS was shown by the 16 percentage-point greater (P <0.05) proportion of responders, the greater (P <0.05) proportion of remitters, and the greater (P <0.05) improvement in the CGI-I score at week 8 in the vortioxetine group than in the placebo group.

Figure 5. CGI-I Score at week 6/8 (FAS/MMRM): short-term, placebo-controlled pool



Pooled analyses for the evaluation of the safety and tolerability of vortioxetine

In order to evaluate the safety and tolerability of vortioxetine, two pools were used, the MDD Short-term Pool, and the MDD Open-label Long-term Pool (Table 7As). The short-term safety data are based on the MDD Short-term Pool, which included 12 short-term placebo-controlled studies, including one study (12541A) in patients aged over 65 years. Studies 202 and CCT-003 were not included in the pool as the former was a flexible-dose study and the later was undertaken wholly in Japanese patients. The safety data for these studies are available upon request.

Table 7. Overview of MDD pools for the evaluation of the safety and tolerability of vortioxetine

Pool	Number of studies included	Study ID
MDD Short-term Pool[a]	12	11492A , 11984A, 305, 13267A, 315, 316, 14122A, CCT-002, 303, 304, and 317, and 12541A
MDD Open-label Long-term Pool[b]	5	11492C, 11984B, 301, 13267B, and 314

Safety and tolerability in the studies in MDD in adults and the elderly

Short-term, placebo-controlled studies

Withdrawals and withdrawals due to adverse events

The safety data cut-off date was 31 July 2013 (consistent with the European regulatory assessment of vortioxetine) for this updated MDD Short-term Pool (as defined in Table 7). The pool included 3,904 patients treated with vortioxetine.

Withdrawals

As shown in Table 8, the withdrawal rate in the vortioxetine total group and the placebo group was similar (17% and 16%, respectively). Also, in the therapeutic vortioxetine dose groups (5, 10, and 20 mg/day), the withdrawal rate was similar to that in the placebo group (15%, 15%, and 17%, respectively), except in the 15mg group, in which the withdrawal rate was slightly higher (22%).

Withdrawals due to adverse events

The most common reason for withdrawal in all the therapeutic vortioxetine dose groups was adverse events. Slightly greater proportions of patients in the therapeutic vortioxetine dose groups than in the placebo group withdrew due to adverse events (vortioxetine: 4.8% [5mg], 5.8% [10mg], 8.0% [15mg], and 7.0% [20mg]; placebo: 4.0% Rates of withdrawals due to specific AEs are presented in Table 9.

Table 8. Patient disposition and withdrawals by primary reason by dose (APTS) - MDD Short-term Pool

	Placebo		Vortioxetine 5mg		Vortioxetine 10mg		Vortioxetine 15mg*		Vortioxetine 20mg		Total vortioxetine	
	n	%	N	%	n	%	n	%	n	%	n	%
All Patients Treated Set (APTS)	1,968		1,157		1,042		449		812		3,460	
Completed	1,653	(84.0)	978	(84.5)	881	(84.5)	351	(78.2)	670	(82.5)	2,880	83.2
Withdrawn	315	(16.0)	179	(15.5)	161	(15.5)	98	(21.8)	142	(17.5)	580	16.8
Adverse event(s)	78	(4.0)	56	(4.8)	60	(5.8)	36	(8.0)	57	(7.0)	209	6.0
Lack of efficacy	64	(3.3)	28	(2.4)	19	(1.8)	8	(1.8)	9	(1.1)	64	1.8
Non-compliance	10	(0.5)	5	(0.4)	5	(0.5)	5	(1.1)	4	(0.5)	19	0.5
Protocol violation	33	(1.7)	15	(1.3)	10	(1.0)	8	(1.8)	17	(2.1)	50	1.4
Withdrawal of consent	58	(2.9)	37	(3.2)	39	(3.7)	21	(4.7)	18	(2.2)	115	3.3
Lost to follow-up	56	(2.8)	30	(2.6)	21	(2.8)	12	(2.7)	27	(3.3)	90	2.6
Administrative or other reasons	16	(0.8)	8	(0.7)	7	(0.7)	8	(1.8)	10	(1.2)	33	1.0

*Vortioxetine 15mg will not be made available in the UK.

Table 9. TEAEs Leading to Withdrawal by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool

Preferred Term	Placebo		Vortioxetine 5mg		Vortioxetine 10 mg		Vortioxetine 15 mg*		Vortioxetine 20 mg		Total vortioxetine	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of Patients	1968		1157		1042		449		812		3460	
Patient years exposure	262.7		149.3		143.4		60.7		112.5		466.0	
Patients with Adverse Events	70	(3.6)	48	(4.1)	51	(4.9)	35	(7.8)	55	(6.8)	189	(5.5)
Nausea	6	(0.3)	13	(1.1)	15	(1.4)	17	(3.8)	27	(3.3)	72	(2.1)
Headache	4	(0.2)	1	(<0.1)	5	(0.5)	4	(0.9)	6	(0.7)	16	(0.5)
Dizziness	6	(0.3)	1	(<0.1)	2	(0.2)	2	(0.4)	4	(0.5)	9	(0.3)
Constipation	0		1	(<0.1)	1	(<0.1)	0		3	(0.4)	5	(0.1)
Vomiting	2	(0.1)	1	(<0.1)	5	(0.5)	2	(0.4)	3	(0.4)	11	(0.3)
Erection increased (SS)	0		0		0		0		1	(0.4)	1	(<0.1)
Abdominal pain	1	(<0.1)	0		0		0		2	(0.2)	2	(<0.1)
Abdominal pain upper	3	(0.2)	0		2	(0.2)	1	(0.2)	2	(0.2)	5	(0.1)
Hypertension	0		0		1	(<0.1)	0		2	(0.2)	3	(<0.1)
Irritability	2	(0.1)	0		1	(<0.1)	1	(0.2)	2	(0.2)	4	(0.1)
Sedation	0		0		1	(<0.1)	0		2	(0.2)	3	(<0.1)
Alcoholic liver disease	0		0		0		0		1	(0.1)	1	(<0.1)
Anorgasmia	0		0		0		0		1	(0.1)	1	(<0.1)
Anxiety	4	(0.2)	2	(0.2)	2	(0.2)	2	(0.4)	1	(0.1)	7	(0.2)
Asthenia	0		1	(<0.1)	0		0		1	(0.1)	2	(<0.1)
Bronchopneumonia	0		0		0		0		1	(0.1)	1	(<0.1)
Chest discomfort	0		1	(<0.1)	0		1	(0.2)	1	(0.1)	3	(<0.1)
Diarrhoea	2	(0.1)	2	(0.2)	3	(0.3)	3	(0.7)	1	(0.1)	9	(0.3)

Dry mouth	0		2	(0.2)	0		0		1	(0.1)	3	(<0.1)
Feeling cold	0		0		0		0		1	(0.1)	1	(<0.1)
Flatulence	0		0		1	(<0.1)	0		1	(0.1)	2	(<0.1)
Hot flush	0		0		0		0		1	(0.1)	1	(<0.1)
Hypersensitivity	0		0		0		0		1	(0.1)	1	(<0.1)
Influenza like illness	0		0		0		0		1	(0.1)	1	(<0.1)
Irritable bowel syndrome	0		0		0		0		1	(0.1)	1	(<0.1)
Myalgia	0		0		0		0		1	(0.1)	1	(<0.1)
Palpitations	1	(<0.1)	0		0		0		1	(0.1)	1	(<0.1)
Renal pain	0		0		0		0		1	(0.1)	1	(<0.1)
Sleep disorder	1	(<0.1)	0		0		0		1	(0.1)	1	(<0.1)
Suicidal ideation	3	(0.2)	0		1	(<0.1)	0		1	(0.1)	2	(<0.1)
Suicide attempt	0		1	(<0.1)	1	(<0.1)	0		1	(0.1)	3	(<0.1)
Tension	0		0		1	(<0.1)	0		1	(0.1)	2	(<0.1)
Urinary retention	0		0		0		0		1	(0.1)	1	(<0.1)
Urticaria	0		0		0		1	(0.2)	1	(0.1)	2	(<0.1)
Vertigo	0		1	(<0.1)	0		0		1	(0.1)	2	(<0.1)
Abdominal discomfort	1	(<0.1)	1	(<0.1)	1	(<0.1)	0		0		2	(<0.1)
Agitation	2	(0.1)	1	(<0.1)	0		0		0		1	(<0.1)
Akathisia	1	(<0.1)	0		0		0		0		0	
Alanine aminotransferase increased	2	(0.1)	0		0		0		0		0	
Anaemia	0		0		0		1	(0.2)	0		1	(<0.1)
Anal fissure	0		1	(<0.1)	0		0		0		1	(<0.1)
Anger	1	(<0.1)	0		0		0		0		0	
Angina pectoris	1	(<0.1)	0		0		0		0		0	

Arthralgia	0		0		0		1	(0.2)	0		1	(<0.1)
Aspartate aminotransferase increased	1	(<0.1)	0		0		0		0		0	
Atrial fibrillation	0		1	(<0.1)	0		0		0		1	(<0.1)
Atrioventricular block first degree	0		0		1	(<0.1)	0		0		1	(<0.1)
Balance disorder	1	(<0.1)	0		0		0		0		0	
Blood alkaline phosphatase increased	0		1	(<0.1)	0		0		0		1	(<0.1)
Blood creatine phosphokinase increased	0		2	(0.2)	1	(<0.1)	0		0		3	(<0.1)
Blood pressure increased	0		0		1	(<0.1)	0		0		1	(<0.1)
Chest pain	0		0		1	(<0.1)	0		0		1	(<0.1)
Chills	0		1	(<0.1)	1	(<0.1)	0		0		2	(<0.1)
Chronic obstructive pulmonary disease	0		0		1	(<0.1)	0		0		1	(<0.1)
Confusional state	1	(<0.1)	0		0		0		0		0	
Convulsion	0		1	(<0.1)	0		0		0		1	(<0.1)
Crying	2	(0.1)	0		0		0		0		0	
Decreased appetite	0		1	(<0.1)	0		0		0		1	(<0.1)
Depressed mood	1	(<0.1)	0		0		0		0		0	
Depression	9	(0.5)	0		5	(0.5)	0		0		5	(0.1)
Depressive symptom	0		0		0		2	(0.4)	0		2	(<0.1)
Dermatitis allergic	0		0		0		1	(0.2)	0		1	(<0.1)
Dermatitis bullous	1	(<0.1)	0		0		0		0		0	
Diabetes mellitus	0		0		1	(<0.1)	0		0		1	(<0.1)
Distractibility	1	(<0.1)	0		0		0		0		0	

Disturbance in attention	2	(0.1)	0		0		0		0		0	
Dizziness postural	0		0		1	(<0.1)	0		0		1	(<0.1)
Dry eye	0		0		0		1	(0.2)	0		1	(<0.1)
Dry skin	1	(<0.1)	0		0		0		0		0	
Dysgeusia	1	(<0.1)	0		0		0		0		0	
Dyspepsia	2	(0.1)	0		0		0		0		0	
Dyspnoea	2	(0.1)	0		0		0		0		0	
Echocardiogram abnormal	1	(<0.1)	0		0		0		0		0	
Eczema	0		0		1	(<0.1)	0		0		1	(<0.1)
Enteritis infectious	1	(<0.1)	0		0		0		0		0	
Epigastric discomfort	0		0		0		1	(0.2)	0		1	(<0.1)
Face oedema	0		0		0		1	(0.2)	0		1	(<0.1)
Fatigue	1	(<0.1)	1	(<0.1)	2	(0.2)	0		0		3	(<0.1)
Feeling jittery	1	(<0.1)	0		0		0		0		0	
Gamma-glutamyltransferase increased	0		1	(<0.1)	0		0		0		1	(<0.1)
Glossodynia	1	(<0.1)	0		0		0		0		0	
Head injury	0		1	(<0.1)	0		0		0		1	(<0.1)
Hepatic function abnormal	0		0		1	(<0.1)	0		0		1	(<0.1)
Herpes zoster	0		1	(<0.1)	0		0		0		1	(<0.1)
Hiatus hernia	1	(<0.1)	0		0		0		0		0	
Hyperhidrosis	1	(<0.1)	1	(<0.1)	1	(<0.1)	0		0		2	(<0.1)
Hypoaesthesia	1	(<0.1)	0		0		0		0		0	
Hypomania	0		0		1	(<0.1)	0		0		1	(<0.1)
Increased appetite	1	(<0.1)	0		0		1	(0.2)	0		1	(<0.1)

Injury	0		1	(<0.1)	0		0		0		1	(<0.1)
Insomnia	1	(<0.1)	5	(0.4)	1	(<0.1)	1	(0.2)	0		7	(0.2)
Intentional overdose	0		1	(<0.1)	0		0		0		1	(<0.1)
Kidney infection	0		0		1	(<0.1)	0		0		1	(<0.1)
Laceration	0		0		0		1	(0.2)	0		1	(<0.1)
Laryngeal cancer	1	(<0.1)	0		0		0		0		0	
Loss of libido	0		1	(<0.1)	0		0		0		1	(<0.1)
Lumbar radiculopathy	1	(<0.1)	0		0		0		0		0	
Major depression	0		1	(<0.1)	0		1	(0.2)	0		2	(<0.1)
Malaise	0		0		1	(<0.1)	0		0		1	(<0.1)
Memory impairment	1	(<0.1)	0		0		0		0		0	
Menorrhagia (SS)	0		0		0		1	(0.3)	0		1	(<0.1)
Mood swings	1	(<0.1)	0		0		0		0		0	
Mouth ulceration	1	(<0.1)	0		0		0		0		0	
Mucosal dryness	0		0		1	(<0.1)	0		0		1	(<0.1)
Muscle fatigue	0		0		1	(<0.1)	0		0		1	(<0.1)
Oedema peripheral	1	(<0.1)	0		0		0		0		0	
Overdose	1	(<0.1)	0		0		0		0		0	
Pain in extremity	0		0		1	(<0.1)	0		0		1	(<0.1)
Pancreatitis	0		0		1	(<0.1)	0		0		1	(<0.1)
Panic attack	0		1	(<0.1)	0		0		0		1	(<0.1)
Parosmia	1	(<0.1)	0		0		0		0		0	
Pelvic fracture	0		0		1	(<0.1)	0		0		1	(<0.1)
Peptic ulcer	1	(<0.1)	0		0		0		0		0	
Pregnancy (SS)	1	(<0.1)	0		0		0		0		0	

Pruritus	1	(<0.1)	0		1	(<0.1)	0		0		1	(<0.1)
Pruritus generalised	0		1	(<0.1)	3	(0.3)	1	(0.2)	0		5	(0.1)
Rash erythematous	0		0		0		1	(0.2)	0		1	(<0.1)
Rash macular	1	(<0.1)	0		0		1	(0.2)	0		1	(<0.1)
Rash maculo-papular	0		0		2	(0.2)	0		0		2	(<0.1)
Rash pruritic	0		0		0		1	(0.2)	0		1	(<0.1)
Rash pustular	1	(<0.1)	0		0		0		0		0	
Restlessness	1	(<0.1)	1	(<0.1)	0		0		0		1	(<0.1)
Serotonin syndrome	1	(<0.1)	0		0		0		0		0	
Sexual dysfunction	0		0		0		1	(0.2)	0		1	(<0.1)
Skin burning sensation	0		0		1	(<0.1)	0		0		1	(<0.1)
Sleep apnoea syndrome	0		0		0		1	(0.2)	0		1	(<0.1)
Somnolence	2	(0.1)	1	(<0.1)	1	(<0.1)	0		0		2	(<0.1)
Stress fracture	0		0		0		1	(0.2)	0		1	(<0.1)
Tachycardia	1	(<0.1)	0		0		0		0		0	
Tension headache	1	(<0.1)	0		1	(<0.1)	0		0		1	(<0.1)
Tinnitus	0		1	(<0.1)	0		1	(0.2)	0		2	(<0.1)
Tremor	1	(<0.1)	2	(0.2)	0		1	(0.2)	0		3	(<0.1)
Upper limb fracture	0		1	(<0.1)	0		0		0		1	(<0.1)
Urinary tract infection bacterial	0		0		1	(<0.1)	0		0		1	(<0.1)
Vision blurred	2	(0.1)	1	(<0.1)	0		1	(0.2)	0		2	(<0.1)
Weight increased	1	(<0.1)	1	(<0.1)	0		0		0		1	(<0.1)
White blood cell count decreased	1	(<0.1)	0		0		0		0		0	

(SS) Sex Specific Dictionary: MedDRA 14.1. * Vortioxetine 15 mg will not be made available in the UK.

Treatment-emergent adverse events

The Treatment-emergent adverse event (TEAE) with the highest incidence in all the active treatment groups was nausea. The incidence of nausea was 8% in the placebo group and 31% in the vortioxetine 15mg group, which was the treatment group with the highest incidence.

Headache, which was the TEAE with the highest incidence in the placebo group, had similar incidences in all the treatment groups (approximately 13%).

For the majority of the remaining TEAEs, the incidences in the therapeutic vortioxetine dose groups were either slightly higher than those in the placebo group or at placebo level. The incidences were generally higher in the 15mg and 20mg groups than in the 5mg and 10mg groups.

For the majority of the patients with TEAEs, the TEAEs were mild or moderate. The incidence of severe TEAEs was similar in the placebo group and in the vortioxetine total group (4.4% and 5.6%, respectively).

In the therapeutic vortioxetine dose groups, the incidence of severe TEAEs ranged from 4.1% in the 20mg group to 7.0% in the 5mg group.

Data on the occurrence of severe TEAEs by preferred term are provided in Table 10. The severe TEAEs with an incidence ≥1% in any of the therapeutic vortioxetine dose groups were nausea and headache. The incidence of severe nausea was 0.1% (2 patients) in the placebo group and 1.6% (7 patients) in the vortioxetine 15 mg group, which was the therapeutic vortioxetine dose group with the highest incidence. The incidence of severe headache was 0.6% (12 patients) in the placebo group and 1.4% (16 patients) in the vortioxetine 5mg group, which was the therapeutic vortioxetine dose group with the highest incidence.

Table 10 provides a summary of the TEAEs reported by ≥5% subjects in the MDD placebo-controlled short-term pool studies in MDD.

Table 10. Severe TEAEs by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool

Preferred Term	Placebo		Vortioxetine 5 mg		Vortioxetine 10 mg		Vortioxetine 15 mg*		Vortioxetine 20 mg		Total vortioxetine	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of Patients	1968		1157		1042		449		812		3460	
Patient years exposure	262.7		149.3		143.4		60.7		112.5		466.0	
Patients with Adverse Events	87	(4.4)	81	(7.0)	56	(5.4)	22	(4.9)	33	(4.1)	192	(5.5)
Headache	12	(0.6)	16	(1.4)	10	(1.0)	1	(0.2)	7	(0.9)	34	(1.0)
Nausea	2	(0.1)	5	(0.4)	10	(1.0)	7	(1.6)	7	(0.9)	29	(0.8)
Vomiting	0		3	(0.3)	3	(0.3)	2	(0.4)	3	(0.4)	11	(0.3)
Sedation	1	(<0.1)	0		0		0		2	(0.2)	2	(<0.1)
Abdominal distension	0		0		0		0		1	(0.1)	1	(<0.1)
Abdominal pain	1	(<0.1)	0		0		0		1	(0.1)	1	(<0.1)
Anxiety	4	(0.2)	1	(<0.1)	0		1	(0.2)	1	(0.1)	3	(<0.1)
Back pain	3	(0.2)	2	(0.2)	0		1	(0.2)	1	(0.1)	4	(0.1)
Constipation	1	(<0.1)	1	(<0.1)	2	(0.2)	0		1	(0.1)	4	(0.1)
Dizziness	6	(0.3)	0		1	(<0.1)	2	(0.4)	1	(0.1)	4	(0.1)
Dysgeusia	0		0		0		0		1	(0.1)	1	(<0.1)
Dyspepsia	1	(<0.1)	1	(<0.1)	1	(<0.1)	0		1	(0.1)	3	(<0.1)
Fatigue	3	(0.2)	4	(0.3)	1	(<0.1)	0		1	(0.1)	6	(0.2)
Flatulence	1	(<0.1)	0		0		0		1	(0.1)	1	(<0.1)
Gastroenteritis	1	(<0.1)	0		1	(<0.1)	1	(0.2)	1	(0.1)	3	(<0.1)
Influenza	0		1	(<0.1)	0		0		1	(0.1)	2	(<0.1)
Influenza like illness	0		0		0		0		1	(0.1)	1	(<0.1)
Insomnia	9	(0.5)	6	(0.5)	2	(0.2)	2	(0.4)	1	(0.1)	11	(0.3)

Irritability	3	(0.2)	0		0		0		1	(0.1)	1	(<0.1)
Middle insomnia	0		0		0		0		1	(0.1)	1	(<0.1)
Myoclonus	0		0		0		0		1	(0.1)	1	(<0.1)
Orgasm abnormal	0		0		0		0		1	(0.1)	1	(<0.1)
Overdose	0		1	(<0.1)	0		0		1	(0.1)	2	(<0.1)
Renal pain	0		0		0		0		1	(0.1)	1	(<0.1)
Salivary gland pain	0		0		0		0		1	(0.1)	1	(<0.1)
Salivary hypersecretion	0		0		0		0		1	(0.1)	1	(<0.1)
Tension	0		0		0		0		1	(0.1)	1	(<0.1)
Urinary retention	0		0		0		0		1	(0.1)	1	(<0.1)
Urticaria	0		0		0		0		1	(0.1)	1	(<0.1)
Abdominal discomfort	1	(<0.1)	0		0		0		0		0	
Abdominal pain upper	1	(<0.1)	1	(<0.1)	1	(<0.1)	1	(0.2)	0		3	(<0.1)
Abnormal dreams	0		1	(<0.1)	0		0		0		1	(<0.1)
Accidental overdose	2	(0.1)	3	(0.3)	1	(<0.1)	1	(0.2)	0		5	(0.1)
Agitation	2	(0.1)	1	(<0.1)	0		0		0		1	(<0.1)
Alcoholism	0		0		0		1	(0.2)	0		1	(<0.1)
Anorgasmia	0		0		1	(<0.1)	0		0		1	(<0.1)
Anxiety disorder	1	(<0.1)	0		0		0		0		0	
Arthralgia	0		0		1	(<0.1)	0		0		1	(<0.1)
Asthenia	0		1	(<0.1)	0		0		0		1	(<0.1)
Asthma	1	(<0.1)	0		0		0		0		0	
Atrial fibrillation	0		1	(<0.1)	0		0		0		1	(<0.1)
Blood creatine phosphokinase increased	1	(<0.1)	1	(<0.1)	0		0		0		1	(<0.1)

Blood creatinine increased	1	(<0.1)	0		0		0		0		0	
Blood uric acid increased	1	(<0.1)	0		0		0		0		0	
Bronchitis	0		1	(<0.1)	0		0		0		1	(<0.1)
Cholelithiasis	1	(<0.1)	0		0		0		0		0	
Contusion	1	(<0.1)	0		0		0		0		0	
Convulsion	0		1	(<0.1)	0		0		0		1	(<0.1)
Cystitis	0		1	(<0.1)	0		0		0		1	(<0.1)
Deep vein thrombosis	0		0		0		1	(0.2)	0		1	(<0.1)
Depression	3	(0.2)	0		4	(0.4)	0		0		4	(0.1)
Diarrhoea	0		0		2	(0.2)	1	(0.2)	0		3	(<0.1)
Disturbance in sexual arousal	0		1	(<0.1)	0		0		0		1	(<0.1)
Dizziness postural	0		0		1	(<0.1)	0		0		1	(<0.1)
Dry mouth	5	(0.3)	1	(<0.1)	2	(0.2)	0		0		3	(<0.1)
Dysmenorrhoea (SS)	1	(<0.1)	2	(0.3)	0		0		0		2	(<0.1)
Ear infection	0		1	(<0.1)	0		0		0		1	(<0.1)
Ejaculation delayed (SS)	0		0		1	(0.3)	0		0		1	(<0.1)
Electrocardiogram qt prolonged	0		0		1	(<0.1)	0		0		1	(<0.1)
Erectile dysfunction (SS)	0		1	(0.3)	0		0		0		1	(<0.1)
Euphoric mood	0		0		1	(<0.1)	0		0		1	(<0.1)
Facial pain	0		0		1	(<0.1)	0		0		1	(<0.1)
Fall	1	(<0.1)	0		0		0		0		0	
Feeling hot	1	(<0.1)	0		0		0		0		0	
Flushing	0		1	(<0.1)	0		0		0		1	(<0.1)
Foreign body in eye	0		0		0		1	(0.2)	0		1	(<0.1)
Furuncle	0		1	(<0.1)	0		0		0		1	(<0.1)

Gastritis	0		1	(<0.1)	0		0		0		1	(<0.1)
Gastroenteritis viral	1	(<0.1)	0		2	(0.2)	0		0		2	(<0.1)
Gastrooesophageal reflux disease	1	(<0.1)	0		0		0		0		0	
Glossitis	0		1	(<0.1)	0		0		0		1	(<0.1)
Head injury	0		1	(<0.1)	0		0		0		1	(<0.1)
Herpes zoster	0		1	(<0.1)	0		0		0		1	(<0.1)
Hot flush	1	(<0.1)	0		0		0		0		0	
Hyperhidrosis	1	(<0.1)	0		1	(<0.1)	0		0		1	(<0.1)
Hypertension	1	(<0.1)	0		1	(<0.1)	0		0		1	(<0.1)
Hypoaesthesia	1	(<0.1)	0		0		0		0		0	
Increased appetite	0		1	(<0.1)	0		1	(0.2)	0		2	(<0.1)
Initial insomnia	1	(<0.1)	0		0		0		0		0	
Injury	0		1	(<0.1)	0		0		0		1	(<0.1)
Intentional overdose	0		1	(<0.1)	0		0		0		1	(<0.1)
Intertrigo	0		0		1	(<0.1)	0		0		1	(<0.1)
Joint swelling	0		0		1	(<0.1)	0		0		1	(<0.1)
Kidney infection	0		0		1	(<0.1)	0		0		1	(<0.1)
Laceration	1	(<0.1)	0		0		0		0		0	
Laryngeal cancer	1	(<0.1)	0		0		0		0		0	
Libido decreased	0		1	(<0.1)	1	(<0.1)	0		0		2	(<0.1)
Liver function test abnormal	0		1	(<0.1)	0		0		0		1	(<0.1)
Loss of libido	0		1	(<0.1)	0		0		0		1	(<0.1)
Lumbar radiculopathy	1	(<0.1)	0		0		0		0		0	
Major depression	0		1	(<0.1)	0		1	(0.2)	0		2	(<0.1)

Memory impairment	0		0		1	(<0.1)	0		0		1	(<0.1)
Micturition frequency decreased	1	(<0.1)	0		0		0		0		0	
Migraine	1	(<0.1)	2	(0.2)	2	(0.2)	0		0		4	(0.1)
Mucosal dryness	0		0		1	(<0.1)	0		0		1	(<0.1)
Muscle spasms	0		1	(<0.1)	0		0		0		1	(<0.1)
Musculoskeletal discomfort	1	(<0.1)	0		0		0		0		0	
Neck pain	0		1	(<0.1)	0		0		0		1	(<0.1)
Neuralgia	0		1	(<0.1)	0		0		0		1	(<0.1)
Oropharyngeal pain	1	(<0.1)	0		0		0		0		0	
Pain in extremity	1	(<0.1)	0		1	(<0.1)	0		0		1	(<0.1)
Palpitations	0		1	(<0.1)	0		0		0		1	(<0.1)
Pancreatitis	1	(<0.1)	0		0		0		0		0	
Panic attack	0		1	(<0.1)	0		0		0		1	(<0.1)
Pelvic fracture	0		0		1	(<0.1)	0		0		1	(<0.1)
Pelvic pain	0		1	(<0.1)	0		0		0		1	(<0.1)
Peptic ulcer	1	(<0.1)	0		0		0		0		0	
Plantar fasciitis	0		0		1	(<0.1)	0		0		1	(<0.1)
Pneumonia	1	(<0.1)	0		2	(0.2)	0		0		2	(<0.1)
Pneumonia mycoplasmal	0		1	(<0.1)	0		0		0		1	(<0.1)
Polyarthritis	1	(<0.1)	0		0		0		0		0	
Polyuria	0		0		1	(<0.1)	0		0		1	(<0.1)
Procedural pain	0		1	(<0.1)	0		1	(0.2)	0		2	(<0.1)
Pruritus	0		1	(<0.1)	0		0		0		1	(<0.1)
Pruritus generalised	1	(<0.1)	0		0		0		0		0	
Pulpitis dental	0		1	(<0.1)	0		0		0		1	(<0.1)

Renal colic	0		1	(<0.1)	0		0		0		1	(<0.1)
Restlessness	0		1	(<0.1)	0		0		0		1	(<0.1)
Road traffic accident	0		0		1	(<0.1)	0		0		1	(<0.1)
Sinusitis	1	(<0.1)	0		0		0		0		0	
Sinusitis bacterial	1	(<0.1)	0		0		0		0		0	
Skin burning sensation	0		0		1	(<0.1)	0		0		1	(<0.1)
Sleep disorder	0		1	(<0.1)	0		0		0		1	(<0.1)
Somnolence	3	(0.2)	1	(<0.1)	2	(0.2)	0		0		3	(<0.1)
Sternal fracture	0		1	(<0.1)	0		0		0		1	(<0.1)
Stress fracture	0		0		0		1	(0.2)	0		1	(<0.1)
Suicide attempt	0		1	(<0.1)	0		0		0		1	(<0.1)
Tachycardia	0		1	(<0.1)	0		0		0		1	(<0.1)
Tension headache	0		0		2	(0.2)	0		0		2	(<0.1)
Thoracic vertebral fracture	0		1	(<0.1)	0		0		0		1	(<0.1)
Tooth abscess	1	(<0.1)	0		0		0		0		0	
Tooth fracture	0		0		1	(<0.1)	0		0		1	(<0.1)
Tooth infection	0		1	(<0.1)	0		0		0		1	(<0.1)
Toothache	1	(<0.1)	1	(<0.1)	2	(0.2)	0		0		3	(<0.1)
Traumatic lung injury	0		1	(<0.1)	0		0		0		1	(<0.1)
Upper limb fracture	0		1	(<0.1)	0		0		0		1	(<0.1)
Urinary tract infection	0		1	(<0.1)	1	(<0.1)	0		0		2	(<0.1)
Uterine leiomyoma (SS)	1	(<0.1)	0		0		0		0		0	
Vertigo	1	(<0.1)	0		0		0		0		0	

(SS) Sex Specific Dictionary: MedDRA 14.1. * Vortioxetine 15 mg will not be made available in the UK.

Table 11. TEAEs with an Incidence of 5% or More by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool

Preferred Term	Placebo		Vortioxetine 5 mg		Vortioxetine 10 mg		Vortioxetine 15 mg		Vortioxetine 20 mg		Total vortioxetine	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of Patients	1968		1157		1042		449		812		3460	
Patient years exposure	262.7		149.3		143.4		60.7		112.5		466.0	
Patients with Adverse Events	1140	(57.9)	749	(64.7)	636	(61.0)	309	(68.8)	529	(65.1)	2223	(64.2)
Nausea	159	(8.1)	237	(20.5)	235	(22.6)	140	(31.2)	221	(27.2)	833	(24.1)
Headache	254	(12.9)	159	(13.7)	132	(12.7)	66	(14.7)	101	(12.4)	458	(13.2)
Dry mouth	111	(5.6)	74	(6.4)	57	(5.5)	27	(6.0)	53	(6.5)	211	(6.1)
Dizziness	104	(5.3)	64	(5.5)	54	(5.2)	32	(7.1)	51	(6.3)	201	(5.8)
Diarrhoea	108	(5.5)	76	(6.6)	56	(5.4)	42	(9.4)	45	(5.5)	219	(6.3)
Nasopharyngitis	77	(3.9)	61	(5.3)	42	(4.0)	16	(3.6)	40	(4.9)	159	(4.6)
Constipation	57	(2.9)	39	(3.4)	38	(3.6)	25	(5.6)	36	(4.4)	138	(4.0)
Vomiting	21	(1.1)	31	(2.7)	38	(3.6)	29	(6.5)	36	(4.4)	134	(3.9)

(SS) Sex Specific Dictionary: MedDRA 14.1. * Vortioxetine 15 mg will not be made available in the UK.

Insomnia and Somnolence

The incidence of insomnia-related TEAEs in the vortioxetine total group was low and similar to that in the placebo group (3.9% and 3.7%, respectively) in the short-term pool (see Table 12).

Table 12. Insomnia-related TEAEs by Preferred Term, Core Treatment Period, by Dose (APTS) - MDD Short-term Pool

Preferred Term	Proportion of subjects (%)	
	Placebo (n=1,968)	Vortioxetine total (n=3,460)
Patients with insomnia-related TEAEs	3.7	3.8
Insomnia	2.5	2.7
Initial insomnia	0.3	0.5
Middle insomnia	0.3	0.3
Sleep disorder	0.4	0.2
Poor quality sleep	0.3	<0.1
Terminal insomnia	0	<0.1
Dyssomnia	0.1	<0.1
Hyposomnia	0	<0.1

Dictionary: MedDRA 14.1

The incidence of somnolence during treatment with vortioxetine was 3.0%, which was similar to that in the placebo group (2.3%). There was no indication of a dose-response relationship in the incidence of somnolence.

Sexual Dysfunction

Sexual Dysfunction based on TEAEs

The overall incidence of sexual dysfunction TEAEs in the vortioxetine total group was low and similar to that in the placebo group (1.6% and 0.9%, respectively).

Sexual Dysfunction based on the Arizona Sexual Experience Scale (ASEX)

Sexual dysfunction was defined as at least one of the following: an ASEX total score ≥19, a score ≥5 on any ASEX item, or a score ≥4 on ≥3 items at the same visit.

The incidence of TESD during treatment was 38% in the vortioxetine total group, which was slightly higher than that in the placebo group (32%) and driven by the highest vortioxetine dose group. The treatment difference to placebo in TESD incidence was 6.3% for the vortioxetine total group.

Table 13. TESD, Core Treatment Period, by Dose (APTS, Mantel-Haenszel) - Studies 11984A, 304, 13267A, 315, 316, 317 and 308

Treatment	N	n	Incidence Difference	
			Estimate (%)	95% CI
Vortioxetine 5mg	136	35	-4.6	[-15.1 ; 6.0]
Placebo	138	41		
Vortioxetine 10mg	190	67	6.1	[-3.4 ; 15.5]
Placebo	182	52		
Vortioxetine 15mg*	126	54	5.2	[-7.1 ; 17.5]
Placebo	121	44		
Vortioxetine 20mg	128	59	9.9	[-1.9 ; 21.7]
Placebo	135	47		
Vortioxetine total	580	215	4.2	[-2.4 ; 10.7]
Placebo	309	99		

N: Number of patients without sexual dysfunction at baseline
n: Number of patients with TESD
* Vortioxetine 15 mg will not be made available in the UK.

Relative risk of short-term adverse events

Table 14 and Figure 9 show the estimated relative risk of adverse events (with 95% confidence intervals) for vortioxetine compared to placebo using the Cochran Mantel-Haenszel approach stratified by study. A relative risk of of 1.0 means no difference to placebo and a relative risk of 2.0 means that the risk of adverse events is double for the active treatment compared with placebo.

The analysis includes data for vortioxetine 5 to 20mg/day from all studies in the MDD Short-term Pool. The analysis includes adverse events with an incidence ≥2% for either vortioxetine 5 to 20mg/day or placebo.

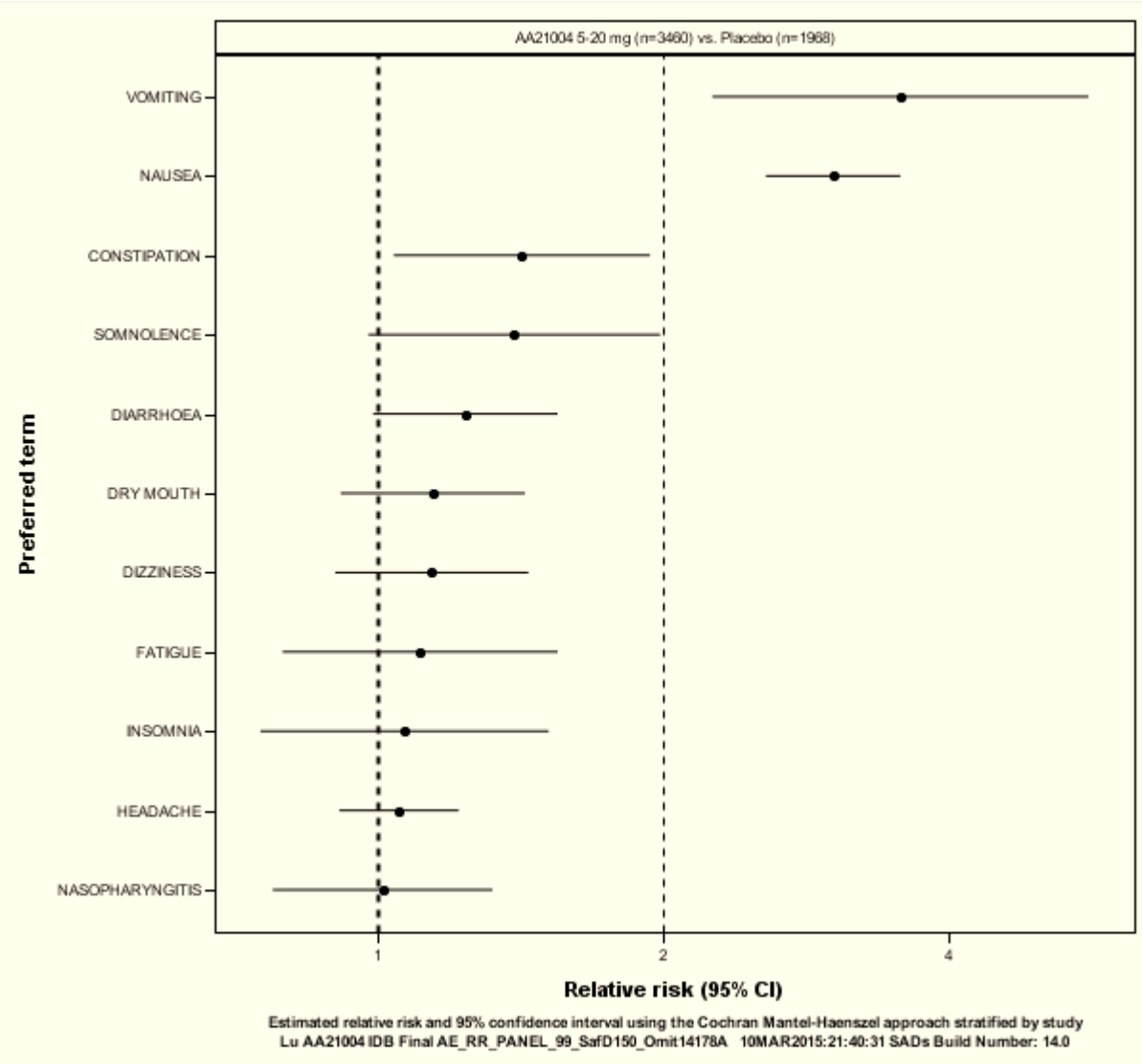
Table 14. TEAEs with an incidence of 2% or more by preferred term, core treatment period (APTS) - MDD Short-term placebo-controlled pool

Preferred term	Vortioxetine 5-20 mg		Placebo		Relative risk (95% CI)
	N	(%)	N	(%)	
Number of patients	3460		1968		
Nausea	833	(24.1)	159	(8.1)	3.02 [2.57 ; 3.55]
Headache	458	(13.2)	254	(12.9)	1.06 [0.91 ; 1.22]
Diarrhoea	219	(6.3)	108	(5.5)	1.24 [0.99 ; 1.55]
Dry mouth	211	(6.1)	111	(5.6)	1.15 [0.92 ; 1.43]
Dizziness	201	(5.8)	104	(5.3)	1.14 [0.90 ; 1.44]
Nasopharyngitis	159	(4.6)	77	(3.9)	1.01 [0.78 ; 1.32]
Constipation	138	(4.0)	57	(2.9)	1.42 [1.04 ; 1.94]

Vomiting	134	(3.9)	21	(1.1)	3.55 [2.25 ; 5.60]
Somnolence	107	(3.1)	45	(2.3)	1.40 [0.98 ; 1.99]
Fatigue	102	(2.9)	53	(2.7)	1.11 [0.80 ; 1.55]
Insomnia	93	(2.7)	50	(2.5)	1.07 [0.76 ; 1.52]

Preferred terms with incidence of 2% or more in overall vortioxetine 5-20 mg or placebo treatment arm
Only studies where both treatments are included. Relative risks stratified by study

Figure 9. Forest plot of relative risk of TEAEs with an incidence of 2% or more by preferred term, core treatment period (APTS) - MDD Short-term placebo-controlled pool: vortioxetine 5-20mg vs. placebo



The analysis shows that, except for an increased risk of vomiting and nausea for patients taking vortioxetine, the risk of adverse events for vortioxetine 5 to 20mg/day is not different from placebo.

Open-label Long-term Pool

The following data has been provided to supplement data reported in *Table B44 "Incidence of TEAEs of ≥5% in the open-label, long-term pool"* in the main submission. Table 15

presents the withdrawal rates due to specific AEs. Table B44 in the submission summarises the TEAEs in the core treatment period with an incidence ≥5% in either group. In addition, Table 16 presents the rates of severe TEAEs from the Open-label Long-term Pool.

Details of the studies included in this pool can be found in Section 6.9.2.1 (page 133) of the submission.

Table 15. TEAEs leading to withdrawal by preferred term, core treatment period, (APTS) - MDD Open-label Long-term Pool

Preferred term	Vortioxetine 2.5-10mg		Vortioxetine 15-20mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Number of patients	1,443		1,144		2,587	
Patient-years exposure	1,097		775.4		1,873	
Patients with adverse events	89	(6.2)	120	(10.5)	209	(8.1)
Nausea	14	(1.0)	31	(2.7)	45	(1.7)
Depression	10	(0.7)	5	(0.4)	15	(0.6)
Vomiting	3	(0.2)	11	(1.0)	14	(0.5)
Headache	2	(0.1)	8	(0.7)	10	(0.4)
Weight increased	2	(0.1)	6	(0.5)	8	(0.3)
Insomnia	2	(0.1)	5	(0.4)	7	(0.3)
Anxiety	5	(0.3)	1	(<0.1)	6	(0.2)
Fatigue	1	(<0.1)	5	(0.4)	6	(0.2)
Somnolence	5	(0.3)	1	(<0.1)	6	(0.2)
Agitation	2	(0.1)	2	(0.2)	4	(0.2)
Dizziness	3	(0.2)	1	(<0.1)	4	(0.2)
Aspartate aminotransferase increased	1	(<0.1)	2	(0.2)	3	(0.1)
Constipation	0		3	(0.3)	3	(0.1)
Diarrhoea	2	(0.1)	1	(<0.1)	3	(0.1)
Disturbance in attention	2	(0.1)	1	(<0.1)	3	(0.1)
Dry mouth	2	(0.1)	1	(<0.1)	3	(0.1)
Dyspepsia	1	(<0.1)	2	(0.2)	3	(0.1)
Flatulence	1	(<0.1)	2	(0.2)	3	(0.1)
Gamma-glutamyltransferase increased	3	(0.2)	0		3	(0.1)
Hepatic enzyme	0		3	(0.3)	3	(0.1)

Preferred term	Vortioxetine 2.5-10mg		Vortioxetine 15-20mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
increased						
Intentional overdose	2	(0.1)	1	(<0.1)	3	(0.1)
Pruritus generalised	1	(<0.1)	2	(0.2)	3	(0.1)
Suicidal ideation	3	(0.2)	0		3	(0.1)
Breast cancer female (SS)	0		2	(0.2)	2	(0.1)
Alanine aminotransferase increased	1	(<0.1)	1	(<0.1)	2	(<0.1)
Arthralgia	0		2	(0.2)	2	(<0.1)
Atrial fibrillation	1	(<0.1)	1	(<0.1)	2	(<0.1)
Blood creatine phosphokinase increased	1	(<0.1)	1	(<0.1)	2	(<0.1)
Blood triglycerides increased	1	(<0.1)	1	(<0.1)	2	(<0.1)
Depressive symptom	2	(0.1)	0		2	(<0.1)
Electrocardiogram qt prolonged	2	(0.1)	0		2	(<0.1)
Fall	2	(0.1)	0		2	(<0.1)
Irritability	2	(0.1)	0		2	(<0.1)
Liver function test abnormal	1	(<0.1)	1	(<0.1)	2	(<0.1)
Major depression	2	(0.1)	0		2	(<0.1)
Memory impairment	1	(<0.1)	1	(<0.1)	2	(<0.1)
Suicide attempt	1	(<0.1)	1	(<0.1)	2	(<0.1)
White blood cell count decreased	2	(0.1)	0		2	(<0.1)
Abortion induced (SS)	1	(0.1)	0		1	(<0.1)
Metrorrhagia (SS)	0		1	(0.1)	1	(<0.1)
Pregnancy (SS)	0		1	(0.1)	1	(<0.1)
Pregnancy test positive (SS)	1	(0.1)	0		1	(<0.1)
Abdominal discomfort	0		1	(<0.1)	1	(<0.1)
Abdominal pain upper	1	(<0.1)	0		1	(<0.1)
Abnormal behaviour	1	(<0.1)	0		1	(<0.1)
Accidental overdose	0		1	(<0.1)	1	(<0.1)
Alcohol abuse	1	(<0.1)	0		1	(<0.1)

Preferred term	Vortioxetine 2.5-10mg		Vortioxetine 15-20mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Blood alkaline phosphatase increased	1	(<0.1)	0		1	(<0.1)
Blood creatinine increased	0		1	(<0.1)	1	(<0.1)
Blood pressure increased	1	(<0.1)	0		1	(<0.1)
Breast cancer stage i	0		1	(<0.1)	1	(<0.1)
Chest pain	1	(<0.1)	0		1	(<0.1)
Cholecystitis acute	0		1	(<0.1)	1	(<0.1)
Cholecystitis chronic	1	(<0.1)	0		1	(<0.1)
Cholelithiasis	0		1	(<0.1)	1	(<0.1)
Confusional state	1	(<0.1)	0		1	(<0.1)
Conjunctivitis	1	(<0.1)	0		1	(<0.1)
Crying	1	(<0.1)	0		1	(<0.1)
Depressed mood	1	(<0.1)	0		1	(<0.1)
Derealisation	0		1	(<0.1)	1	(<0.1)
Dermatitis bullous	0		1	(<0.1)	1	(<0.1)
Dermatitis herpetiformis	1	(<0.1)	0		1	(<0.1)
Diverticulitis	1	(<0.1)	0		1	(<0.1)
Emphysema	0		1	(<0.1)	1	(<0.1)
Feeling jittery	1	(<0.1)	0		1	(<0.1)
Femoral neck fracture	1	(<0.1)	0		1	(<0.1)
Fibromyalgia	0		1	(<0.1)	1	(<0.1)
Flat affect	0		1	(<0.1)	1	(<0.1)
Food craving	0		1	(<0.1)	1	(<0.1)
Gastric ulcer	1	(<0.1)	0		1	(<0.1)
Gastroenteritis	1	(<0.1)	0		1	(<0.1)
Hallucination, auditory	1	(<0.1)	0		1	(<0.1)
Hot flush	0		1	(<0.1)	1	(<0.1)
Hyperhidrosis	0		1	(<0.1)	1	(<0.1)
Hypertension	1	(<0.1)	0		1	(<0.1)
Hypervigilance	1	(<0.1)	0		1	(<0.1)
Increased appetite	0		1	(<0.1)	1	(<0.1)
Influenza	1	(<0.1)	0		1	(<0.1)
Influenza like illness	0		1	(<0.1)	1	(<0.1)

Preferred term	Vortioxetine 2.5-10mg		Vortioxetine 15-20mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Ingrowing nail	0		1	(<0.1)	1	(<0.1)
Lip swelling	0		1	(<0.1)	1	(<0.1)
Malignant melanoma	0		1	(<0.1)	1	(<0.1)
Mania	0		1	(<0.1)	1	(<0.1)
Mastitis	1	(<0.1)	0		1	(<0.1)
Meniscus lesion	1	(<0.1)	0		1	(<0.1)
Monocyte count increased	1	(<0.1)	0		1	(<0.1)
Muscle strain	0		1	(<0.1)	1	(<0.1)
Musculoskeletal chest pain	0		1	(<0.1)	1	(<0.1)
Musculoskeletal pain	0		1	(<0.1)	1	(<0.1)
Neutrophil count decreased	1	(<0.1)	0		1	(<0.1)
Nightmare	1	(<0.1)	0		1	(<0.1)
Palpitations	1	(<0.1)	0		1	(<0.1)
Phlebitis superficial	0		1	(<0.1)	1	(<0.1)
Pneumonia	0		1	(<0.1)	1	(<0.1)
Poor quality sleep	0		1	(<0.1)	1	(<0.1)
Pruritus	0		1	(<0.1)	1	(<0.1)
Psoriasis	1	(<0.1)	0		1	(<0.1)
Rash erythematous	0		1	(<0.1)	1	(<0.1)
Rhinorrhoea	0		1	(<0.1)	1	(<0.1)
Road traffic accident	1	(<0.1)	0		1	(<0.1)
Sedation	0		1	(<0.1)	1	(<0.1)
Sensation of foreign body	0		1	(<0.1)	1	(<0.1)
Sleep apnoea syndrome	0		1	(<0.1)	1	(<0.1)
Sports injury	0		1	(<0.1)	1	(<0.1)
Swelling face	0		1	(<0.1)	1	(<0.1)
Syncope	1	(<0.1)	0		1	(<0.1)
Tearfulness	1	(<0.1)	0		1	(<0.1)
Tension	1	(<0.1)	0		1	(<0.1)
Throat tightness	1	(<0.1)	0		1	(<0.1)
Tinnitus	1	(<0.1)	0		1	(<0.1)

Preferred term	Vortioxetine 2.5-10mg		Vortioxetine 15-20mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Transient ischaemic attack	0		1	(<0.1)	1	(<0.1)
Tremor	1	(<0.1)	0		1	(<0.1)
Urinary retention	1	(<0.1)	0		1	(<0.1)
Urticaria	0		1	(<0.1)	1	(<0.1)
Vertigo	0		1	(<0.1)	1	(<0.1)
Visual impairment	1	(<0.1)	0		1	(<0.1)
Weight decreased	1	(<0.1)	0		1	(<0.1)
Wolff-Parkinson-White syndrome	1	(<0.1)	0		1	(<0.1)

(SS) Sex Specific Dictionary: MedDRA 14.1

Lu AA21004 IDB Final ST_WAE_PT_C_OL 10MAR2015:15:00:27 SADs Build Number: 14.0

Table 16. Severe TEAEs by Preferred Term, Core Treatment Period (APTS) - MDD Open-label Long-term Pool

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Number of patients	1443		1144		2587	
Patient-years exposure	1097		775.4		1873	
Patients with adverse events	135	(9.4)	95	(8.3)	230	(8.9)
Nausea	16	(1.1)	11	(1.0)	27	(1.0)
Headache	9	(0.6)	5	(0.4)	14	(0.5)
Insomnia	7	(0.5)	6	(0.5)	13	(0.5)
Vomiting	6	(0.4)	4	(0.3)	10	(0.4)
Accidental overdose	8	(0.6)	1	(<0.1)	9	(0.3)
Diarrhoea	6	(0.4)	1	(<0.1)	7	(0.3)
Dizziness	5	(0.3)	2	(0.2)	7	(0.3)
Migraine	4	(0.3)	3	(0.3)	7	(0.3)
Bronchitis	2	(0.1)	4	(0.3)	6	(0.2)
Depression	4	(0.3)	2	(0.2)	6	(0.2)
Fatigue	2	(0.1)	4	(0.3)	6	(0.2)
Influenza	4	(0.3)	2	(0.2)	6	(0.2)

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Back pain	3	(0.2)	2	(0.2)	5	(0.2)
Blood creatine phosphokinase increased	3	(0.2)	2	(0.2)	5	(0.2)
Somnolence	4	(0.3)	1	(<0.1)	5	(0.2)
Suicidal ideation	3	(0.2)	2	(0.2)	5	(0.2)
Fall	4	(0.3)	0		4	(0.2)
Male sexual dysfunction (SS)	0		1	(0.3)	1	(0.1)
Anxiety	1	(<0.1)	2	(0.2)	3	(0.1)
Constipation	1	(<0.1)	2	(0.2)	3	(0.1)
Pneumonia	0		3	(0.3)	3	(0.1)
Suicide attempt	2	(0.1)	1	(<0.1)	3	(0.1)
Upper respiratory tract infection	2	(0.1)	1	(<0.1)	3	(0.1)
Abdominal pain	1	(<0.1)	1	(<0.1)	2	(<0.1)
Abdominal pain upper	2	(0.1)	0		2	(<0.1)
Ankle fracture	1	(<0.1)	1	(<0.1)	2	(<0.1)
Appendicitis	2	(0.1)	0		2	(<0.1)
Asthma	0		2	(0.2)	2	(<0.1)
Dry mouth	0		2	(0.2)	2	(<0.1)
Dyspepsia	2	(0.1)	0		2	(<0.1)
Gastroenteritis	1	(<0.1)	1	(<0.1)	2	(<0.1)
Haemorrhoids	0		2	(0.2)	2	(<0.1)
Hot flush	1	(<0.1)	1	(<0.1)	2	(<0.1)
Increased appetite	1	(<0.1)	1	(<0.1)	2	(<0.1)
Irritability	1	(<0.1)	1	(<0.1)	2	(<0.1)
Nasopharyngitis	2	(0.1)	0		2	(<0.1)
Nephrolithiasis	1	(<0.1)	1	(<0.1)	2	(<0.1)
Night sweats	0		2	(0.2)	2	(<0.1)
Pain in extremity	2	(0.1)	0		2	(<0.1)
Panic attack	2	(0.1)	0		2	(<0.1)
Pharyngitis streptococcal	0		2	(0.2)	2	(<0.1)
Plantar fasciitis	0		2	(0.2)	2	(<0.1)
Sedation	0		2	(0.2)	2	(<0.1)
Toothache	1	(<0.1)	1	(<0.1)	2	(<0.1)
Abortion spontaneous (SS)	0		1	(0.1)	1	(<0.1)

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Amenorrhoea (SS)	1	(0.1)	0		1	(<0.1)
Breast cancer female (SS)	0		1	(0.1)	1	(<0.1)
Haemorrhagic ovarian cyst (SS)	0		1	(0.1)	1	(<0.1)
Menorrhagia (SS)	0		1	(0.1)	1	(<0.1)
Uterine leiomyoma (SS)	0		1	(0.1)	1	(<0.1)
Vulval abscess (SS)	0		1	(0.1)	1	(<0.1)
Abdominal discomfort	0		1	(<0.1)	1	(<0.1)
Abscess limb	1	(<0.1)	0		1	(<0.1)
Acne cystic	0		1	(<0.1)	1	(<0.1)
Agitation	0		1	(<0.1)	1	(<0.1)
Alcohol abuse	1	(<0.1)	0		1	(<0.1)
Anaemia	0		1	(<0.1)	1	(<0.1)
Antibiotic resistant staphylococcus test positive	1	(<0.1)	0		1	(<0.1)
Arthralgia	0		1	(<0.1)	1	(<0.1)
Arthritis	1	(<0.1)	0		1	(<0.1)
Aspartate aminotransferase increased	0		1	(<0.1)	1	(<0.1)
Asthenia	1	(<0.1)	0		1	(<0.1)
Atrial fibrillation	1	(<0.1)	0		1	(<0.1)
Blood albumin increased	1	(<0.1)	0		1	(<0.1)
Blood triglycerides increased	0		1	(<0.1)	1	(<0.1)
Bradykinesia	0		1	(<0.1)	1	(<0.1)
Breast cancer in situ	1	(<0.1)	0		1	(<0.1)
Breast cancer stage i	0		1	(<0.1)	1	(<0.1)
Bronchitis viral	0		1	(<0.1)	1	(<0.1)
Bruxism	1	(<0.1)	0		1	(<0.1)
Cat scratch disease	1	(<0.1)	0		1	(<0.1)
Cellulitis	1	(<0.1)	0		1	(<0.1)
Cholecystitis	0		1	(<0.1)	1	(<0.1)
Cholecystitis acute	0		1	(<0.1)	1	(<0.1)
Complicated migraine	0		1	(<0.1)	1	(<0.1)
Dental caries	1	(<0.1)	0		1	(<0.1)
Depressive symptom	1	(<0.1)	0		1	(<0.1)

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Disturbance in attention	1	(<0.1)	0		1	(<0.1)
Diverticulitis	1	(<0.1)	0		1	(<0.1)
Dupuytren`s contracture	1	(<0.1)	0		1	(<0.1)
Ear injury	1	(<0.1)	0		1	(<0.1)
Electrocardiogram qt prolonged	1	(<0.1)	0		1	(<0.1)
Femur fracture	1	(<0.1)	0		1	(<0.1)
Fibromyalgia	1	(<0.1)	0		1	(<0.1)
Fibula fracture	1	(<0.1)	0		1	(<0.1)
Flatulence	1	(<0.1)	0		1	(<0.1)
Foot fracture	0		1	(<0.1)	1	(<0.1)
Gastric ulcer	1	(<0.1)	0		1	(<0.1)
Gastritis	1	(<0.1)	0		1	(<0.1)
Gastroenteritis viral	1	(<0.1)	0		1	(<0.1)
Gastrointestinal infection	1	(<0.1)	0		1	(<0.1)
H1N1 influenza	1	(<0.1)	0		1	(<0.1)
Haematoma	1	(<0.1)	0		1	(<0.1)
Hip fracture	1	(<0.1)	0		1	(<0.1)
Hyperglycaemia	0		1	(<0.1)	1	(<0.1)
Hyperhidrosis	0		1	(<0.1)	1	(<0.1)
Ingrowing nail	1	(<0.1)	0		1	(<0.1)
Intentional overdose	0		1	(<0.1)	1	(<0.1)
Laryngitis	1	(<0.1)	0		1	(<0.1)
Latent syphilis	0		1	(<0.1)	1	(<0.1)
Libido increased	1	(<0.1)	0		1	(<0.1)
Ligament sprain	1	(<0.1)	0		1	(<0.1)
Major depression	1	(<0.1)	0		1	(<0.1)
Malignant melanoma	0		1	(<0.1)	1	(<0.1)
Melanosis coli	0		1	(<0.1)	1	(<0.1)
Meniscus lesion	1	(<0.1)	0		1	(<0.1)
Muscle spasms	1	(<0.1)	0		1	(<0.1)
Musculoskeletal pain	0		1	(<0.1)	1	(<0.1)
Onychoclasis	1	(<0.1)	0		1	(<0.1)
Onychomadesis	1	(<0.1)	0		1	(<0.1)

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Osteoarthritis	1	(<0.1)	0		1	(<0.1)
Pancreatitis acute	0		1	(<0.1)	1	(<0.1)
Papilloedema	1	(<0.1)	0		1	(<0.1)
Periarthritis	0		1	(<0.1)	1	(<0.1)
Pharyngitis	1	(<0.1)	0		1	(<0.1)
Post-traumatic neck syndrome	1	(<0.1)	0		1	(<0.1)
Pregnancy of partner	1	(<0.1)	0		1	(<0.1)
Procedural pain	0		1	(<0.1)	1	(<0.1)
Pyrexia	1	(<0.1)	0		1	(<0.1)
Retinopathy hypertensive	1	(<0.1)	0		1	(<0.1)
Road traffic accident	1	(<0.1)	0		1	(<0.1)
Sciatica	1	(<0.1)	0		1	(<0.1)
Seasonal allergy	0		1	(<0.1)	1	(<0.1)
Sinusitis	0		1	(<0.1)	1	(<0.1)
Slow speech	0		1	(<0.1)	1	(<0.1)
Sports injury	0		1	(<0.1)	1	(<0.1)
Stress urinary incontinence	0		1	(<0.1)	1	(<0.1)
Supraventricular tachycardia	1	(<0.1)	0		1	(<0.1)
Syncope	1	(<0.1)	0		1	(<0.1)
Tachycardia paroxysmal	1	(<0.1)	0		1	(<0.1)
Tension headache	1	(<0.1)	0		1	(<0.1)
Thyroiditis	1	(<0.1)	0		1	(<0.1)
Tibia fracture	1	(<0.1)	0		1	(<0.1)
Tonsillitis	0		1	(<0.1)	1	(<0.1)
Tooth abscess	1	(<0.1)	0		1	(<0.1)
Tooth extraction	1	(<0.1)	0		1	(<0.1)
Transient ischaemic attack	0		1	(<0.1)	1	(<0.1)
Umbilical hernia, obstructive	1	(<0.1)	0		1	(<0.1)
Upper gastrointestinal haemorrhage	1	(<0.1)	0		1	(<0.1)
Upper respiratory tract inflammation	1	(<0.1)	0		1	(<0.1)
Urinary retention	1	(<0.1)	0		1	(<0.1)
Urinary tract infection	0		1	(<0.1)	1	(<0.1)
Vertigo	0		1	(<0.1)	1	(<0.1)

Preferred Term	Vortioxetine 2.5-10 mg		Vortioxetine 15-20 mg		Vortioxetine total	
	n	(%)	n	(%)	n	(%)
Vertigo positional	0		1	(<0.1)	1	(<0.1)
Viral infection	0		1	(<0.1)	1	(<0.1)
Viral upper respiratory tract infection	0		1	(<0.1)	1	(<0.1)
Vision blurred	1	(<0.1)	0		1	(<0.1)
Weight increased	0		1	(<0.1)	1	(<0.1)
Wolff-parkinson-white syndrome	1	(<0.1)	0		1	(<0.1)
Wrist fracture	0		1	(<0.1)	1	(<0.1)
(SS) Sex Specific Dictionary: MedDRA 14.1						
Lu AA21004 IDB Final ST_AE_SEV_PT_C_OL 07FEB2014:15:07:16 SADs Build Number: 14.0						

Meta-analyses (external)

Lundbeck is also aware of three externally-produced meta-analyses (Pae 2014[16], Berhan 2014[17] and Citrome 2014[18]).

The company believes the analysis undertaken by Pae is fundamentally flawed as it includes active reference arms as if they were active comparators. For reasons already explained in this document and in the main submission section 1.4.1 (*"Active reference arms do not allow valid head-to-head comparison")* section 2.8.2 *("The use of active references"*) of the main submission, the comparison of efficacy between active reference and vortioxetine is invalid and the results cannot be considered reliable.

Meta-regression

In addition to the three active comparator trials that have been undertaken to date as part of the vortioxetine development programme, Lundbeck has published an indirect comparison in the full MDD population a meta-regression of placebo-controlled short-term trials (Llorca 2015)[19].

The conclusions of the Llorca analysis, concentrating on comparators widely use in the UK, are as follows:

- There are no statistically significant differences in efficacy (either remission or response) between vortioxetine and escitalopram, venlafaxine, sertraline and duloxetine
- With respect to withdrawals due to adverse events, there are no statistically significant differences between vortioxetine and duloxetine and escitalopram, but vortioxetine is superior to sertraline and venlafaxine.

Analyses included in reimbursement submissions to authorities

Further comparative analyses have been undertaken where necessary to meet the evidence base requirements of local HTA agencies as below:

- The Pharmaceutical Benefits Advisory Committee (PBAC), Australia; details of these are included in the public summary document[22].
- The Canadian Agency for Drugs and Technologies in Health (CADTH); additional information is available on request[23].

Summary

All meta-analyses and evidence synthesis known to Lundbeck are detailed above. To reiterate, these analyses were undertaken using data available in the full MDD population. As stated already in this document and in Section 6.1 of the main submission, efficacy is not transferable between treatment lines whereas tolerability is likely to be. Therefore these analyses only provide relative tolerability to inform the comparison between vortioxetine and other compounds in the switch population.

Indirect treatment comparisons

A16. For the indirect treatment comparison (ITC) analysis, the company assumed that the different definitions of remission across trials (using different depression rating scales) were equivalent and could be pooled in the analysis. Please provide justification for this assumption.

In the studies in which remission rates were reported, remission is defined as the proportion of patients who achieved a depressive symptom score below a threshold value on the rating scale used. The studies that reported remission used either HAM-D or MADRS, and remission was defined as a HAM-D score ≤7 or a MADRS ≤10, which are commonly used definitions[24;25].

*A17. **Priority question**: In the company's submission, the results of its ITC analysis were presented in terms of risk differences. Please present results from the ITC analysis in terms of relative risks.*

ITC parameter inputs: remission rates

Table 17 shows the relative risks of remission calculated from raw remission rates reported in the studies included in the ITC.

Table 17. ITC of remission rates: raw data parameter inputs

Study ID	Parameter	Vortioxetine	Agomel-atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
REVIVE	Remission rate	40.5% (N=252)	29.5% (N=241)	-	-	-	-
	RR vs. vortioxetine	-	0.73	-	-	-	-
	95% CI	-	[0.57; 0.93]	-	-	-	-
Kasper 2013	Remission rate	-	27.9% (N=80)	24.5% (N=96)	-	-	-
	RR vs. agomelatine	-	-	0.91	-	-	-
	95% CI	-	-	[0.55; 1.49]	-	-	-
Rush 2006 (STAR*D)	Remission rate	-	-	17.6% (N=238)	24.8% (N=250)	21.3% (N=239)	-
	RR vs. sertraline	-	-	-	1.41	1.21	-
	95% CI	-	-	-	[0.99; 1.99]	[0.84; 1.75]	-
Lenox-Smith 2008	Remission rate	-	-	-	36.8% (N=57)	-	27.3% (N=55)
	RR vs. venlafaxine	-	-	-	-	-	0.74
	95% CI	-	-	-	-	-	[0.43; 1.28]

RR: relative risk; CI: confidence interval; N: number of patients; XR: extended release; SR: sustained release

ITC parameter estimates: remission rates

Table 18 shows the remission rates estimated by adjusted indirect comparison using relative risks.

Table 18. ITC of remission rates: estimates by adjusted indirect comparison using relative risks

	Vortioxetine	Agomel-atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
Direct comparison of agomelatine vs. vortioxetine through REVIVE						
Remission rate	40.5%	29.5%	-	-	-	-
RR vs. vortioxetine	-	0.73	-	-	-	-
95% CI	-	[0.57; 0.93]	-	-	-	-
Adjusted indirect comparison of sertraline vs. vortioxetine through REVIVE and Kasper 2013						
Remission rate	40.5%	-	26.8%	-	-	-
RR vs. vortioxetine	-	-	0.66	-	-	-
95% CI	-	-	[0.38; 1.15]	-	-	-
Adjusted indirect comparison of venlafaxine XR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Remission rate	40.5%	-	-	37.6%	-	-
RR vs. vortioxetine	-	-	-	0.93	-	-
95% CI	-	-	-	[0.48; 1.79]	-	-
Adjusted indirect comparison of bupropion SR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Remission rate	40.5%	-	-	-	32.4%	-
RR vs. vortioxetine	-	-	-	-	0.80	-
95% CI	-	-	-	-	[0.41; 1.56]	-
Adjusted indirect comparison of citalopram vs. vortioxetine through REVIVE, Kasper 2013, STAR*D and Lenox-Smith 2008						
Remission rate	40.5%	-	-	-	-	27.8%
RR vs. vortioxetine	-	-	-	-	-	0.69
95% CI	-	-	-	-	-	[-0.29; 1.62]

RR: relative risk; CI: confidence interval; XR : extended release; SR: sustained release.

As reported in Table 18, the remission rate associated with vortioxetine was numerically greater than that for sertraline, venlafaxine, bupropion and citalopram, but not statistically significantly so. Using relative risks instead of risk differences slightly reduced the differences in estimated remission rates between vortioxetine and the comparators.

ITC parameter inputs: withdrawal rates due to adverse events

Table 19 shows the relative risks of withdrawal due to AEs calculated from raw withdrawal rates reported in the studies included in the ITC.

Table 19. ITC of withdrawal rates: raw data parameter inputs

Study ID	Parameter	Vortioxetine	Agomel-atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
REVIVE	Withdrawal rate due to AEs	5.9% (N=253)	9.5% (N=242)	-	-	-	-
	RR vs. vortioxetine	-	1.60	-	-	-	-
	95% CI	-	[0.86; 3.00]	-	-	-	-
Kasper 2013	Withdrawal rate due to AEs	-	3.7% (N=80)	12.2% (N=96)	-	-	-
	RR vs. agomelatine	-	-	3.33	-	-	-
	95% CI	-	-	[0.97; 11.40]	-	-	-
Rush 2006 (STAR*D)	Withdrawal rate due to AEs	-	-	21.0% (N=238)	21.2% (N=250)	27.2% (N=239)	-
	RR vs. sertraline	-	-	-	1.01	1.29	-
	95% CI	-	-	-	[0.72; 1.42]	[0.94; 1.79]	-
Lenox-Smith 2008	Withdrawal rate due to AEs	-	-	-	5.5% (N=200)	-	5.3% (N=206)
	RR vs. venlafaxine	-	-	-	-	-	0.97
	95% CI	-	-	-	-	-	[0.43; 2.19]

RR: relative risk; CI: confidence interval; N: number of patients; XR : extended release; SR: sustained release

Table 20 shows the withdrawal rates due to AEs estimated by adjusted indirect comparison using relative risks.

Table 20. ITC of withdrawal rates due to AEs: estimates by adjusted indirect comparison using relative risks

	Vortioxetine	Agomel-atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
Direct comparison of agomelatine vs. vortioxetine through REVIVE						
Withdrawal rate due to AEs	5.9%	9.5%	-	-	-	-
RR vs. vortioxetine	-	1.60	-	-	-	-
95% CI	-	[0.86; 3.00]	-	-	-	-
Adjusted indirect comparison of sertraline vs. vortioxetine through REVIVE and Kasper 2013						
Withdrawal rate due to AEs	5.9%	-	31.6%	-	-	-
RR vs. vortioxetine	-	-	5.33	-	-	-
95% CI	-	-	[1.34; 21.21]	-	-	-
Adjusted indirect comparison of venlafaxine XR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Withdrawal rate due to AEs	5.9%	-	-	31.9%	-	-
RR vs. vortioxetine	-	-	-	5.38	-	-
95% CI	-	-	-	[1.30; 22.32]	-	-
Adjusted indirect comparison of bupropion SR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Withdrawal rate due to AEs	5.9%	-	-	-	40.7%	-
RR vs. vortioxetine	-	-	-	-	6.87	-
95% CI	-	-	-	-	[1.66; 28.39]	-
Adjusted indirect comparison of citalopram vs. vortioxetine through REVIVE, Kasper 2013, STAR*D and Lenox-Smith 2008						
Withdrawal rate due to AEs	5.9%	-	-	-	-	30.9%
RR vs. vortioxetine	-	-	-	-	-	5.22
95% CI	-	-	-	-	-	[1.01; 26.88]

RR: relative risk; CI: confidence interval; XR : extended release; SR: sustained release

Using relative risks in the adjusted ITC, the estimated withdrawal rates due to AEs were statistically significantly higher for sertraline, venlafaxine, bupropion and citalopram than vortioxetine. These rates are also higher than those derived using risk difference and odds ratios.

A18. ***Priority question****: Results for the company's ITC are provided for remission and withdrawal rates because of adverse events only.*

a. Please state which efficacy and safety outcomes were excluded from the ITC, and why.

Table B27 of the main submission document reports the primary and additional/secondary endpoints reported in each of the studies included in the network. No endpoints additional to rates of remission and withdrawals due to adverse events were consistently reported across all studies and hence they could not be included in the ITC.

In light of this the response to questions 18b and 18c both have limitations. For the former, no comparison could be made to citalopram as Lenox-Smith (2008) did not report response. For the latter, assumptions have been made to allow comparative analyses of change from baseline symptom scores. These are discussed in further detail below.

b. Please also provide results from similar analyses using response rate as the outcome.

ITC parameter inputs: response rates

Response rates were extracted from the REVIVE study report and from the Kasper 2013 and Rush 2006 (STAR*D) publications. Different scales were used in each study, and no response data were reported in Lenox-Smith 2008. Hence, comparative response rates could not be calculated versus citalopram.

The following scales and definitions used are summarised below:

Study ID	Scale	Definition
REVIVE	MADRS	At least 50% reduction from baseline MADRS (week 8 data)
Kasper 2013	$HAM\text{-}D_{17}$	At least 50% reduction from baseline HAM-D17
Rush 2006 (STAR*D)	$QIDS\text{-}SR_{16}$	At least 50% reduction from treatment step entry in QIDS-SR16
Lenox-Smith 2008	No results available on response	

Using the raw response rate data from the three studies, Table 21 shows the calculated risk differences, relative risks and odds ratios of response to support estimation of adjusted response rates in the ITC.

Table 21. ITC of response rates: raw data parameter inputs

Study ID	Parameter	Vortioxetine	Agomel-atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
REVIVE	Remission rate	61.5% (N=252)	47.3% (N=241)	-	-	-	-
	RD vs. vortioxetine	-	-14.2%	-	-	-	-
	95% CI	-	[-22.9; -5.5]	-	-	-	-
	RR vs. vortioxetine	-	0.77	-	-	-	-
	95% CI	.	[0.65; 0.91]	-	-	-	-
	OR vs. vortioxetine	.	0.56	-	-	-	-
	95% CI	.	[0.39; 0.80]	-	-	-	-
Kasper 2013	Remission rate	-	67.5% (N=80)	55.2% (N=96)	-	-	-
	RD vs. agomelatine	-	-	-12.3%	-	-	-
	95% CI	-	-	[-26.6; 2.0]	-	-	-
	RR vs. agomelatine	-	-	0.82	-	-	-
	95% CI	-	-	[0.65; 1.04]	-	-	-
	OR vs. agomelatine	-	-	0.59	-	-	-
	95% CI	-	-	[0.32; 1.10]	-	-	-
Rush 2006 (STAR*D)	Remission rate	-	-	26.7% (N=236)	28.2% (N=248)	26.1% (N=238)	-
	RD vs. sertraline	-	-	-	1.5%	-0.6%	-
	95% CI	-	-	-	[-6,4; 9.5]	[-8.6; 7.3]	-
	RR vs. sertraline	-	-	-	1.06	0.98	-
	95% CI	-	-	-	[0.79; 1.41]	[0.72; 1.32]	-
	OR vs. sertraline	-	-	-	1.08	0.97	-
	95% CI	-	-	-	[0.72; 1.61]	[0.64; 1.46]	-

RD: risk difference; RR: relative risk; OR: odds ratio; CI: confidence interval; N: number of patients; XR : extended release; SR: sustained release

Table 22 shows the estimated response rates for sertraline, venlafaxine and bupropion by adjusted indirect comparison using risk differences, relative risks and odds ratios as the input statistics.

Table 22. ITC of response rates: estimates by adjusted indirect comparison using risk differences, relative risks and odds ratios

	Vortioxetine	Agomel-atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
Direct comparison of agomelatine vs. vortioxetine through REVIVE						
Response rate	61.5%	47.3%	-	-	-	-
RD vs. vortioxetine	-	-14.2%	-	-	-	-
95% CI	-	[-22,9; -5.5]	-	-	-	-
RR vs. vortioxetine	-	0.77	-	-	-	-
95% CI	-	[0.65; 0.91]	-	-	-	-
OR vs. vortioxetine	-	0.56	-	-	-	-
95% CI	-	[0.39; 0.80]	-	-	-	-
Adjusted indirect comparison of sertraline vs. vortioxetine through REVIVE and Kasper 2013						
Response rate from RD	61.5%	-	35.0%	-	-	-
RD vs. vortioxetine	-	-	-26.5%	-	-	-
95% CI	-	-	[-43.2; -9,8]	-	-	-
Response rate from RR	-	-	38.8%	-	-	-
RR vs. vortioxetine	-	-	0.63	-	-	-
95% CI	-	-	[0.47; 0.84]	-	-	-
Response rate from OR	-	-	34.7%	-	-	-
OR vs. vortioxetine	-	-	0.33	-	-	-
95% CI	-	-	[0.16; 0.68]	-	-	-
Adjusted indirect comparison of venlafaxine XR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Response rate from RD	61.5%	-	-	36.5%	-	-
RD vs. vortioxetine	-	-	-	-25.0%	-	-
95% CI	-	-	-	[-43.5; -6,5]	-	-
Response rate from RR	-	-	-	41.1%	-	-
RR vs. vortioxetine	-	-	-	0.67	-	-
95% CI	-	-	-	[0.45; 1.01]	-	-
Response rate from OR	-	-	-	36.3%	-	-
OR vs. vortioxetine	-	-	-	0.36	-	-
95% CI	-	-	-	[0.16; 0.81]	-	-
Adjusted indirect comparison of bupropion SR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
Response rate from RD	61.5%	-	-	-	34.4%	-
RD vs. vortioxetine	-	-	-	-	-27.1%	-
95% CI	-	-	-	-	[-45.7; -8.6]	-
Response rate from RR	-	-	-	-	38.1%	-
RR vs. vortioxetine	-	-	-	-	0.62	-
95% CI	-	-	-	-	[0.41; 0.94]	-
Response rate from OR	-	-	-	-	33.8%	-

	Vortioxetine	Agomel-atine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
OR vs. vortioxetine	-	-	-	-	0.32	-
95% CI	-	-	-	-	[0.14; 0.73]	-

RD: risk difference; RR: relative risk; OR: odds ratio; CI: confidence interval; XR : extended release; SR: sustained release

In the adjusted ITC using risk differences, odds ratio and relative risks, the estimated response rates were higher for vortioxetine than sertraline, venlafaxine and bupropion. These differences were statistically significant for all the comparisons using risk difference and odds ratio and for all the comparisons except with venlafaxine when using relative risks. No response rates could be estimated for citalopram due to the absence of response data in Lenox-Smith 2008.

c. Please also provide results from similar analyses using change in depression rating scales from baseline as the outcome (for example, by performing a standardised mean difference analysis). If possible, please provide results for both frequentist and Bayesian models.

The standardised mean difference (SMD) of change from baseline is not strictly calculable in all of the four studies from the data reported. Lundbeck has attempted to implement these requested analyses with the data available by making assumptions as necessary.

The main role of the SMD is to facilitate combining results from trials which have reported outcomes measured on different continuous scales. Here the results are derived using a different scale for each study. The scales as well as the outcome measures available in the publications are presented in Table 23.

Table 23. Comparison of endpoint measurements in studies included in ITC

Study	Scale	Measure	Time point	Analysis
REVIVE	MADRS	Change from baseline	Week 8	MMRM
Kasper 2013	HAM-D_{17}	Score at endpoint	Week 6	Descriptive, LOCF
Rush 2006 (STAR*D)	QIDS-SR_{16}	Score at endpoint	Week 14	Descriptive
Lenox-Smith 2008	HAM-D_{21}	Change from baseline	Week 12	ANCOVA LOCF

Cohen's d SMD

As the number of patients in each arm is between 80 and 252, SMDs between arms were computed using Cohen's d formula, rather than Hedge's G, as:

$$SMD = \frac{Mean_B - Mean_A}{\sqrt{\frac{(N_B - 1)^* SD_B^2 + (N_A - 1)^* SD_A^2}{N_B + N_A - 2}}}$$

The corresponding standard deviation (SD) was computed as:

$$SD_{SMD} = \sqrt{\frac{N_B + N_A}{N_B * N_A} + \frac{SMD^2}{2 * N_B + 2 * N_A}}$$

Data inputs

The data inputs used to perform the ITC are described below.

REVIVE data

Using Panel 22 from REVIVE CSR "Analysis of change from baseline in MADRS total score at week 8 (FAS, MMRM)", the SD per treatment arm was estimated as the product of the SE per treatment arm by the square root of the number of patients in the treatment arm and the effect size can then be computed using the formula described in previous section.

Table 24. Effect size estimation: REVIVE, using MADRS change from baseline

	Vortioxetine	Agomelatine
N	*220*	*190*
Change from baseline – mean	*-16.53*	*-14.38*
Change from baseline – SE	*0.48*	*0.51*
Change from baseline – SD	7.12	7.03
Difference agomelatine vs. vortioxetine		
Mean difference		2.15
Common SD		7.08
Effect size agomelatine vs. vortioxetine		
Effect size		0.304
SE of effect size		0.100
95% CI lower bound		0.109
95% CI upper bound		0.499

Data in *italics* are directly extracted from the source.

Kasper 2013 data

Results on change from baseline are not available from Kasper 2013. However, an SMD was estimated by making the following assumptions, while acknowledging their limitations.

Assumption 1: The patients in both arms have comparable baseline values.

This assumption is supported by the fact that, as expected by the randomisation process, the mean MADRS baseline values on the whole population (Table 2 in Kasper 2010) are very similar with small and similar standard deviation (SD): 26.1 (SD=2.8) and 26.5 (SD=3) for agomelatine and sertraline, respectively.

Assumption 2: The SD of change from baseline = SD of value at endpoint.

This was observed to be the case in the REVIVE trial. The SDs of the MADRS total score at week 8 (FAS, OC cf. Table 31 of REVIVE CSR) are 7.80 and 7.55, respectively, for the vortioxetine and agomelatine arms. The corresponding SDs of change from baseline on MADRS at week 8 (FAS, OC cf. Table 31 of REVIVE CSR) are 7.65 and 7.35.

Let us therefore assume that the SMD of change from baseline is equal to the SMD of value at endpoint.

Using Tables 3 and 4 from Kasper 2013, the effect size is estimated as shown in Table 25.

Table 25. Effect size estimation: Kasper 2013, using HAM-D_{17} change from baseline

	Agomelatine	Sertraline
N	*80*	*96*
Value at endpoint – mean	*11.1*	*13*
Value at endpoint – SD	*7*	*8.7*
Difference sertraline vs. agomelatine		
Mean difference		1.9
Common SD		7.97
Effect size sertraline vs. agomelatine		
Effect size		0.238
SE of effect size		0.152
95% CI lower bound		-0.059
95% CI upper bound		0.536

Data in *italics* are directly extracted from the source.

Rush 2006 (STAR*D) data

As with Kasper 2013, results on change from baseline are not available in the Rush 2006 publication.

Assumption 1: The patients of both arms have comparable baseline values.

This assumption is supported by the fact that, as expected by the randomisation process, the mean QIDS-SR_{16} baseline values on the whole population (Table 1 in Rush 2006) are very similar with small and similar SDs : 13.3 (SD=4.7) and 13.1 (SD=5) and 13.2 (SD=4.9) for sertraline, venlafaxine and bupropion, respectively.

Assumption 2: The SD of change from baseline = SD of value at endpoint.

As with the Kasper 2013 data above, this assumption is made by analogy with data from REVIVE.

Let us therefore assume that the SMD of change from baseline is equal to the SMD of value at endpoint. Using data from Rush 2006, the effect size is estimated as shown in Table 26.

Table 26. Effect size estimation: Rush 2006 (STAR*D), using QIDS-SR$_{16}$ change from baseline

	Sertraline	Venlafaxine	Bupropion
N	*237*	*248*	*239*
Value at endpoint – mean	*10.1*	*10.2*	*10.5*
Value at endpoint – SD	*5.9*	*6.1*	*6*
Difference vs. sertraline			
Mean difference		0.1	0.4
Common SD		6.00	5.95
Effect size vs. sertraline			
Effect size		0.017	0.067
SE of effect size		0.091	0.092
95% CI lower bound		-0.161	-0.113
95% CI upper bound		0.195	0.247

Data in *italics* are directly extracted from the source.

Lenox-Smith 2008 data

In the Lenox-Smith 2008 publication (Efficacy and primary analyses, page 116), only the change from baseline by treatment arm and the P-value of the difference between arms are provided.

Assumption 1: the P-value is assumed to come from a simple *t* test.

The *t* statistic is obtained from the P-value and the degrees of freedom (DF). The standard error of the difference in means is then obtained as:

SE=MD/*t* , where MD is the difference in means.

Assumption 2: The SD of change from baseline for each arm are not provided. It is assumed that the SD of change from baseline in the venlafaxine arm is equal to the SD of change from baseline in the citalopram arm.

The common SD was calculated as follows:

$$SD = \frac{SE}{\sqrt{\frac{1}{N_E} + \frac{1}{N_C}}}$$

Table 27. Effect size estimation: Lenox-Smith 2008 (STAR*D), using HAM-D_{21} change from baseline

	Venlafaxine	Citalopram
N	*194*	*202*
Change from baseline – mean	*-17*	*-16.5*
Difference citalopram vs. venlafaxine in change from baseline		
P-value		*0.4778*
t statistic (DF=394)		0.7105
SE		0.7037
Mean difference		0.5
Common SD		7.0
Effect size citalopram vs. venlafaxine		
Effect size		0.071
SE of effect size		0.101
95% CI lower bound		-0.126
95% CI upper bound		0.269

Data in *italics* are directly extracted from the source.

Summary of inputs

The below tables presents a summary of the inputs for the ITC calculated as described in the previous sections.

Table 28. Standardised mean difference of change from baseline on efficacy assessment scales: inputs

Study ID (scale used)	Parameter	Vortioxetine	Agomelatine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
REVIVE (MADRS)	N	252	241	-	-	-	-
	SMD vs. vortioxetine	-	0.304	-	-	-	-
	95% CI	-	[0.109; 0.499]	-	-	-	-
Kasper 2013 ($HAM\text{-}D_{17}$)	N	-	80	96	-	-	-
	SMD vs. agomelatine	-	-	0.238	-	-	-
	95% CI	-	-	[-0.059; 0.536]	-	-	-
Rush 2006 ($QIDS\text{-}SR_{16}$)	N	-	-	237	248	239	-
	SMD vs. sertraline	-	-	-	0.017	0.067	-
	95% CI	-	-	-	[-0.161; 0.195]	[-0.113; 0.247]	-
Lenox-Smith 2008 ($HAM\text{-}D_{21}$)	N	-	-	-	194	-	202
	SMD vs. venlafaxine	-	-	-	-	-	0.071
	95% CI	-	-	-	-	-	[-0.126; 0.269]

SMD: standardised mean difference. A positive SMD favours the reference treatment. CI: confidence interval; N: number of patients

REVIVE and Kasper report effect sizes above 0.2 (clinically detectable), but only REVIVE leads to a significant difference on SMD between treatments. For the two other studies, differences on SMD between treatments were all below 0.2 and non-significant[26].

Results of the ITC using SMDs: frequentist analysis

As for the binary outcomes, Bucher's method was used to perform an adjusted ITC using the estimated SMDs.

Table 29. Adjusted indirect comparison with SMD of change from baseline

	Vortioxetine	Agomelatine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
Direct comparison of agomelatine vs. vortioxetine through REVIVE						
SMD vs. vortioxetine	-	0.304	-	-	-	-
95% CI	-	[0.109; 0.499]	-	-	-	-
Adjusted indirect comparison of sertraline vs. vortioxetine through REVIVE and Kasper 2013						
SMD vs. vortioxetine	-	-	0.542	-	-	-
95% CI	-	-	[0.186; 0.898]	-	-	-
Adjusted indirect comparison of venlafaxine XR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
SMD vs. vortioxetine	-	-	-	0.559	-	-
95% CI	-	-	-	[0.161; 0.957]	-	-
Adjusted indirect comparison of bupropion SR vs. vortioxetine through REVIVE, Kasper 2013 and STAR*D						
SMD vs. vortioxetine	-	-	-	-	0.609	-
95% CI	-	-	-	-	[0.210; 1.008]	-
Adjusted indirect comparison of citalopram vs. vortioxetine through REVIVE, Kasper 2013, STAR*D and Lenox-Smith 2008						
SMD vs. vortioxetine	-	-	-	-	-	0.630
95% CI	-	-	-	-	-	[0.186; 1.074]

SMD: standardised mean difference. A positive SMD favours vortioxetine. CI: confidence interval.

Although the above estimates of SMD are approximations, given the need to make some assumptions where data were missing, statistically significant differences in favour of vortioxetine are observed versus all five included comparators. These differences are seen in spite of the loss of power (squared standard errors add up all along the chain of evidence) resulting from the indirect comparison process.

In terms of magnitude of effect, the difference versus agomelatine exceeds the 0.2 threshold value that normally indicates a clinically detectable difference between treatments, while the difference versus all other treatments exceeds the 0.5 threshold that indicates a “medium” difference between treatments.

Results of the ITC using SMDs: Bayesian analysis

Table 30 summarises the results of the fixed-effect model for SMD of change from baseline comparing vortioxetine to agomelatine, sertraline, venlafaxine, buproprion and citalopram, respectively. The results are consistent with the frequentist analysis undertaken using the Bucher methodology.

Table 30. Bayesian indirect comparison with SMD of change from baseline (fixed effect)

TT1	vs	TT2	Median SMD	95% CrI
Vortioxetine	vs	Agomelatine	-0.304	[-0.499;-0.108]
Vortioxetine	vs	Sertraline	-0.541	[-0.899;-0.182]

TT1	vs	TT2	Median SMD	95% CrI
Vortioxetine	vs	Venlafaxine	-0.558	[-0.957;-0.156]
Vortioxetine	vs	Bupropion	-0.607	[-1.008;-0.208]
Vortioxetine	vs	Citalopram	-0.628	[-1.073;-0.185]

Both the frequestist and Bayesian analyses based on SMDs support the findings from the corresponding analyses on binary outcomes.

A19. Please explain why the TAK318 trial was excluded from the ITC analysis.

TAK318 was designed to explore the impact of treatment on a specific side-effect, treatment-emergent sexual dysfunction (TESD), in otherwise well-controlled patents (mean MADRS, 7.9 and 8.3 for vortioxetine and escitalopram, respectively). REVIVE and other studies in the ITC were designed to explore efficacy in poorly-controlled patients (mean MADRS scores at baseline of 26 to 36). As TAK 318 was intended to explore a completely different question to the ITC, and involved a different population, it did not meet the eligibility criteria for inclusion in the ITC.

Although TAK318 is a "switch" study comparing vortioxetine to an active comparator and is therefore relevant to the STA decision problem, it does not provide information that can readily be incorporated into the economic evaluation. TAK318 is seen rather as stand-alone, supportive evidence for an aspect of the favourable side-effect profile of vortioxetine.

A20. Table B39, last line (page 124 of the company's submission): please clarify how the adjusted indirect comparison estimated rate of withdrawals because of AEs was 18.0% for citalopram, compared with 5.3% in the original publication (Lenox-Smith et al. 2008).

Applying the Bucher method on risk difference to the inputs below implies simple addition of the risk differences between treatments. The analysis results in a withdrawal rate due to adverse events for citalopram of 18%, which is calculated as follows: 5.9+3.6+8.5+0.2-0.2. The most influential driver of this result is the 8.5% difference between agomelatine and sertraline in the Kasper 2013 study.

Table 31. Calculation of risk differences for withdrawal due to AEs by Bucher method

Study	Outcome	Vortioxetine	Agomelatine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
REVIVE	Withdrawal rate	5.9% (N=253)	9.5% (N=242)	-	-	-	-
	Diff vs vortioxetine	-	3.6%	-	-	-	-
	CI 95%	-	[-1.1; 8.3]	-	-	-	-
Kasper 2013	Withdrawal rate	-	3.7% (N=80)	12.2% (N=96)	-	-	-
	Difference vs.	-	-	8.5%	-	-	-

Study	Outcome	Vortioxetine	Agomelatine	Sertraline	Venlafaxine XR	Bupropion SR	Citalopram
	agomelatine						
	CI 95%	-	-	[0.8; 16.2]	-	-	-
STAR*D	Withdrawal rate	-	-	21.0% (N=238)	21.2% (N=250)	27.2% (N=239)	-
	Difference vs. sertraline	-	-	-	0.2%	6.2%	-
	CI 95%	-	-	-	[-7.0; 7.4]	[-1.5; 13.9]	-
Lenox-Smith	Withdrawal rate	-	-	-	5.5% (N=200)	-	5.3% (N=206)
	Difference vs. venlafaxine	-	-	-	-	-	-0.2%
	CI 95%	-	-	-	-	-	[-4.6; 4.2]

A21. Please provide details of the recruitment setting for trials included in the ITC (that is, primary care, secondary care).

Table 32 below gives details on the recruitment setting for the studies included in the ITC. It should be noted that the treatment setting for depression varies between countries. Expert advice suggests that in some countries, for example, Czech Republic and USA, the majority of patients with depression are treated in secondary care whereas in the UK they would be treated in primary care.

Table 32. Recruitment and treatment settings for the studies included in the ITC

Study details	Recruitment and treatment setting
Montgomery 2014 (REVIVE)	Recruitment was undertaken via advertisements (in Austria, Germany, Estonia, Russia, Sweden and the UK) or referrals from general practitioners and hence represent a mix of primary and secondary care patients. Of the patients in the study only 2.8% were inpatients. The treatment setting for the study was secondary care - 71 psychiatric inpatient and outpatient settings in 14 countries (Austria, Belgium, Bulgaria, Czech Republic, Estonia, Germany, Italy, Lithuania, Poland, Romania, Russia, Spain, Sweden and the UK).
Kasper 2010	The published paper reports that patients were outpatients with MDD requiring anti-depressant therapy from France, Germany, Austria, Spain, Italy and Poland.
Rush 2006 (STAR*D)	The study reported the inclusion of outpatients from both primary and psychiatric, public and private practice settings. In total 41 clinical sites across the US, more specifically 18 primary- and 23 psychiatric-care settings (Ref. Rush 2009).
Lenox-Smith 2008	The recruitment setting was not fully defined. Both inpatients and outpatients were eligible to be included in the study, however the summary states *'participants were adult outpatients'*. This therefore implies that only outpatients were recruited.

Clear descriptions of the study settings were not given in Kasper 2010 and Lenox-Smith 2008. The following websites were searched to try to retrieve additional information:

- www.controlled-trials.com
- WHO clinical trials registry

- www.clinicaltrials.gov

Kasper 2010 is listed in www.controlled-trials.com (ISRCTN 49376288) but no details of the study setting are given. No record for Lenox-Smith (2008) could be found in any of the registries.

In the absence of further information on these study settings advice was sought from within Lundbeck's clinical team together with a review of the clinicians involved in the above studies. The clinical team believes most pharmaceutical company sponsored studies in depression (such as Kasper 2010 and Lenox-Smith 2008) are conducted in secondary care, but recruit from both primary and secondary care settings and it is concluded that that is likely to be the case for these two studies.

Adverse events

A22. Table B44 (page 133 of the company's submission), please provide the number and percentage of patients with a severe adverse event, and the number of discontinuations because of an adverse event per dosage (2.5-10.0 mg; 15-20 mg).

Data provided in answer to A15.

A23. ***Priority question****: The scope of the literature search for adverse event studies was expanded to include 'non-switch populations' (see Section 6.9.1.2 of the company's submission). Given this, please clarify why most vortioxetine trials listed in Table B4, (page 64 of the company's submission), were not included in this review. If available, please provide summary adverse event data, including severe adverse events and discontinuation because of an adverse event, for all trials of vortioxetine and for all comparator treatment arms (including placebo). For example, by providing relative risks or risk differences between treatments, and results from meta-analyses, if these have been performed.*

As stated in the submission "the relative efficacy of antidepressants cannot be assumed to be constant between initial and switch usage" whereas clinical opinion suggests that tolerability is likely to be. Hence the search was widened to include non-switch populations.

The NICE template states in Section 6.9.1.:

"If any of the main trials are designed primarily to *assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results."*

Therefore, the expanded search undertaken to identify the safety studies in the non-switch population focused on those trials which included a safety primary endpoint. Hence the retrieval of only the long-term safety studies rather than all of the studies detailed in Table B4 of the submission.

In any case, the meta-analysed safety and tolerability results for both the short- and long-term pool of studies from the full MDD package are presented in response to question A15 in this document.

Section B: Clarification on cost-effectiveness data

Model time horizon

Table 33. Base case scenario: 12-month horizon (NHS/PSS perspective)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Venlafaxine	£964	0.675	-	-	£378	-
Vortioxetine	£971	0.694	£7	0.019	NA	£378
Citalopram	£976	0.664	£5	-0.030	Dominant	Dominated
Sertraline	£977	0.664	£0	-0.001	Dominant	Dominated
Agomelatine	£1,082	0.676	£105	0.012	Dominant	Dominated

B1. It is noted that the recovery period in the company's economic model denotes a period of 4 months where the patient is not at-risk. Please carry out exploratory analyses around the time horizon, and present the cost-effectiveness results for time horizons of 2 and 8 months.

The results of reducing the time horizon to two months increase both the cost and effectiveness of vortioxetine relative to venlafaxine, sertraline and citalopram (ICERs: £1,878, £1,686 and £5,620, respectively, see Table 34). This compares to the base-case analysis, in which the increased costs of vortioxetine at 2 months are offset over the 12-month period in the comparison with citalopram and sertraline (Table 33). Vortioxetine is a dominant strategy compared to agomelatine whether the time horizon is 2 months or 12 months. In the analysis versus venlafaxine, vortioxetine becomes a more cost-effective strategy over a longer time horizon. This analysis also demonstrates that at 2 months citalopram is a preferential strategy compared to sertraline and venlafaxine, as both the latter are dominated. Vortioxetine remains below the £20,000/QALY threshold at two months compared to citalopram.

Table 34. Scenario: 2-month time horizon (NHS/PSS perspective)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Citalopram	£220	0.099	-	-	£5,620	-
Sertraline	£229	0.096	£10	-0.002	£1,686	Dominated
Venlafaxine	£231	0.098	£2	0.002	£1,878	Dominated
Vortioxetine	£239	0.102	£8	0.004	-	£5,620
Agomelatine	£264	0.100	£25	-0.002	Dominant	Dominated

If the time horizon of the model decreases to 8 months (i.e. no recovery phase) vortioxetine continues to be a dominant strategy compared to citalopram, sertraline and agomelatine (Table 35). The gains in QALYs attributable to the final four-month recovery phase in the base case model are now not observed in the eight-month analysis. This is evident from the reduction in total QALYs for all the treatments.

Table 35: Scenario: 8-month time horizon (NHS/PSS perspective)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Venlafaxine	£964	0.440	-	-	£507	-
Vortioxetine	£971	0.454	£7	0.014	-	£507
Citalopram	£976	0.434	£5	-0.020	Dominant	Dominated
Sertraline	£977	0.434	£1	0.000	Dominant	Dominated
Agomelatine	£1,082	0.443	£105	0.009	Dominant	Dominated

B2. According to NICE's guidance on depression in adults (see NICE Clinical Guideline 90), patients at risk of relapse should be treated with anti-depressants for at least 2 years. Please incorporate an additional scenario in the economic model where this is included and present the revised cost-effectiveness results for vortioxetine compared with each of the comparators.

In this analysis the time horizon of the model increased by one year (i.e. two years). Unlike in the base case, cost of treatment and monitoring are now considered for patients even when they reach the recovery phase.

To extrapolate for a further year, the Markov component of the model was extended by adding additional cycles of two months up to 24 months. This was then reflected in the switch formula in the decision tree. For example, if a patient switched due to lack of efficacy in the maintenance phase (i.e. after 5 months), they would now spend 19 months in the Markov component of the model compared to 7 months in the base-case. In addition, patients who reached recovery now incurred costs associated with treatment and monitoring as it was assumed that, contrary to the base case, patients would continue receiving treatment even after reaching recovery. A discount rate of 3.5% was assumed for the second year for both costs and outcomes.

These changes had an impact on the incremental cost. Although citalopram was associated with the lowest cost, all other treatments (particularly vortioxetine) made greater gains in terms of effectiveness. Vortioxetine now moves from being a dominant strategy in the base case versus citalopram and sertraline to being cost-effective in the two-year model, with ICERs of £4,570 and £4,586 per QALY gained, respectively (see Table 36. The difference in ICERs compared to the base case can be explained by the fact that in this scenario, patients in recovery continue receiving treatment up to two years. In all analyses, the ICER remains well below a threshold of £20,000/QALY.

Table 36. Scenario: 2-year time horizon (NHS/PSS perspective)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Citalopram	£1,127	1.337	-	-	£4,570	-
Sertraline	£1,146	1.341	£20	0.004	£4,586	£4,373
Venlafaxine	£1,215	1.363	£69	0.018	£5,475	£3,234

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Vortioxetine	£1,391	1.395	£176	0.032	-	£5,475
Agomelatine	£1,515	1.360	£124	-0.035	Dominant	Dominated

EQ-5D data

B3. ***Priority question****: Using results from the REVIVE trial, please provide average baseline and week 8 EQ-5D scores (and associated standard errors) for 'remitters' and 'non-remitters' separately. Please do this separately for those treated with vortioxetine and for those treated with agomelatine, as well as, a combined analysis. Please present the results according to the observed cases [OC], last observation carried forward [LOCF] and mixed model for repeated measures [MMRM] methods (that is, an expanded version of Table B15, page 91 of the company's submission).*

Table 37 to Table 41 below detail EQ-5D scores by remission status for vortioxetine, agomelatine and the total population based on each of the following methods of analysis:

- FAS, MMRM
- FAS, OC
- FAS, LOCF

Please note these are descriptive analyses, so commentary on numerical differences should not be read as statistical inference.

Table 37 shows that EQ-5D scores at week 8 differed according to remission status, with remitters achieving a higher mean score, but that this difference was independent of treatment assignment. This finding suggests that the superiority in mean EQ-5D improvement (as reported in the main submission) for vortioxetine compared with agomelatine was driven by the superior remission rates for patients treated with vortioxetine.

Table 37. EQ-5D summary index (FAS, MMRM): MADRS non-remitters and remitters

		Non-remitters			Remitters		
Treatment Group	**Week**	**N**	**Mean EQ-5D score**	**SE**	**N**	**Mean EQ-5D score**	**SE**
VOR	8	119	0.68	0.02	101	0.84	0.01
AGO	8	119	0.66	0.02	70	0.84	0.02
Total	8	238	0.67	0.02	171	0.84	0.01

Among the non-remitters, baseline EQ-5D scores were well matched between the treatment groups. However, among the remitters, patients assigned to agomelatine had a slightly greater mean baseline score than those on vortioxetine, as Table 38 to Table 41 illustrate. The pattern of results was insensitive to the choice of analytic method.

Table 38. EQ-5D summary index (FAS, OC): MADRS non-remitters

								Percentiles		
Treatment Group	**Week**	**N**	**Mean**	**SD**	**SE**	**Min**	**Max**	**25%**	**50%**	**75%**
VOR	0	119	0.53	0.27	0.02	-0.18	0.85	0.27	0.62	0.71
	8	119	0.69	0.21	0.02	0.02	1.00	0.64	0.73	0.81
AGO	0	120	0.53	0.25	0.02	-0.18	0.85	0.38	0.62	0.69
	8	119	0.66	0.24	0.02	-0.16	1.00	0.62	0.71	0.81
Total	0	239	0.53	0.26	0.02	-0.18	0.85	0.32	0.62	0.69
	8	238	0.67	0.23	0.01	-0.16	1.00	0.62	0.73	0.81

Table 39. EQ-5D summary index (FAS, OC): MADRS remitters

								Percentiles		
Treatment Group	**Week**	**N**	**Mean**	**SD**	**SE**	**Min**	**Max**	**25%**	**50%**	**75%**
VOR	0	101	0.54	0.29	0.03	-0.18	0.88	0.29	0.69	0.81
	8	101	0.84	0.12	0.01	0.59	1.00	0.73	0.85	1.00
AGO	0	70	0.60	0.22	0.03	0.08	0.85	0.38	0.69	0.81
	8	70	0.85	0.16	0.02	0.26	1.00	0.81	0.85	1.00
Total	0	171	0.57	0.26	0.02	-0.18	0.88	0.36	0.69	0.81
	8	171	0.85	0.14	0.01	0.26	1.00	0.76	0.85	1.00

Table 40. EQ-5D Summary Index (FAS, LOCF): MADRS non-remitters

								Percentiles		
Treatment Group	**Week**	**N**	**Mean**	**SD**	**SE**	**Min**	**Max**	**25%**	**50%**	**75%**
VOR	0	150	0.52	0.28	0.02	-0.18	0.85	0.27	0.62	0.73
	8	140	0.65	0.25	0.02	-0.24	1.00	0.62	0.72	0.81
AGO	0	170	0.53	0.28	0.02	-0.48	0.85	0.29	0.62	0.73
	8	162	0.62	0.27	0.02	-0.18	1.00	0.52	0.69	0.81
Total	0	320	0.52	0.28	0.02	-0.48	0.85	0.27	0.62	0.73
	8	302	0.63	0.26	0.02	-0.24	1.00	0.59	0.69	0.81

Table 41. EQ-5D summary index (FAS, LOCF): MADRS remitters

								Percentiles		
Treatment Group	Week	N	Mean	SD	SE	Min	Max	25%	50%	75%
VOR	0	102	0.54	0.29	0.03	-0.18	0.88	0.26	0.69	0.81
	8	102	0.84	0.12	0.01	0.59	1.00	0.73	0.85	1.00
AGO	0	71	0.60	0.22	0.03	0.08	0.85	0.38	0.69	0.81
	8	71	0.85	0.16	0.02	0.26	1.00	0.81	0.85	1.00
Total	0	173	0.56	0.26	0.02	-0.18	0.88	0.36	0.69	0.81
	8	173	0.85	0.14	0.01	0.26	1.00	0.76	0.85	1.00

B4. ***Priority question****: Using results from the REVIVE trial, please provide average change in EQ-5D scores from baseline at week 8 (and associated standard errors) for remitters and non-remitters separately. Please do this separately for those treated with vortioxetine and for those treated with agomelatine, as well as, a combined analysis. Please present the results according to the OC, LOCF and MMRM methods.*

Table 42 to Table 45 detail change from baseline EQ-5D scores by remission status defined by MADRS score for vortioxetine, agomelatine and the combined groups based on the following method of analysis:

- FAS, MMRM
- FAS, OC
- FAS, LOCF

Once again, these are descriptive analyses and commentary on numerical differences should not be read as statistical inference.

Both remitters and non-remitters showed increases in mean EQ-5D over 8 weeks of treatment. As expected, the increase was greater among patients who remitted. Among remitters, mean change in EQ-5D score was consistent between treatment groups, but among non-remitters there is a suggestion that patients on vortioxetine achieved slightly greater increases than those on agomelatine. This may possibly be explained by differences in the pattern of adverse events between groups; although the overall incidence of AEs did not differ between groups, fewer patients in the vortioxetine group withdrew due to AEs. No formal analysis of AEs by remission status has been performed, so the above explanation should be regarded as tentative only. The analyses of change were insensitive to the choice of analytic method for remitters, but for the non-remitters the LOCF analysis resulted in smaller estimates of change over 8 weeks than MMRM and OC analyses, which is an unsurprising finding.

Table 42. Changes from baseline in EQ-5D summary index (FAS, MMRM): MADRS non-remitters and remitters

		Non-remitters			Remitters		
Treatment Group	**Week**	**N**	**Mean EQ-5D score**	**SE**	**N**	**Mean EQ-5D score**	**SE**
VOR	8	119	0.15	0.02	101	0.28	0.01
AGO	8	119	0.13	0.02	70	0.28	0.02
Total	8	238	0.14	0.02	171	0.28	0.01

Table 43. Change from baseline in EQ-5D summary index (FAS, OC): MADRS non-remitters

								Percentiles		
Treatment Group	**Week**	**N**	**Mean**	**SD**	**SE**	**Min**	**Max**	**25%**	**50%**	**75%**
VOR	8	119	0.16	0.33	0.03	-0.66	1.18	0.00	0.07	0.43
AGO	8	119	0.13	0.28	0.03	-0.71	0.79	0.00	0.04	0.31
Total	8	238	0.15	0.31	0.02	-0.71	1.18	0.00	0.07	0.43

Table 44. Changes from baseline in EQ-5D summary index (FAS, OC): MADRS remitters

								Percentiles		
Treatment Group	Week	**N**	**Mean**	**SD**	**SE**	**Min**	**Max**	**25%**	**50%**	**75%**
VOR	8	101	0.30	0.28	0.03	-0.12	1.18	0.04	0.19	0.52
AGO	8	70	0.25	0.24	0.03	-0.43	0.92	0.07	0.19	0.43
Total	8	171	0.28	0.27	0.02	-0.43	1.18	0.04	0.19	0.49

Table 45. Changes from baseline in EQ-5D summary index (FAS, LOCF): MADRS non-remitters

								Percentiles		
Treatment Group	**Week**	**N**	**Mean**	**SD**	**SE**	**Min**	**Max**	**25%**	**50%**	**75%**
VOR	8	140	0.12	0.34	0.03	-0.82	1.18	0.00	0.05	0.31
AGO	8	162	0.08	0.30	0.02	-0.83	0.79	0.00	0.00	0.23
Total	8	302	0.10	0.32	0.02	-0.83	1.18	0.00	0.04	0.26

Table 46. Changes from baseline in EQ-5D summary index (FAS, LOCF): MADRS remitters

								Percentiles		
Treatment Group	**Week**	**N**	**Mean**	**SD**	**SE**	**Min**	**Max**	**25%**	**50%**	**75%**
VOR	8	102	0.30	0.28	0.03	-0.12	1.18	0.04	0.19	0.52
AGO	8	71	0.25	0.24	0.03	-0.43	0.92	0.07	0.19	0.43
Total	8	173	0.28	0.26	0.02	-0.43	1.18	0.05	0.19	0.49

Costs data

B5. It is noted that there is a 'switch cost' associated with changing therapy in the company's economic model. Please justify why this is additional to GP/specialist care visits, and whether switching would take place in primary or secondary care.

In the base case, the cost of an additional visit to a GP to switch treatment was assumed. Data for GP visits during the acute phase were taken from the UK whole population. As switch patients were not differentiated in this population, it was assumed in our model that patients would have an additional GP visit when switching to another treatment

As a sensitivity analysis the model has been run assuming patients requiring a treatment switch do not require an additional GP visit to allow their switch in therapy. The results are shown in the table below. The ICERs in the sensitivity analysis are slightly higher compared to the base case.

Table 47. Results when GP visit for switch set to zero (NHS/PSS perspective)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vortioxetine vs. comparator	ICER incremental
Venlafaxine	£933	0.675	NA	NA	£553	NA
Vortioxetine	£941	0.664	£8	-0.011	£74	Dominated
Citalopram	£943	0.664	£2	0.000	£25	Dominated
Sertraline	£943	0.694	£0	0.030	NA	£553
Agomelatine	£1,049	0.676	£106	-0.028	Dominant	Dominated

Probabilistic analysis

B6. ***Priority question****: Please clarify how distributions have been assigned to the model parameter inputs in tables B59 and B60, pages 168 and 171 of the company's submission. Please present the data that underpins them, for example, standard deviation, standard error, number of observations etc.*

Please refer to commentary in Table 48 and Table 49.

Table 48. Model parameter inputs: utility values

Event	Input utility value	Distribution	Comment	Source
Acute phase				
Depression at baseline	0.54			REVIVE
Remission	0.85	Beta (α:1,083;β:191)	SE estimated as median utility *0.25/1.96	
No remission	0.62	Beta (α:365; β:223)	Weighted average of non-responders and responding non-remitters at 8 weeks; SE = 0.02	
Maintenance phase				
Remission	0.85	Beta (α:8; β:1)	SE estimated as median utility *0.25/1.96	Sapin 2004
Relapse	0.58	Beta (α:25; β:18)		
Recovery	0.85			
Disutilities of side-effects				
Sexual dysfunction	0.049		Directly reported by Sullivan	Sullivan 2004
Headache	0.115			
Diarrhoea	0.044			
Somnolence	0.085		Lundbeck applied Sullivan value reported for drowsiness*	
Nausea	0.065		Sullivan assumed avera0e of GI AEs	
Insomnia	0.129		Sullivan assumed equivalent utility to anxiety	
Dry mouth	0†		No data available	
Dizziness	0†			
Sweating	0†			
Weight gain	0.032		Calculation (see below)	Dixon 2004, REVIVE CSR

*Drowsiness is normally considered less severe than somnolence, therefore utility estimate for somnolence may be conservative. †As no utility values were available, no utility decrement was assumed for these AEs in the base-case of the economic evaluation.

Table 49. Model parameter inputs: healthcare resource utilisation

Resource	No. of visits	Distribution	Comments	Proportion of patients with ≥1 visit	Distribution	Comments	Source
GP consultations							
Remission 0-8 weeks	2.50	Gamma (α:61.47; β:0.04)		100.0%	Uniform (α:75; β:100)		PERFORM
No remission 0-8 weeks	2.80	Gamma (α:61.47; β:0.05)	SE estimated as mean visits*0.25/1.96	100.0%	Uniform (α:75; β:100)	Assumptions as the proportion was 100%	PERFORM
Remission after 8 weeks	2.15	Gamma (α:61.47; β:0.03)		100.0%	Uniform (α:75; β:100)		Byford 2011
Relapse after 8 weeks	2.89	Gamma (α:61.47; β:0.05)		100.0%	Uniform (α:75; β:100)		Byford 2011
Psychiatrist consultations							
Remission 0-8 weeks	0.00	-		0.0%	Beta (α:0; β:71)	n=0; N=71	PERFORM
No remission 0-8 weeks	1.00	Gamma (α:61.47; β:0.02)	SE estimated as mean visits*0.25/1.96	1.3%	Beta (α:2; β:152)	n=2; N=152	PERFORM
Remission after 8 weeks	0.23	Gamma (α:61.47; β:0.00)		2.9%	Beta (α:60; β:1,997)	SE estimated as mean visits*0.25/1.96	Byford 2011
Relapse after 8 weeks	0.23	Gamma (α:61.47; β:0.00)		5.0%	Beta (α:58; β:1,109)		Byford 2011
Psychotherapy or counselling							
Remission 0-8 weeks	1.20	Gamma (α:9.00; β:0.13)	SE=0.4	12.7%	Beta (α:9; β:62)	n=9; N=71	PERFORM
No remission 0-8 weeks	2.10	Gamma (α:1.96; β:1.07)	SE=1.5	18.8%	Beta (α:29; β:125)	n=29; N=152	PERFORM
Remission after 8 weeks	0.0	-		0.2%	Beta (α:61; β:30,609)	SE estimated as mean visits*0.25/1.96	Byford 2011
Relapse after 8 weeks	0.0	-		0.2%	Beta (α:61; β:30,609)		Byford 2011
Psychiatric ward admissions							
Remission 0-8 weeks	0.0	-		0.0%	Beta (α:0; β:71)	n=0; N=71	PERFORM
No remission 0-8 weeks	0.0	-		0.0%	Beta (α:0; β:154)	n=0; N=154	PERFORM
Remission after 8 weeks	0.22	Gamma (α:61.47; β:0.00)	SE estimated as mean visits*0.25/1.96	5.2%	Beta (α:58; β:1,061)	SE estimated as mean visits*0.25/1.96	Byford 2011
Relapse after 8 weeks	0.23	Gamma (α:61.47; β:0.00)		5.7%	Beta (α:58; β:958)		Byford 2011
General ward admissions							
Remission 0-8 weeks	0.0	-		0.0%	Beta (α:0; β:0)		PERFORM
No remission 0-8 weeks	1.0	Gamma (α:0,35; β:2.89)	SE=1.7	0.5%	Beta (α:1; β:153)	n=1; N=154	PERFORM
Remission after 8 weeks	0.0	-		0.0%	Beta (α:0; β:0)		Assumption
Relapse after 8 weeks	1.0	Gamma (α:61.47; β:0.02)	SE estimated as mean visits*0.25/1.96	0.5%	Beta (α:61; β:11,924)	SE estimated as mean visits*0.25/1.96	Mean assumed equivalent to acute phase
Accident & Emergency visits							
Remission 0-8 weeks	0.0			0.0%	Beta (α:0; β:71)	n=0; N=71	PERFORM
No remission 0-8 weeks	0.0	-		0.0%	Beta (α:0; β:154)	n=0; N=154	PERFORM
Remission after 8 weeks	0.22	Gamma (α:61.47; β:0.00)	SE estimated as mean visits*0.25/1.96	3.1%	Beta (α:60; β:1,861)	SE estimated as mean visits*0.25/1.96	Byford 2011
Relapse after 8 weeks	0.25	Gamma (α:61.47; β:0.00)		3.3%	Beta (α:59; β:1,741)		Byford 2011

References to sources: Byford 2011[252], PERFORM[36,45,250].

Appendix: Rationale for subgroup analysis between US and non-US trials

Over the past 2 to 3 decades, there has been a steady decline worldwide in the antidepressant-placebo difference in clinical studies.[137] In recent years, this decline appears to be particularly pronounced in studies conducted in the United States, although the reasons for this remain elusive. No single causative factor can be isolated to explain the differences between studies conducted in the United States and those conducted outside the United States. It does seem, however, that issues around study conduct, including patient selection and adherence to the protocol and IMP regimen, are critical. This smaller antidepressant-placebo difference is reflected in the studies in the vortioxtine clinical development programme conducted in the United States. In the population pharmacokinetic analysis of the phase II/III studies, the vortioxetine plasma concentrations were lower and more variable in US patients than in non-US patients (including a higher proportion of samples with plasma concentrations below the lower limit of quantification in US patients). This finding cannot be explained by demographics or other covariates and indicates poorer compliance by US. This finding may partially explain the smaller antidepressant-placebo difference observed in the US. Furthermore, in the pharmacokinetic/pharmacodynamic (PK/PD) analysis, region was a significant covariate, with worse efficacy in the United States than outside the United States.

It was therefore relevant to analyse the effect of vortioxetine based solely on the non-US studies, therefore, a meta-analysis was performed that only included Studies 11492A, 11984A, 305, 13267A, 14122A, and CCT□002.

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