IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Vortioxetine – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Vortioxetin – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 July 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revision
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAM-D	Hamilton Depression Rating Scale
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MADRS	Montgomery-Åsberg Depression Rating Scale
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
SSRI	selective serotonin reuptake inhibitor

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug vortioxetine. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 4 May 2015.

Research questions

The aim of this report was to assess the added benefit of vortioxetine compared with the appropriate comparator therapy (ACT) in adult patients with major depressive episodes.

The G-BA specified the ACT as follows:

- Mild major depressive episode:

  Antidepressants are usually not required to treat mild depressive episodes: no drug treatment.

- Moderate major depressive episode:

  Drug treatment, if indicated, is conducted with an antidepressant of the drug group of selective serotonin reuptake inhibitors (SSRIs).

- Severe major depressive episode:

  Drug treatment is conducted with an antidepressant of the drug group of SSRIs.

  The patient should be offered psychotherapeutic treatment.

For the benefit assessment, 2 research questions resulted from the Summary of Product Characteristics (SPC) of vortioxetine. These are the treatment of acute symptoms (acute treatment) and relapse prevention after remission (relapse prevention under maintenance treatment). However, the company only investigated the research question of acute treatment in the dossier.

For the acute treatment, the company presented no studies for patients with mild major depressive episodes.

For the assessment of acute treatment of moderate and severe major depressive episodes, the company chose only drug treatment with the SSRI citalopram as comparator therapy. In the choice of the comparator therapy for patients with severe episodes, the company did not consider the offer of psychotherapy and thus deviated from the specification of the ACT.

Following the choice of the company, citalopram as a representative of SSRI was used as ACT in the present benefit assessment. Concurring with the G-BA, the offer of psychotherapeutic treatment was considered to be part of the ACT for the treatment of patients with severe major depressive episodes.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 6 weeks were considered for the acute treatment. This deviates from the company's approach, which limited the study duration to 6 to 8 weeks.

Additional research question of the company

The company additionally presented an RCT with a direct comparison of vortioxetine and agomelatine in its dossier. Deviating from the company, this comparison was not considered in the present benefit assessment because agomelatine is no ACT.

Results

Research question 1: acute treatment

Corresponding to its definition of the comparator therapy, the company initially considered the patients with moderate or severe episodes jointly and subsequently investigated possible effect modification by severity grade.

Based on the specification of the ACT for patients with severe episodes it was checked whether psychotherapeutic treatment was offered in the company's studies. This check showed that ongoing or planned psychotherapeutic treatment was excluded in all studies with vortioxetine. Likewise, psychotherapy was an exclusion criterion in most studies on citalopram or there was no information on this. Under consideration of the therapeutic indication and patient participation in treatment decisions it was assumed in the present benefit assessment that the patients with severe episodes had decided against psychotherapeutic treatment in the framework of their decision to participate in the studies presented by the company. Hence on the basis of these studies, an added benefit could be derived only for patients with moderate episodes and for patients with severe episodes who decide against psychotherapy.

The results presented by the company in Module 4 A were unsuitable for deriving an added benefit of vortioxetine in comparison with the ACT, however. This was largely due to the fact that the company made an inadequate limitation of the study pool for the meta-analyses of the indirect comparison, which resulted in an incomplete consideration of the available evidence. Furthermore, the study pool of the company had been potentially incomplete already before studies were chosen for the indirect comparison, and also contained studies that are not relevant because of dosages that were not in compliance with the approval.

Criticism of the company's approach in the choice of studies for the meta-analyses for the indirect comparison

Since there were no RCTs of direct comparison, the company conducted an adjusted indirect comparison according to Bucher of vortioxetine versus citalopram with placebo as common comparator. The company initially identified 14 studies on vortioxetine and 10 studies on citalopram for the indirect comparison. Subsequently, the company chose studies for the meta-analyses within the indirect comparison, however. It used a 2-step approach to do this.

Checking the homogeneity of the studies on the vortioxetine side in the framework of a meta-analysis of the outcome "change in symptoms of depression", the company identified regionality of the studies (Europe: studies with ≥ 80% European patients, USA: studies with 100% patients from the USA, and others: studies that could be neither allocated to Europe nor to the USA) as decisive explaining factor for the substantial heterogeneity in the pool of vortioxetine studies. Due to the considerations regarding heterogeneity on the vortioxetine side, the company limited the study pool for the indirect comparison to studies with mainly European patients (studies with ≥ 80% Europeans in the total population).

Subsequently, the company chose the pool of studies with ≥ 80% Europeans in the total population also on the citalopram side, although there was no heterogeneity in the total pool of citalopram studies. As a result of the limitation to studies with a proportion of ≥ 80% Europeans, only 3 of the 14 vortioxetine studies and 4 of the 10 citalopram studies were considered, which constituted an important limitation of the evidence for the indirect comparison.

Irrespective of the question whether the limitation to European patients is justified, it would have been possible for the company to include the results of the subpopulations of European patients from 5 further vortioxetine studies with a relevant proportion of Europeans (between 50 and 70%), which it allocated the region "others", in the analysis. The company did not make use of this possibility, although the individual patient data were available to the company.

Even if the company had not had this possibility, it would have had to investigate at least whether the results would have been influenced by the exclusion of the studies with a relevant proportion of Europeans.

A further criticism of the company's approach concerns the factors considered by the company in its considerations regarding heterogeneity. The company only investigated whether the factors "dose" and "region" can explain the heterogeneity in the vortioxetine studies. In addition, it only considered the outcome "change in symptoms of depression". However, the company would have had to check in how far other factors (e.g. disease severity, sex or possibly even the interaction of several factors) can explain the heterogeneity and whether this heterogeneity occurs in further outcomes.

Irrespective of this, also the investigation of "regional heterogeneity" conducted by the company is insufficient. The company provided several reasons, which, from the company's point of view, may cause the "regional heterogeneity". These reasons included factors such as ethnic genetic factors and differences in the conduct of the study, in the recruitment of patients and the health care systems. However, the company did not investigate which of these individual factors may possibly explain the "regional heterogeneity" and therefore would have to be preferred in the choice of studies for the meta-analyses for the indirect comparison instead of its construct "regionality".

Research question 2: relapse prevention under maintenance treatment

Module 4 A of the dossier contained no results for the derivation of an added benefit of vortioxetine in comparison with the ACT for the research question of relapse prevention under maintenance treatment.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

Based on the results presented, the extent and probability of the added benefit of vortioxetine in acute treatment are assessed as follows: There was no hint of an added benefit of vortioxetine in comparison with the ACT for patients of all severity grades and irrespective of their decision for or against psychotherapy; an added benefit is therefore not proven.

There was also no hint of an added benefit of vortioxetine in comparison with the ACT in relapse prevention under maintenance treatment; an added benefit is therefore not proven.

Table 2 presents a summary of the extent and probability of the added benefit of vortioxetine in comparison with the ACT.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

Table 2: Vortioxetine – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Major depressive episodes in adults[b]		
▪ mild episodes	▪ no drug treatment	▪ added benefit not proven
▪ moderate episodes	▪ SSRI: **citalopram**	▪ added benefit not proven
▪ severe episodes	▪ SSRI: **citalopram** The patient should be offered psychotherapeutic treatment	▪ added benefit not proven[c]
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: Acute treatment and relapse prevention under maintenance treatment. c: Both in patients who have decided against psychotherapy and in patients who have decided to have psychotherapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SSRI: selective serotonin reuptake inhibitor		

The G-BA decides on the added benefit.

2.2 Research questions

The aim of this report was to assess the added benefit of vortioxetine compared with the ACT in adult patients with major depressive episodes.

The G-BA specified the ACT as follows:

- Mild major depressive episode:

  Antidepressants are usually not required to treat mild depressive episodes: no drug treatment.

- Moderate major depressive episode:

  Drug treatment, if indicated, is conducted with an antidepressant of the drug group of SSRIs.

- Severe major depressive episode:

  Drug treatment is conducted with an antidepressant of the drug group of SSRIs.

  The patient should be offered psychotherapeutic treatment.

For the benefit assessment, 2 research questions resulted from the SPC of vortioxetine [3]. On the one hand, this is the treatment of acute symptoms (acute treatment, Section 2.3) and, on the other, relapse prevention after remission (relapse prevention under maintenance treatment, Section 2.4). However, the company only investigated the research question of acute treatment in the dossier.

For the acute treatment, the company presented no studies for patients with mild major depressive episodes.

For the assessment of acute treatment of moderate and severe major depressive episodes, the company chose only drug treatment with the SSRI citalopram as comparator therapy. In the choice of the comparator therapy for patients with severe episodes, the company did not consider the offer of psychotherapy, however. Moreover, the company used citalopram only for the assessment of the added benefit for the subpopulation of patients without pretreatment defined by the company (see Section 2.6.1 of the full dossier assessment).

In the present benefit assessment, there was no limitation to the subpopulation without pretreatment; the assessment was conducted for all patients irrespective of their pretreatment. Regarding the ACT, the choice of the company was followed to choose citalopram as representative of SSRIs. Concurring with the G-BA, the offer of psychotherapeutic treatment was considered to be part of the ACT for the treatment of patients with severe major depressive episodes.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier. RCTs with a minimum duration of 6 weeks were considered for the acute treatment. This deviates from the company's approach, which limited the study duration to 6 to 8 weeks.

Additional research question of the company

The company additionally presented an RCT with a direct comparison of vortioxetine and agomelatine in its dossier. Deviating from the company, this comparison was not considered in the present benefit assessment because agomelatine is no ACT. See Section 2.6.1 of the full dossier assessment for more details.

2.3 Research question 1: acute treatment

Comment on the company's presentation of the research question

For acute treatment, the following 3 patient populations resulted from the ACT:

- patients with mild major depressive episodes
- patients with moderate major depressive episodes
- patients with severe major depressive episodes

The company presented no studies for patients with mild major depressive episodes.

For patients with moderate or severe major depressive episodes, the company compared vortioxetine with citalopram as representative of SSRIs. It did not consider the fact that the ACT for patients with severe major depressive episodes also includes the offer of psychotherapy. Corresponding to its definition of the comparator therapy, the company

initially considered the patients with moderate or severe episodes jointly and subsequently investigated possible effect modification by severity grade (see Section 2.6.1 of the full dossier assessment).

Based on the specification of the ACT for patients with severe episodes it was checked whether psychotherapeutic treatment was offered in the company's studies. This check showed that ongoing or planned psychotherapeutic treatment was excluded in all studies with vortioxetine. Likewise, psychotherapy was an exclusion criterion in most studies on citalopram or there was no information on this. Following the company, and under consideration of the therapeutic indication and patient participation in treatment decisions it was assumed in the present benefit assessment that the patients with severe episodes had decided against psychotherapeutic treatment in the framework of their decision to participate in the studies presented by the company. Hence on the basis of these studies, an added benefit could be derived only for patients with moderate episodes and for patients with severe episodes who decide against psychotherapy.

Hence the difference in the ACT for patients with moderate episodes and with severe episodes who have decided against psychotherapy was omitted in the present benefit assessment so that these patients are initially considered jointly in the following assessment. The influence of disease severity was to be clarified by investigating the corresponding effect modifications. The added benefit in patients with severe episodes who decide to have psychotherapy could not be assessed because the company presented no evidence for them.

For patients with severe episodes, this approach deviates from the company insofar as the company used its studies for all patients with severe episodes and hence did not make a limitation to patients who have decided against psychotherapy.

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information. It should be noted in the compilation of the sources that the company is the marketing authorization holder of both vortioxetine and citalopram.

Sources of the company in the dossier:

- study list on vortioxetine (studies completed up to 3 February 2015)
- bibliographical literature search on vortioxetine (last search on 3 February 2015)
- search in trial registries for studies on vortioxetine (last search on 25 March 2015)
- study list on the ACT (studies completed up to 3 February 2015)
- bibliographical literature search on the ACT (last search on 3 February 2015)
- search in trial registries for studies on the ACT (last search on 25 March 2015)

To check the completeness of the study pool:

- search in trial registries for studies on vortioxetine (last search on 23 April 2015)
- bibliographical literature search on the ACT (last search on 24 April 2015)
- search in trial registries for studies on the ACT (last search on 24 April 2015)

No RCTs on the direct comparison of vortioxetine versus citalopram were identified from the check of the completeness of the study pool. This concurs with the company's assessment.

Since there were no RCTs of direct comparison, the company conducted an adjusted indirect comparison according to Bucher [4] of vortioxetine versus citalopram with placebo as common comparator. The check of the completeness of the company's study pool for the indirect comparison produced 3 additional potentially relevant studies [5-7]. The company's study pool for the indirect comparison was therefore potentially incomplete.

Overall, the company's approach for the choice of studies for the indirect comparison had substantial deficiencies so that the indirect comparison conducted by the company was unsuitable for the assessment of the added benefit. This was largely due to the fact that the company made an inadequate limitation of the study pool for the meta-analyses of the indirect comparison, which resulted in an incomplete consideration of the available evidence (see Section 2.3.1.3). Furthermore, the study pool of the company had been potentially incomplete already before the studies were chosen for the indirect comparison, and also contained studies that are not relevant because of dosages that were not in compliance with the approval.

Below, first the study pool of the company is described. Then the company's approach for the choice of the studies for the indirect comparison is summarized and the individual points of criticisms are explained in detail.

2.3.1.1 Study pool

The company initially included 14 studies on vortioxetine and 10 studies on citalopram for the indirect comparison. Deviating from the company, 4 studies (vortioxetine studies 303 [8] and 304 [9], citalopram studies Fraguas 2009 [10] and 97205 [11]) were not included in the benefit assessment because of dosages that did not comply with the approval (for reasons, see Section 2.6.2.3.2 of the full dossier assessment). The potentially relevant studies with approval-compliant dosages of vortioxetine and citalopram are listed in Table 3.

Table 3: Study pool – potentially relevant RCTs in the company's study pool, indirect comparison: vortioxetine vs. citalopram

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with vortioxetine			
CCT-002 [12]	No	No[b]	Yes
CCT-003 [13]	No	No[b]	Yes
11492A [14]	Yes	Yes	No
11984A [15]	Yes	Yes	No
12541A [16]	Yes	Yes	No
13267A [17]	Yes	Yes	No
14122A [18]	Yes	Yes	No
202 [19]	No	No[b]	Yes
305 [20]	Yes	No[b, c]	Yes[c]
315 [21]	Yes	No[b]	Yes
316 [22]	Yes	No[b]	Yes
317 [23]	No	No[b]	Yes
Studies with citalopram			
Gastpar 2006 [24]	No	No	Yes
89303 [25]	No	Yes	No
89306[d] [26]	No	Yes	No
91206 [27]	No	Yes	No
99003 [28]	No	Yes	No
99007 [29]	No	No	Yes
99008[d] [26]	No	No	Yes
29060/785 [30]	No	No	Yes

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
b: The company Takeda was sponsor of this study; vortioxetine is marketed jointly by the company and Takeda (see [31], for example).
c: In collaboration with H. Lundbeck A/S.
d: No publicly available source available.
RCT: randomized controlled trial; vs.: versus

In addition, 3 additional potentially relevant studies were identified from the check of the completeness of the company's study pool. The company also identified these studies in its literature search, but excluded them from the assessment because of its selection criteria regarding study duration (limitation to studies with a duration of 6 to 8 weeks, see Section 2.6.2.1 of the full dossier assessment). Correspondingly, the company did not check whether these studies were suitable for an indirect comparison. The duration of the studies (10 to 12 weeks) is no adequate reason for exclusion; the studies were therefore potentially relevant. The additional potentially relevant studies are listed in Table 4.

Table 4: Study pool – additional potentially relevant RCTs identified from the check of the study pool, indirect comparison: vortioxetine vs. citalopram

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Brown 2005 [5]	No	No	Yes
CREATE [6]	No	No	Yes
Mathews 2015 [7]	No	No	Yes

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
RCT: randomized controlled trial; vs.: versus

2.3.1.2 Study characteristics

Potentially relevant studies with vortioxetine and citalopram

The potentially relevant studies with vortioxetine and citalopram were double-blind, placebo- and partly active-controlled RCTs. Adult patients with an acute major depressive episode of at least moderate severity according to the Diagnostic and Statistical Manual of Mental Disorders (fourth edition [DSM-IV-TR] or third edition [DSM-III-R]). One study on vortioxetine (12541A) investigated only older patients (≥ 65 years). In all other studies on vortioxetine and citalopram, patients ≥ 65 years were either not included or their proportion was small.

Patients who were having psychotherapy at inclusion in the study or who were planning to start psychotherapy during the study were excluded from the studies on vortioxetine. Psychotherapy was an exclusion criterion in 5 studies on citalopram; there was no information for the 3 remaining studies. Hence these studies may only be suitable for the derivation of an added benefit for patients with moderate episodes and for patients with severe episodes who have decided against psychotherapy.

Depending on the study, vortioxetine was administered in different dosages from 1 to 20 mg/day. The dosage of citalopram was 10 to 60 mg/day, depending on the study. The study arms with dosages that were not compliant with the approval were excluded from the benefit assessment. These were the arms with vortioxetine 1 or 2.5 mg/day irrespective of age, and 5 mg/day for patients < 65 years, as well as the arms with citalopram 10 mg/day (for patients ≤ 65 years) and 60 mg/day. All other study arms, in which the doses were in compliance with the approval, but in which partly either fixed dosages or dosages with fixed titration were investigated, were included as being potentially relevant. However, deviating from the company, the certainty of results was downgraded for these studies because it remained unclear whether an unbiased estimation of benefit and harm of vortioxetine in comparison with citalopram is possible on the basis of these studies (for reasons, see Section 2.6.2.3.2 of the full dossier assessment).

In addition to the placebo arm, the vortioxetine studies 11984A, 12541A, 13267A, 202 and 315 had a duloxetine arm, and the study 11492A had a venlafaxine arm as active control. The citalopram studies had the following active control arms besides the placebo arm: St. John's Wort in Gastpar 2006, escitalopram in the studies 99003, 99007 and 99008, and 2 arms with paroxetine in the study 29060/785.

The potentially relevant studies on vortioxetine and citalopram are described in table format in Appendix A of the full dossier assessment. The studies on vortioxetine and citalopram that were excluded due to dosage, are presented in Appendix B of the full dossier assessment.

Additional potentially relevant studies with citalopram identified from the check of the study pool

The additional potentially relevant studies identified from the check of the study pool were double-blind RCTs with adult patients with an acute major depressive episode according to the DSM-IV or DSM-IV-TR criteria. Patients in the CREATE study additionally had to have stable coronary heart disease; patients in the Brown 2005 study had drug-treated asthma as somatic comorbidity. The inclusion criteria of all studies regarding severity grade ensured that the patients had at least a moderate major depressive episode.

The studies Mathews 2015 and Brown 2005 contained no information on psychotherapy. In the CREATE study, in contrast, interpersonal psychotherapy was part of the randomized study treatment in the framework of a factorial design (citalopram versus placebo, each randomized with or without interpersonal psychotherapy).

The citalopram dosages were between 20 and 40 mg/day. In the Brown 2005 study, the dosage could additionally be increased to 60 mg/day from week 8 and was then outside the approved range. Hence for this study, the results after week 8 would not be evaluable for the benefit assessment.

The additional potentially relevant studies on citalopram are described in table format in Appendix C of the full dossier assessment.

Summary

Regarding the population investigated, dosage of vortioxetine or citalopram and duration of the study, the potentially relevant RCTs with vortioxetine and citalopram were, in principle, suitable to answer the research question of acute treatment. It was not checked, however, whether they fulfilled the assumption of similarity for an adjusted indirect comparison using the common comparator placebo because the company's approach for choosing the studies for the meta-analyses of the indirect comparison was inadequate. The same applies to the additional potentially relevant studies with citalopram.

2.3.1.3 Approach of the company in the choice of studies/patients for the meta-analyses of the indirect comparison

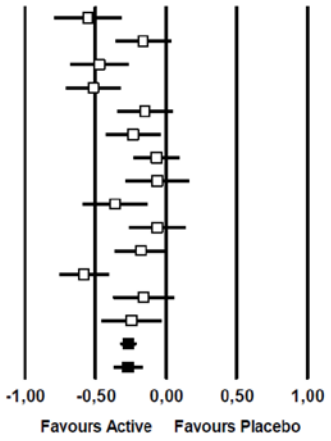
As mentioned above, the company initially included 14 studies on vortioxetine and 10 studies on citalopram for the indirect comparison. Subsequently, the company chose studies for the meta-analyses within the indirect comparison, however. It used a 2-step approach to do this. Firstly, the company considered the studies on the vortioxetine side in the framework of a meta-analysis. Due to the considerations regarding heterogeneity, the company limited the study pool to studies with mainly European patients (studies with ≥ 80% Europeans in the total population). Subsequently, it chose the pool of studies with ≥ 80% Europeans in the total population also on the citalopram side, although there was no heterogeneity in the total pool of citalopram studies. As a result of the limitation to studies with a proportion of ≥ 80% Europeans, only 3 of the 14 vortioxetine studies and 4 of the 10 citalopram studies were considered, which constituted an important limitation of the evidence for the indirect comparison.

Choice of studies on the vortioxetine side

Based on the assumption that the study characteristics of the 14 studies with vortioxetine are sufficiently comparable, the company conducted a meta-analysis with Hedges' g as effect measure for the outcome "change in symptoms of depression" measured with the Montgomery-Åsberg Depression Rating Scale (MADRS) or with the Hamilton Depression Rating Scale (HAM-D) 24. In studies with several vortioxetine arms, it summarized these arms and in each case used a Hedges' g value for the comparison of vortioxetine versus placebo in the meta-analysis. It also considered dosages that were not in compliance with the approval. It was unclear how the different vortioxetine arms were pooled.

Since there was important heterogeneity in the meta-analysis ($I^2 = 72.0\%$, $p < 0.001$, see Figure 1), the company checked whether this heterogeneity can be explained by a dose effect. Since heterogeneity was still shown within the 4 dose steps (5, 10, 15, 20 mg/day), the company concluded that the heterogeneity cannot be solely explained by the different dosages.

Model	Study	Outcome	Hedges's g	Standard error	Lower limit	Upper limit	p-Value	Vortioxetine	Placebo
	VOR01	MADRS	-0,553	0,121	-0,791	-0,315	0,0000	208	105
	VOR02	MADRS	-0,163	0,101	-0,360	0,035	0,1065	306	145
	VOR03	HAM-D 24	-0,473	0,105	-0,679	-0,267	0,0000	278	139
	VOR04	MADRS	-0,514	0,100	-0,709	-0,319	0,0000	300	158
	VOR05	MADRS	-0,149	0,100	-0,345	0,046	0,1343	292	153
	VOR06	MADRS	-0,234	0,099	-0,428	-0,040	0,0179	302	155
	VOR07	HAM-D 24	-0,066	0,083	-0,229	0,097	0,4252	292	286
	VOR08	HAM-D 24	-0,063	0,115	-0,288	0,162	0,5830	153	149
	VOR09	HAM-D 24	-0,362	0,116	-0,589	-0,134	0,0019	155	145
	VOR14	MADRS	-0,062	0,101	-0,260	0,136	0,5380	285	149
	VOR15	MADRS	-0,178	0,095	-0,364	0,007	0,0595	438	150
	VOR16	MADRS	-0,584	0,089	-0,758	-0,409	0,0000	397	194
	VOR17	MADRS	-0,158	0,111	-0,375	0,059	0,1530	241	123
	VOR18	MADRS	-0,244	0,108	-0,456	-0,031	0,0244	175	167
Fixed			-0,266	0,027	-0,319	-0,213	0,0000	3822	2218
Random			-0,270	0,052	-0,371	-0,169	0,0000	3822	2218



Heterogeneity: $I^2 = 72.0\%$, $p < 0.001$

VOR01 = 11492A; VOR02 = 11984A; VOR03 = 305; VOR04 = 13267A; VOR05 = 315; VOR06 = 316; VOR07 = 303; VOR08 = 304; VOR09 = 12541A; VOR14 = 317; VOR15 = CCT-002; VOR16 = 14122A; VOR17 = CCT-003; VOR18 = 202

CI: confidence interval; HAM-D 24: Hamilton Depression Rating Scale (24 questions); MADRS: Montgomery-Åsberg Depression Rating Scale; RCT: randomized controlled trial

Figure 1: Meta-analysis of the company for the outcome "change in symptoms of depression" from RCTs; vortioxetine versus placebo

In the next step, the company checked whether the heterogeneity can be explained by regionality. For this purpose, it divided its studies into the following regions: Europe (studies with ≥ 80% of European patients), USA (studies with 100% patients from the USA) and others (studies that could be allocated neither to Europe nor to the USA). The analysis showed no heterogeneity within the study pool of the 5 studies in which only US Americans were included (studies 303, 304, 315, 316 and 317; $I^2 = 0.0\%$, $p = 0.664$). There was also no heterogeneity in the study pool of the 3 studies in which ≥ 80% Europeans were included (studies 11492A, 13267A and 305; $I^2 = 0.0\%$, $p = 0.882$). There was still important heterogeneity in the remaining 6 studies, which included < 80% patients from the USA and Europe (with one study only including Japanese participants) ($I^2 = 68.4\%$, $p = 0.007$). The company concluded from these analyses that the different regionality of the studies was the decisive explaining factor for the substantial heterogeneity. The company did not investigate further potential effect modifiers.

The company provided several reasons, which, from the company's point of view, may cause the "regional heterogeneity". These reasons included factors such as ethnic genetic factors and differences in the conduct of the study, in the recruitment of patients and the health care systems (see Section 2.6.2.3.2 of the full dossier assessment). However, the company did not investigate which of these individual factors may possibly explain the "regional

heterogeneity" and therefore would have to be preferred in the choice of studies for the meta-analyses for the indirect comparison instead of its construct "regionality".

Then the company analysed the change in symptoms of depression in the 3 studies with ≥ 80% Europeans separately for the subpopulations with moderate and severe major depressive episodes. There was no heterogeneity for the subpopulation with moderate episodes ($I^2 = 0.0\%$, $p = 0.496$), whereas there was substantial heterogeneity in the subpopulation with severe episodes ($I^2 = 60.1\%$, $p = 0.082$). Unlike above, however, the company did not conclude from this heterogeneity that the studies cannot be pooled.

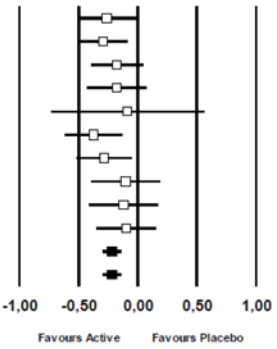
Based on the heterogeneity of this single outcome (change in symptoms of depression), and despite the above inconsistency in handling the heterogeneity, the company conducted the analysis of all remaining outcomes and the corresponding subgroup analyses only on the basis of the 3 studies with ≥ 80% Europeans.

The company did not consider that the studies it had allocated to the pool "others" also included studies with a relevant proportion of Europeans (study CCT-002: about 69%, study 11984A: about 62%, study 12541A: about 60%, study 14122A: about 65%, study 202: about 50%). It provided no reasons why it did not include the subpopulation of European from these studies in its analysis.

Choice of studies on the citalopram side

The company initially used the same approach in the choice of studies on the citalopram side as it had done on the vortioxetine side. In contrast to the studies on the vortioxetine side, the meta-analysis of the 10 citalopram studies produced no important heterogeneity, however ($I^2 = 0.0\%$, $p = 0.852$, see Figure 2).

Model	Study	Outcome	Statistics for each study					Sample size	
			Hedges's g	Standard error	Lower limit	Upper limit	p-Value	Citalopram	Placebo
	CIT03	MADRS	-0,260	0,128	-0,512	-0,009	0,0424	125	119
	CIT04	MADRS	-0,291	0,104	-0,494	-0,087	0,0052	370	124
	CIT05	MADRS	-0,176	0,113	-0,398	0,045	0,1190	159	154
	CIT06	MADRS	-0,178	0,128	-0,429	0,073	0,1641	119	125
	CIT07	HAM-D 17	-0,085	0,332	-0,735	0,565	0,7975	19	16
	CIT08	HAM-D 17	-0,375	0,125	-0,621	-0,129	0,0028	127	130
	CIT09	MADRS	-0,285	0,122	-0,525	-0,045	0,0199	199	101
	CIT12	HAM-D 24	-0,101	0,151	-0,397	0,196	0,5055	84	90
	CIT14	MADRS	-0,119	0,150	-0,413	0,175	0,4265	134	66
	CIT15	MADRS	-0,095	0,129	-0,348	0,157	0,4586	185	89
Fixed			-0,218	0,042	-0,299	-0,136	0,0000	1521	1014
Random			-0,218	0,042	-0,299	-0,136	0,0000	1521	1014



Heterogeneity: $I^2 = 0.0\%$, $p = 0.852$

CIT03 = 99007; CIT04 = 91206; CIT05 = 99003; CIT06 = 99008; CIT07 = Fraguas 2009; CIT08 = Gastpar 2006; CIT09 = 29060/785; CIT12 = 97205; CIT14 = 89303; CIT15 = 89306

CI: confidence interval; HAM-D 24: Hamilton Depression Rating Scale (17 or 24 questions); MADRS: Montgomery-Åsberg Depression Rating Scale; RCT: randomized controlled trial

Figure 2: Meta-analysis of the company for the outcome "change in symptoms of depression" from RCTs; citalopram versus placebo

In addition, the company showed in a further meta-analysis that there was no heterogeneity within the 3 study pools when the study pool was divided into regions (USA, Europe and others). Nonetheless, the company limited the study pool of the citalopram studies to studies with ≥ 80% Europeans. It justified this approach with the comparability with the study populations in the vortioxetine studies and with the transferability to the German health care context. The company's study pool for citalopram therefore included only the studies Gastpar 2006, 99003, 89303 and 89306. The company conducted no further analyses (hence also no analysis by dosage) to investigate further potential effect modifiers. No Europeans were included in the remaining potentially relevant studies.

Criticism of the company's approach in the choice of studies for the meta-analyses for the indirect comparison

As mentioned above, due to the company's limitation to studies with mainly European patients (≥ 80% of the total population), only 3 of the 14 vortioxetine studies and 4 of the 10 citalopram studies were considered in the indirect comparison. Hence, the company limited the evidence to a relevant degree.

Irrespective of the question whether the limitation to European patients is justified, it would have been possible for the company to include the results of the subpopulations of European patients from the 5 vortioxetine studies with a relevant proportion of Europeans (between 50 and 70%), which it allocated to the region "others", in the analysis because the individual patient data were available to the company.

Even if the company had not had this possibility, it would have had to investigate at least whether the results were influenced by the exclusion of the studies with a relevant proportion of Europeans.

A further criticism of the company's approach concerns the factors considered by the company in its considerations regarding heterogeneity. The company only investigated whether the factors "dose" and "region" can explain the heterogeneity in the vortioxetine studies. In addition, it only considered the outcome "change in symptoms of depression". However, the company would have had to check in how far other factors (e.g. disease severity, sex or possibly even the interaction of several factors) can explain the heterogeneity and whether this heterogeneity occurs in further outcomes.

Irrespective of this, also the investigation of "regional heterogeneity" conducted by the company is insufficient. The company provided several reasons, which, from the company's point of view, may cause the "regional heterogeneity". These reasons included factors such as ethnic genetic factors and differences in the conduct of the study, in the recruitment of patients and the health care systems. However, the company did not investigate which of these individual factors may possibly explain the "regional heterogeneity" and therefore would have to be preferred in the choice of studies for the meta-analyses for the indirect comparison instead of its construct "regionality".

Finally, the company included 4 studies in its consideration of heterogeneity that were not evaluable for the benefit assessment because of dosages that were not in compliance with the approval.

Conclusion from the company's approach

Due to the approach in the choice of studies for the indirect comparison, the analyses presented by the company in Module 4 A were not evaluable for deriving an added benefit of vortioxetine in comparison with citalopram. The available evidence was severely limited without the company providing convincing justification. There were no sensitivity analyses investigating the effects of the company's approach. It is unclear whether a different approach would lead to a different result. Furthermore, the company in its meta-analyses included studies and study arms that are not relevant, and that the initial study pool of the company was potentially incomplete because of the exclusion of studies due to the study duration.

2.3.2 Results on added benefit

Module 4 A of the dossier contained no evaluable analyses on the derivation of an added benefit of vortioxetine in comparison with citalopram (see Section 2.3.1.3, and Sections 2.6.2.2 and 2.6.2.3.2 of the full dossier assessment). There was therefore no hint of an added benefit of vortioxetine in comparison with the ACT in the acute treatment of patients with major depressive episodes; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

The dossier contained no data for patients with mild major depressive episodes and for patients with severe episodes who decide to have psychotherapeutic treatment.

The company presented no evaluable analyses for patients with moderate episodes and for patients with severe episodes who decide against psychotherapy.

Hence there was no hint of an added benefit of vortioxetine in comparison with the ACT for patients of all severity grades and irrespective of their decision for or against psychotherapy; an added benefit is therefore not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This assessment deviates from that of the company. The company derived proof of a major added benefit for patients with moderate episodes and proof of non-quantifiable added benefit for patients with severe episodes. Overall, the company claimed proof of major added benefit.

The G-BA decides on the added benefit.

2.3.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.4 Research question 2: relapse prevention under maintenance treatment

2.4.1 Information retrieval and study pool

The research question of relapse prevention under maintenance treatment resulted from the SPC of vortioxetine [3] and from the treatment goals of treatment of major depression. This research question could not be investigated, however. The company did not consider this research question in its dossier. Hence it conducted no information retrieval in Module 4 A and presented no results.

It was clear from the documents provided by the company for acute treatment, however, that the company possibly could have presented results on this research question. At least it could have justified why it did not present any results for this research question. There are no studies of direct comparisons in comparison with the ACT. However, the added benefit could have been proven in an indirect comparison of studies suitable for such a comparison.

There is both a vortioxetine study [32] (study 11985A) and a citalopram study [26] (study 89305) with a study design that fulfils the requirements of the European Medicines Agency [33] for the investigation of relapse prevention under maintenance treatment. To investigate the added benefit of vortioxetine in relapse prevention, the company would have had to check whether these studies are suitable for answering the research question and for an indirect comparison with regard to the population and the dosages. If these 2 studies had not been

suitable for an indirect comparison, it could have been checked whether an indirect comparison is possible in comparison with a different representative of the SSRI drug class.

2.4.2 Results on added benefit

Module 4 A of the dossier contained no results for the derivation of an added benefit of vortioxetine in comparison with the ACT for the research question of relapse prevention under maintenance treatment. There was therefore no hint of an added benefit of vortioxetine in comparison with the ACT in relapse prevention under maintenance treatment of patients with major depressive episodes; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

In Module 4 A, the company presented no data on relapse prevention under maintenance treatment for patients with major depressive episodes. There was therefore no hint of an added benefit of vortioxetine in comparison with the ACT in relapse prevention under maintenance treatment; an added benefit is therefore not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

The company did not investigate this research question.

The G-BA decides on the added benefit.

2.4.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.5 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of vortioxetine in comparison with the ACT is summarized in Table 5.

Table 5: Vortioxetine – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Major depressive episodes in adults[b]		
▪ mild episodes	▪ no drug treatment	▪ added benefit not proven
▪ moderate episodes	▪ SSRI: **citalopram**	▪ added benefit not proven
▪ severe episodes	▪ SSRI: **citalopram** The patient should be offered psychotherapeutic treatment	▪ added benefit not proven[c]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: Acute treatment and relapse prevention under maintenance treatment.
c: Both in patients who have decided against psychotherapy and in patients who have decided to have psychotherapy.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SSRI: selective serotonin reuptake inhibitor

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Please see full dossier assessment for full reference list.

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