

# Vortioxetine in Subgroups of Patients with Major Depressive Disorder and Early-Stage Dementia: Further Results from the MEMORY Study

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**Background:** Depression and dementia are common in older adults; however, many antidepressants have limited effectiveness in patients with major depressive disorder (MDD) comorbid with dementia. In the MEMORY study (NCT04294654), significant improvements in depressive symptom severity, cognitive performance, overall functioning, and health-related quality of life were seen in patients with MDD and early-stage dementia during treatment with vortioxetine. This subgroup analysis was undertaken to further explore the effectiveness of vortioxetine in this patient population.

**Methods:** MEMORY was a multinational, open-label, Phase IV study. Patients ( $n = 82$ ) aged 55–85 years with MDD and early-stage dementia were treated with vortioxetine (5–20 mg/day) for 12 weeks. This was a post-hoc analysis for four key subgroups of patients in this study: (i) those with Alzheimer's disease ( $n = 35$ ), (ii) those with mixed-type dementia ( $n = 22$ ), (iii) those receiving concomitant drugs for dementia ( $n = 34$ ), and (iv) those with severe depression (Montgomery–Åsberg Depression Rating Scale [MADRS] total score  $\geq 30$ ) at baseline ( $n = 42$ ).

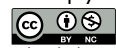
**Results:** Significant improvement in depressive symptom severity was seen in all patient subgroups from week 1 onwards ( $P < 0.05$ ). At week 12, the mean change from baseline ranged from approximately  $-12$  to  $-14$  for MADRS total score ( $P < 0.0001$ ),  $-6$  to  $-8$  for MADRS anhedonia subscore ( $P < 0.0001$ ), and  $+3$  to  $+6$  for Digit Symbol Substitution Test score ( $P < 0.05$ ). Improvements in verbal memory, ability to perform activities of daily living, health-related quality of life, and overall disease severity were also observed in all patient subgroups.

**Conclusion:** Our findings provide further support for the effectiveness and tolerability of vortioxetine in patients with MDD and early-stage dementia. Clinically significant improvement in depressive symptoms, cognitive performance, and health-related quality of life during treatment with vortioxetine was observed in patients with Alzheimer's disease, those with mixed-type dementia, patients receiving concomitant treatment with drugs for dementia, and those with severe depression.

**Keywords:** Alzheimer's disease, cognitive performance, early-stage dementia, major depressive disorder, mixed-type dementia, vortioxetine

## Introduction

Dementia is a global public health concern. Current estimates suggest that more than 55 million people worldwide were living with dementia in 2019, with prevalence predicted to increase to approximately 150 million by 2050.<sup>1</sup> Dementia is a leading cause of disability and dependency in the elderly, imposing a substantial socioeconomic burden. The global cost of dementia was estimated to be US\$ 1.3 trillion in 2019 and this is projected to more than double by 2030.<sup>2</sup> Alzheimer's disease is the most common form of dementia, accounting for 60–70% of cases.<sup>3</sup> Patients may be affected by mixed dementia types (most commonly, Alzheimer's disease and vascular dementia).



Depression is common in people living with dementia,<sup>4,5</sup> and is often an initial symptom of early-stage dementia.<sup>6</sup> Individuals with dementia have been shown to have a two-fold greater risk of depression than healthy age-matched controls.<sup>7</sup> In people with dementia, depression has been shown to be associated with greater cognitive decline, reduced health-related quality of life, loss of independence, increased caregiver burden, a greater risk of suicide, and increased overall mortality.<sup>8–14</sup>

The relationship between depression and dementia appears bidirectional. Depression may arise because of the cognitive and functional impairments experienced by individuals with dementia. However, depression is also recognized to be a potentially modifiable risk factor for all types of dementia.<sup>15–17</sup> A recent analysis of data from the UK Biobank for over 350,000 individuals aged 50–70 years found those with a diagnosis of depression at baseline to have a 50% higher risk of subsequently developing dementia over the 12 years of follow-up.<sup>18</sup> Individuals who were receiving treatment for their depression (ie, drugs for depression, psychotherapy, or a combination of the two approaches) were found to be less likely to develop dementia than those not receiving treatment. Effective treatment of depression is therefore recommended to potentially reduce dementia risk across the life course.<sup>17</sup>

Recognizing depression in older patients can be difficult, particularly in those affected by dementia.<sup>19,20</sup> In patients with dementia, anhedonia is often the most typical symptom of depression.<sup>20</sup> Rather than depressed mood, patients and their caregivers also tend to report less specific symptoms, such as gastrointestinal issues, fatigue, sleep disturbances or insomnia, pain, social isolation and withdrawal, and increased dependency.<sup>19</sup> There is currently no clear consensus concerning the optimum management of depression in patients with dementia. Many antidepressants have limited effectiveness in this population.<sup>21–23</sup> Tolerability of antidepressant treatment is also of particular concern in older individuals who may also be receiving other medications for comorbid medical conditions increasing the potential for pharmacokinetic drug interactions.

Vortioxetine is an antidepressant with a multimodal mechanism of action that acts both as an inhibitor of the serotonin transporter and as a modulator of various serotonin receptor subtypes.<sup>24–26</sup> As such, vortioxetine directly and indirectly influences the activity of multiple neurotransmitters implicated in the regulation of mood and cognition, including not only serotonin, but also acetylcholine, dopamine, gamma-aminobutyric acid, glutamate, histamine, and norepinephrine.<sup>27</sup> Vortioxetine has well documented efficacy across the spectrum of symptoms seen in patients with MDD,<sup>24–26</sup> including anhedonia.<sup>28–30</sup> The procognitive effects of vortioxetine in patients with MDD are also well-documented,<sup>26,31–33</sup> including in elderly patients.<sup>34,35</sup> Vortioxetine may therefore be considered an attractive option for the treatment of MDD in patients with dementia.

Vortioxetine has demonstrated effectiveness for improving mood, cognitive symptoms, objective cognitive performance, and global functioning in patients with major depressive disorder and comorbid Alzheimer's disease.<sup>36–40</sup> Vortioxetine has also been shown to have beneficial effects on cognitive performance in older adults with mild cognitive impairment who were not experiencing depressive symptoms.<sup>41</sup> In the MEMORY study, patients with MDD and a confirmed diagnosis of early-stage dementia experienced statistically and clinically significant improvements in depressive symptoms, cognitive performance, daily and global functioning, and health-related quality of life during treatment with vortioxetine for 12 weeks.<sup>42</sup> Early improvement was seen across all study outcomes and vortioxetine treatment was well-tolerated.

Given the relative paucity of data concerning the use of antidepressants in patients with MDD comorbid with dementia, this post-hoc analysis of data from the MEMORY study was undertaken to further explore the effectiveness of vortioxetine in four key patient subgroups, namely: those with two of the most common types of dementia (Alzheimer's disease and mixed-type dementia); those receiving concomitant treatment with one or more drugs for dementia; and those with severe depressive symptoms at baseline.

## Methods

### Study Design

MEMORY was a multinational, open-label, Phase IV study undertaken to investigate the effectiveness of vortioxetine in improving depressive symptoms and cognitive performance in patients aged 55–85 years with MDD and early-stage dementia (NCT04294654). The study design has been reported in detail previously.<sup>42</sup> In brief, the study was conducted at psychiatric outpatient sites in Estonia, France, Italy, Poland, and Spain from February 2020 to July 2022. Eligible patients

had a primary diagnosis of MDD (with onset before the age of 55 years of age) and comorbid early-stage dementia (not associated with vitamin B12 or folate deficiency and diagnosed at least 6 months before screening and after the patient had already been diagnosed with MDD). All patients were experiencing a current major depressive episode (duration <6 months and confirmed using the Mini-International Neuropsychiatric Interview). Other inclusion criteria were a Montgomery–Åsberg Depression Rating Scale (MADRS) total score  $\geq 26$  (ie, moderate to severe depression) and a Mini-Mental State Examination-2 (MMSE-2) total score of 20–24 (ie, mild dementia).

Patients received treatment with vortioxetine for 12 weeks. Vortioxetine was initiated at a dose of 5 mg/day (ie, the recommended starting dosage for elderly patients), with dosage up-titrated to 10 mg/day in all patients after one week. Thereafter, vortioxetine dosage could be adjusted (5–20 mg/day) at the investigator's discretion. Use of other drugs for depression was not permitted during the study. However, patients were permitted to continue treatment with acetylcholinesterase inhibitors or memantine during the study provided they had been receiving these medications at a stable dosage for  $\geq 3$  months before screening. No change in dementia medication was permitted during the study. Patients who had received treatment with anti-amyloid-beta or anti-tau protein monoclonal antibodies within 1 year of study entry were excluded.

## Study Assessments

Effectiveness assessments were performed at baseline and weeks 1, 4, 8 (MADRS only) and 12. An overview of the different assessment scales used to evaluate treatment effectiveness is provided in [Supplementary Table 1](#). Depression severity was assessed by MADRS total score. The MADRS anhedonia score was also calculated; this is the sum of the scores for MADRS items 1 (apparent sadness), 2 (reported sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel). MADRS anhedonia score ranges from 0 to 30, with higher scores indicative of more severe symptoms.

Cognitive performance was assessed using the Digit Symbol Substitution Test (DSST) and the Rey Auditory Verbal Learning Test (RAVLT). For the RAVLT, the primary outcome measure was the RAVLT total score (ie, the sum of the scores for Trials I to V assessing short recall; see [Supplementary Table 1](#)). To reduce the potential for learning effects that could contribute to any improvement in cognitive performance over time, patients were required to undertake a familiarity test for the DSST prior to baseline. Patients did not undertake familiarity training for the RAVLT. In addition, cognitive performance was not assessed at the week 8 visit resulting in a 2-month gap between the two on-treatment assessments for both scales to minimize any learning effects related to these two neuropsychological tests.

Daily functioning was assessed using the Instrumental Activities of Daily Living (IADL) scale, health-related quality of life was assessed using the Bath Assessment of Subjective Quality of Life in Dementia (BASQID) scale, and overall disease severity and clinical improvement were assessed using the Clinical Global Impression (CGI) scale.

Safety was assessed by monitoring of treatment-emergent adverse events (TEAEs) throughout the study period in the four patient subgroups.

## Statistical Analysis

This was a post-hoc analysis of effectiveness and safety in four patient subgroups: (i) those with Alzheimer's disease; (ii) those with mixed-type dementia; (iii) those receiving concomitant treatment with one or more drugs for dementia; and (iv) those with severe depressive symptoms (defined as MADRS total score  $\geq 30$ ) at baseline. Individual patients could be eligible for inclusion in more than one subgroup. For each subgroup, effectiveness was analyzed in all patients who received at least one dose of study medication and had data available at baseline and at least one subsequent time point (full analysis set). Safety was analyzed in all patients who received at least one dose of vortioxetine (all patients treated set).

The least-squares (LS) mean change from baseline in MADRS, DSST, RAVLT, IADL, BASQID and Clinical Global Impression–Severity of Illness (CGI-S) scores was calculated at each available time point using a mixed model for repeated measurements (MMRM). As previously described,<sup>42</sup> the model included week and site as fixed factors and baseline score as a covariate. The interaction between baseline score and week was also included in the model and an unstructured covariance matrix was applied. Clinical Global Impression–Improvement (CGI-I) scores were analyzed in the same way, using CGI-S score at baseline as the baseline covariate. Results are shown with 95% confidence intervals (CI). For all endpoints except CGI-I scores, *P* values are based on change from baseline; for CGI-I scores, *P* values were

calculated using the null hypothesis that CGI-I = 4 (ie, no improvement). Reported *P* values are nominal and no correction for multiplicity was applied. *P* values < 0.05 were considered significant.

Safety endpoints were summarized descriptively. All analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA).

## Results

### Patients

Of the 82 patients who were enrolled and received at least one dose of vortioxetine, 35 (43%) had Alzheimer's disease, 22 (27%) had mixed-type dementia, 34 (41%) were receiving concomitant treatment with at least one drug for dementia, and 42 (51%) had severe depression (ie, MADRS total score  $\geq 30$ ) at baseline. A total of 13 patients (16%) withdrew from the overall study population (6 due to adverse events, 5 due to withdrawal of consent, and 4 due to lack of effectiveness; some patients provided more than one reason for withdrawal). Rates of withdrawal were broadly similar to that in the overall study population for all patient subgroups.

Baseline demographic and clinical characteristics were broadly similar across the four patient subgroups and were in line with those of the overall study population (Table 1). At baseline, the median MMSE score was 22 in all patient subgroups. The proportion of patients who had received prior antidepressant treatment ranged from 64% to 79% across the four patient subgroups. Of the 34 patients receiving concomitant treatment with drugs for dementia, 29 were receiving donepezil (85%), 9 memantine (26%), and 3 rivastigmine (9%). Some patients were taking more than one drug for dementia.

### Effectiveness

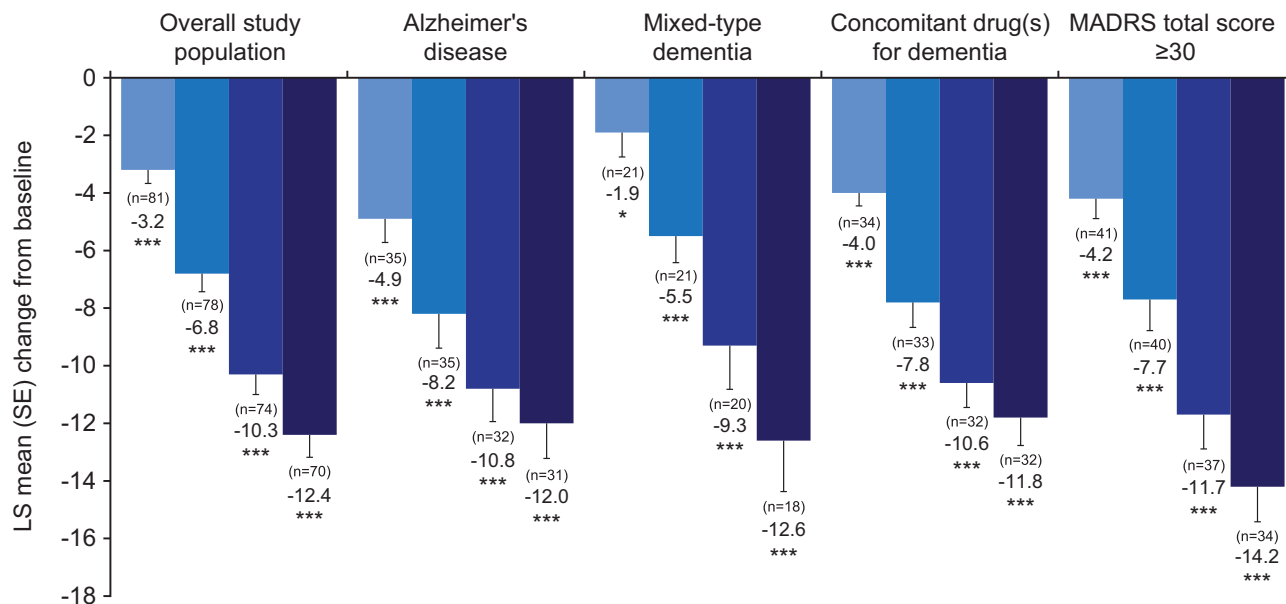
In line with the results for the overall study population, statistically significant improvement in the severity of overall depressive symptoms was seen in all patient subgroups from week 1 onwards (Figure 1A). As shown, the LS mean [95% CI] change in MADRS total score from baseline after 12 weeks of vortioxetine treatment was  $-11.8$  [ $-13.8, -9.9$ ] in patients receiving concomitant treatment with drugs for dementia ( $n = 32$ ),  $-12.0$  [ $-14.4, -9.5$ ] in patients with Alzheimer's disease

**Table 1** Baseline Patient Demographics and Clinical Characteristics in the Overall Study Population and the Four Patient Subgroups (All Treated Patients)

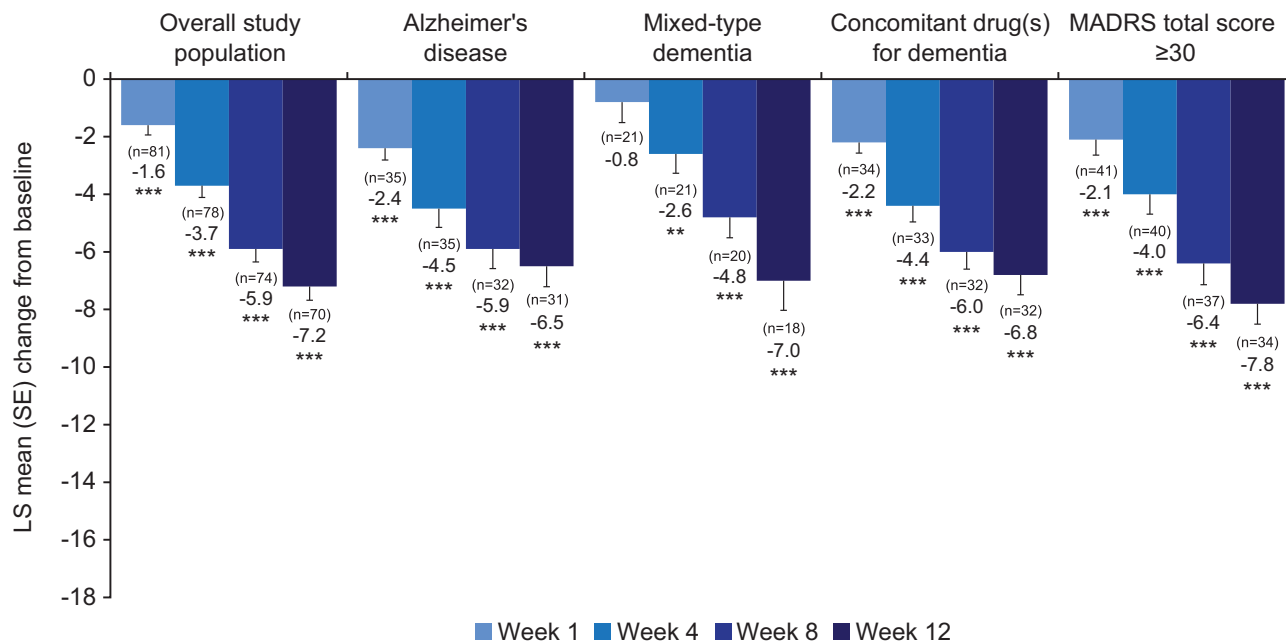
	Overall Population	Alzheimer's Disease	Mixed-Type Dementia	Concomitant Drug(s) for Dementia	MADRS Total Score $\geq 30$
No. of patients	82	35	22	34	42
Age (years), mean $\pm$ SD	70.3 $\pm$ 7.3	71.0 $\pm$ 7.8	71.0 $\pm$ 7.4	69.5 $\pm$ 7.3	69.8 $\pm$ 7.9
Female, n (%)	54 (66)	24 (69)	13 (59)	20 (59)	29 (69)
White, n (%)	78 (95)	33 (94)	22 (100)	33 (97)	41 (98)
Prior antidepressant treatment, n (%)	57 (70)	25 (71)	14 (64)	27 (79)	28 (67)
Clinical assessment scores, mean $\pm$ SD					
MMSE total score	21.9 $\pm$ 1.3	22.0 $\pm$ 1.4	22.2 $\pm$ 1.1	21.9 $\pm$ 1.4	22.2 $\pm$ 1.2
MADRS total score	30.4 $\pm$ 3.9	29.1 $\pm$ 3.5	31.2 $\pm$ 3.5	29.2 $\pm$ 2.8	33.2 $\pm$ 3.5
MADRS anhedonia score	19.0 $\pm$ 2.5	18.6 $\pm$ 2.3	19.1 $\pm$ 2.4	18.4 $\pm$ 2.6	20.1 $\pm$ 2.5
DSST	23.3 $\pm$ 12.8	23.4 $\pm$ 10.8	26.0 $\pm$ 18.7	23.8 $\pm$ 9.9	20.0 $\pm$ 9.6
RAVLT total score	28.7 $\pm$ 9.3	29.6 $\pm$ 9.8	27.4 $\pm$ 7.0	28.3 $\pm$ 9.3	28.5 $\pm$ 9.6
IADL polytomous total score	15.6 $\pm$ 4.4	15.4 $\pm$ 4.5	14.1 $\pm$ 3.4	16.8 $\pm$ 4.6	15.6 $\pm$ 4.9
BASQID total score (%)	31.3 $\pm$ 12.4	31.8 $\pm$ 12.5	34.0 $\pm$ 11.8	30.5 $\pm$ 12.6	28.4 $\pm$ 11.8
CGI-S	4.6 $\pm$ 0.7	4.6 $\pm$ 0.7	4.7 $\pm$ 0.6	4.7 $\pm$ 0.7	4.7 $\pm$ 0.6

**Abbreviations:** BASQID, Bath Assessment of Subjective Quality of Life in Dementia; CGI-S, Clinical Global Impression–Severity of Illness; DSST, Digit Symbol Substitution Test; IADL, Instrumental Activities of Daily Living; MADRS, Montgomery–Åsberg Depression Rating Scale; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Visual Learning Test; SD, standard deviation.

## A. MADRS total score



## B. MADRS anhedonia score



**Figure 1** LS mean (SE) change from baseline by patient subgroup for (A) MADRS total score and (B) MADRS anhedonia subscore.

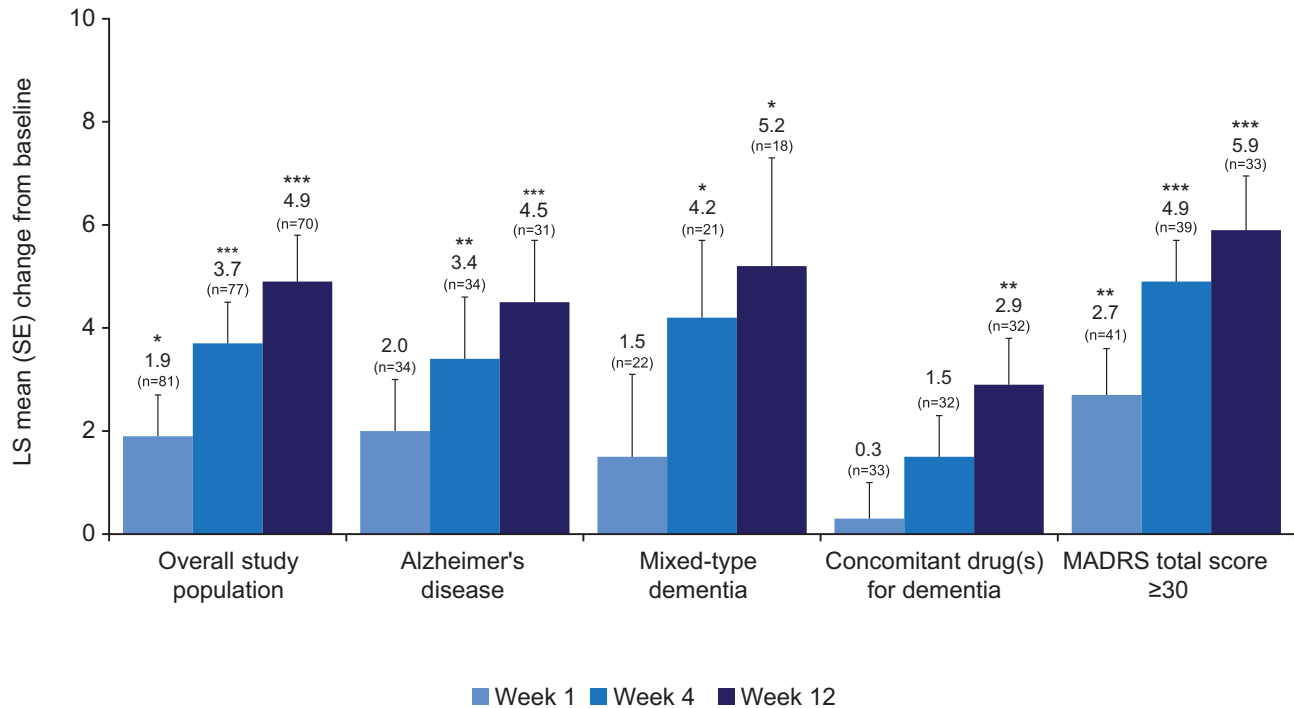
**Notes:** \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

**Abbreviations:** LS, least-squares; MADRS; Montgomery–Åsberg Depression Rating Scale; SE, standard error.

( $n = 31$ ),  $-12.6 [-16.3, -8.8]$  in patients with mixed-type dementia ( $n = 18$ ), and  $-14.2 [-16.7, -11.7]$  in patients with severe depressive symptoms at baseline ( $n = 34$ ;  $P < 0.0001$  for all subgroups). Significant improvement in MADRS anhedonia score from baseline to week 12 was also seen across all patient subgroups (all  $P < 0.0001$ ; Figure 1B).

Significant improvement in cognitive performance assessed using the DSST was also seen after 12 weeks of vortioxetine treatment in all patient subgroups (Figure 2). At week 12, the mean change in DSST score from baseline

## DSST total score



**Figure 2** LS mean (SE) change from baseline by patient subgroup for DSST total score.

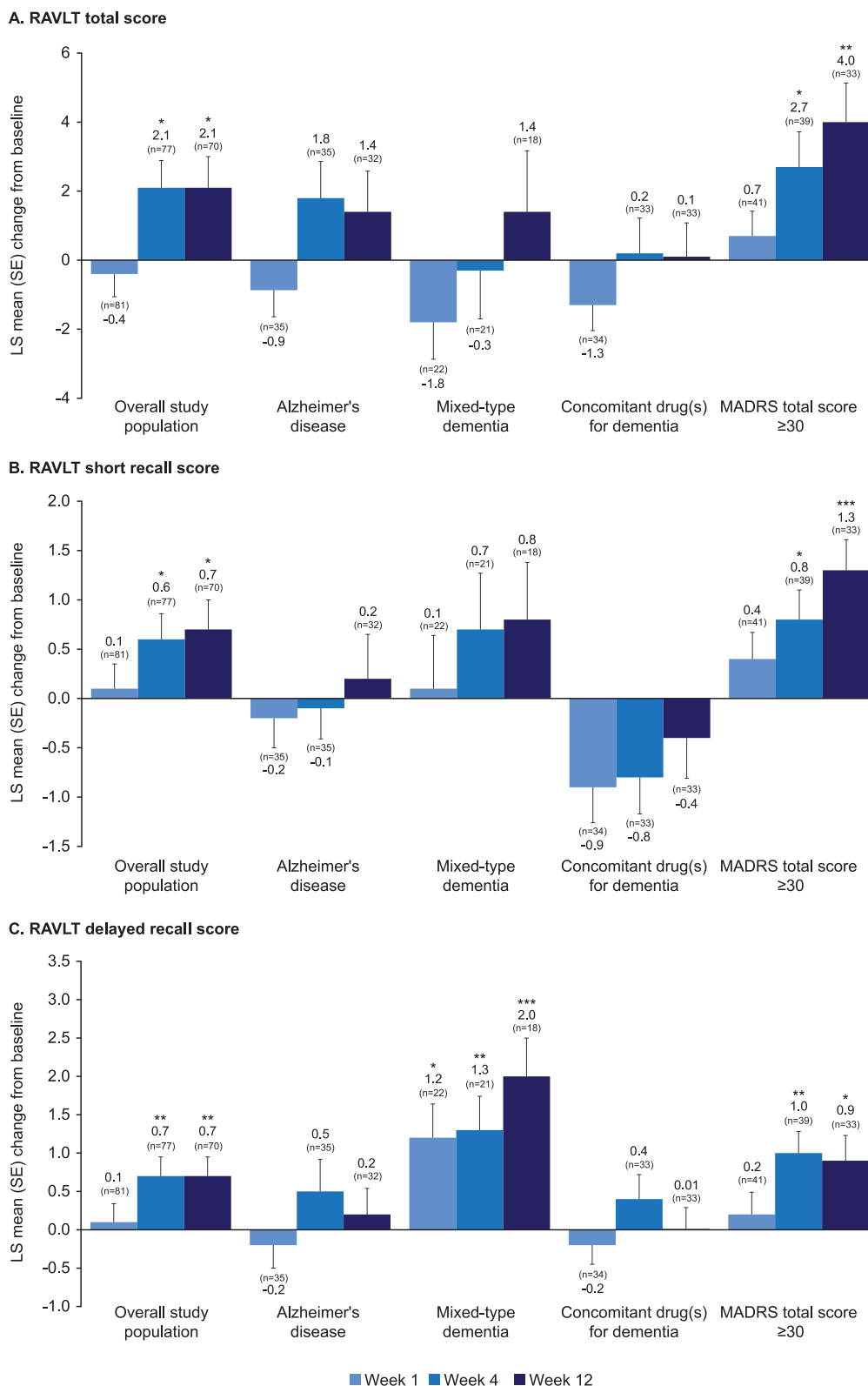
**Notes:** \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

**Abbreviations:** DSST, Digit Symbol Substitution Test; LS, least-squares; SE, standard error.

was 2.9 [1.0, 4.8] in patients receiving concomitant treatment with drugs for dementia ( $n = 32$ ;  $P < 0.01$ ), 4.5 [2.0, 7.0] in patients with Alzheimer's disease ( $n = 31$ ;  $P < 0.001$ ), 5.2 [0.9, 9.4] in patients with mixed-type dementia ( $n = 18$ ;  $P < 0.05$ ), and 5.9 [3.8, 8.1] in those with severe depressive symptoms at baseline ( $n = 33$ ;  $P < 0.0001$ ). The mean change in RAVLT total score from baseline after 12 weeks of vortioxetine treatment was 0.1 [-1.9, 2.1] in patients receiving concomitant treatment with drugs for dementia ( $n = 33$ ; not significant), 1.4 [-1.0, 3.8] in patients with Alzheimer's disease ( $n = 32$ ; not significant), 1.4 [-2.3, 5.1] in patients with mixed-type dementia ( $n = 18$ ; not significant), and 4.0 [1.6, 6.3] in those with severe depressive symptoms at baseline ( $n = 33$ ;  $P < 0.01$ ) (Figure 3A). At week 12, the mean change in RAVLT short recall score from baseline (Figure 3B) ranged from -0.4 [-1.3, 0.4] in patients receiving concomitant treatment with drugs for dementia ( $n = 33$ ; not significant) to 1.3 [0.6, 1.9] in patients with severe depressive symptoms at baseline ( $n = 33$ ;  $P < 0.001$ ). The corresponding mean change in RAVLT delayed recall score from baseline (Figure 3C) ranged from 0.01 [-0.6, 0.6] in patients receiving concomitant treatment with drugs for dementia ( $n = 33$ ; not significant) to 2.0 [1.0, 3.1] in patients with mixed-type dementia ( $n = 18$ ;  $P < 0.001$ ).

Improvement in daily functioning assessed by the IADL polytomous score was seen in all patient subgroups during treatment with vortioxetine (Figure 4A). At week 12, the mean change in IADL polytomous total score was -0.3 [-1.1, 0.4] in patients receiving concomitant treatment with drugs for dementia ( $n = 33$ ; not significant), -0.5 [-1.2, 0.2] in patients with Alzheimer's disease ( $n = 32$ ; not significant), -0.7 [-1.6, 0.3] in patients with mixed-type dementia ( $n = 19$ ; not significant), and -1.0 [-2.0, -0.0] in patients with severe depressive symptoms at baseline ( $n = 36$ ;  $P < 0.05$ ).

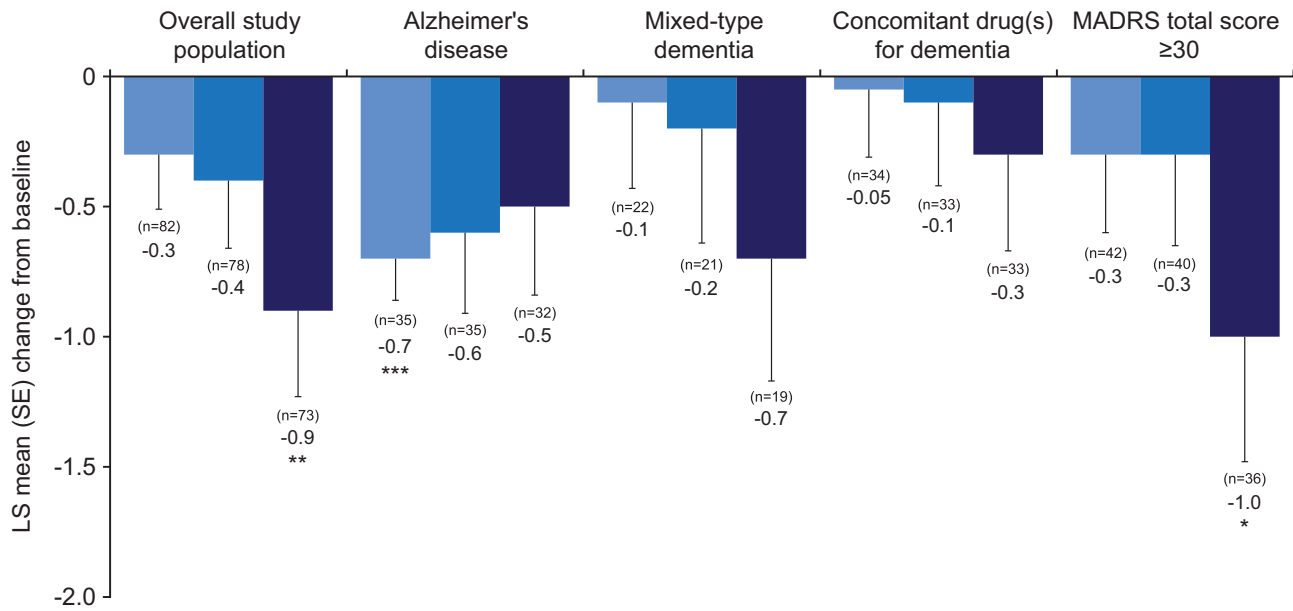
Significant improvement in health-related quality of life assessed using the BASQID was observed from week 4 onwards across all four patient subgroups (Figure 4B). After 12 weeks of vortioxetine treatment, the mean change from baseline in percentage BASQID total score was 8.2 [4.2, 12.1] in patients with Alzheimer's disease ( $n = 32$ ), 8.9 [4.6, 13.2] in patients with mixed-type dementia ( $n = 18$ ), 10.2 [7.0, 13.5] in patients receiving concomitant treatment with



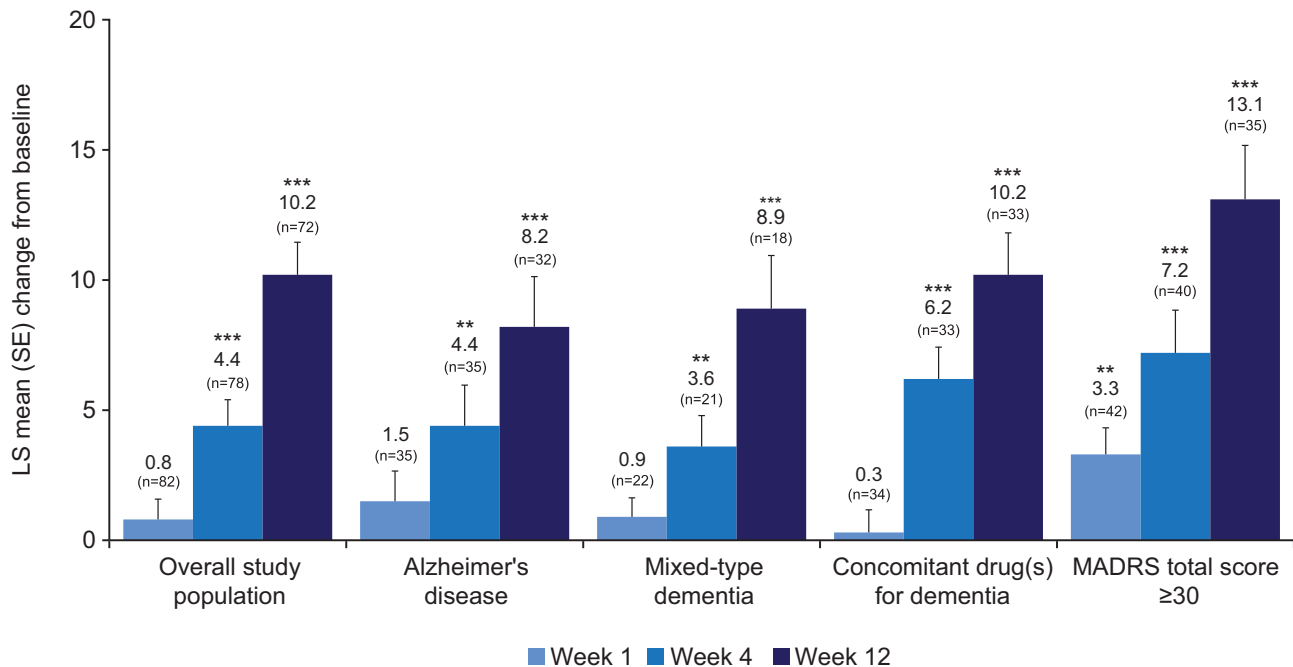
**Figure 3** LS mean (SE) change from baseline by patient subgroup for (A) RAVLT total score, (B) RAVLT short recall score, and (C) RAVLT delayed recall score. Notes: \*P < 0.05; \*\*P < 0.01; \*\*\*P < 0.001.

Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; LS, least-squares; SE, standard error.

**A. IADL polytomous total score**



**B. BASQID total percentage score**



**Figure 4** LS mean (SE) change from baseline by patient subgroup for (A) IADL polytomous score and (B) percentage BASQID total score by patient subgroup.

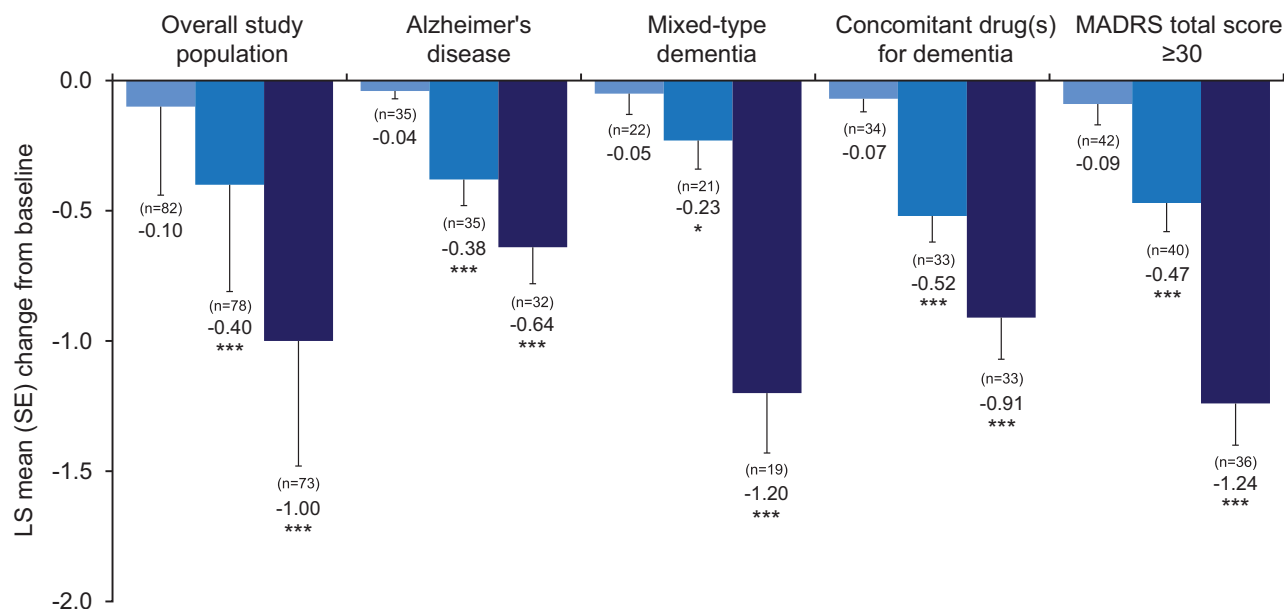
**Notes:** \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

**Abbreviations:** BASQID, Bath Assessment of Subjective Quality of Life in Dementia; IADL, Independent Activities of Daily Living; LS, least-squares; SE, standard error.

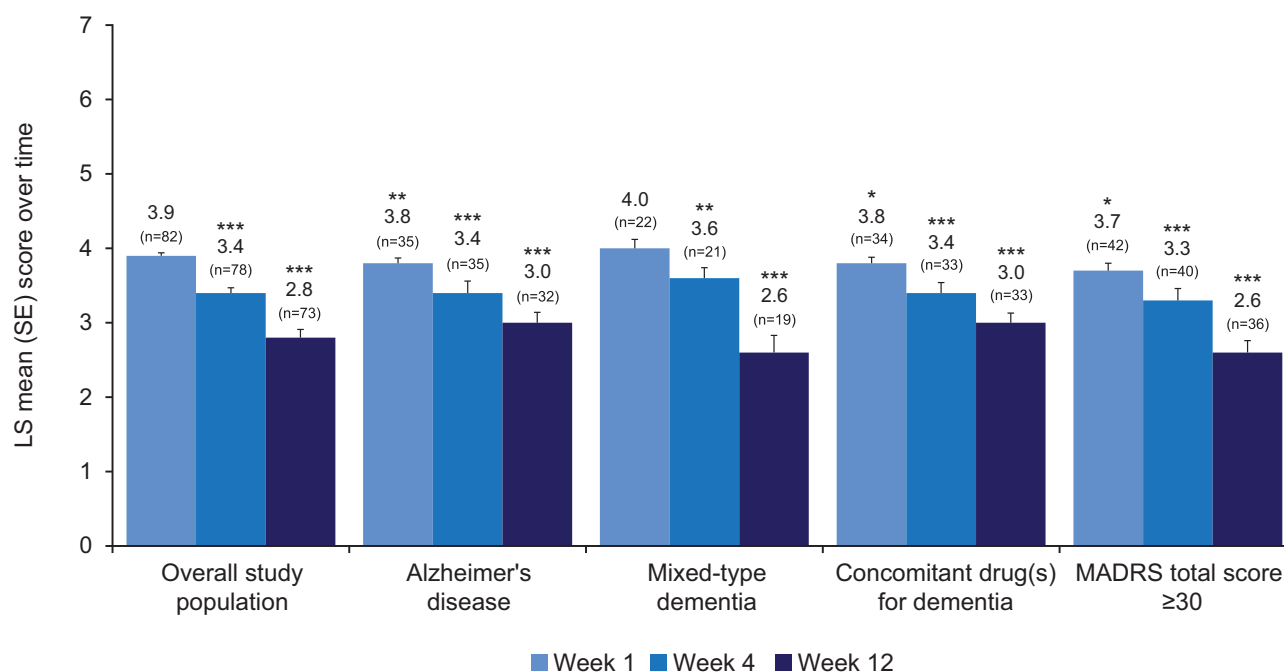
drugs for dementia ( $n = 33$ ), and 13.1 [8.9, 17.3] in those who had severe depression at baseline ( $n = 35$ ) ( $P < 0.0001$  for all subgroups).

Significant improvement in overall disease severity and its impact on global functioning assessed using the CGI-S and CGI-I was also seen in all patient subgroups over the 12 weeks of vortioxetine treatment (Figure 5).

## A. CGI-S score



## B. CGI-I score



**Figure 5 (A)** LS mean (SE) change in Clinical Global Impression–Severity of Illness score from baseline and **(B)** LS mean (SE) Clinical Global Impression–Improvement score over time.

**Notes:** \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ . As a baseline score is not available for CGI-I score,  $P$  values were calculated using the null hypothesis that CGI-I = 4 (ie, no improvement).

**Abbreviations:** CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity of Illness; LS, least-squares; SE, standard error.

## Safety

Treatment with vortioxetine was well tolerated, with no unexpected TEAEs reported in any of the patient subgroups (Supplementary Table 2). The tolerability profile of vortioxetine was in line with that seen in the overall study population across all patient subgroups. In the overall study population, TEAEs were mostly mild or moderate and only one serious

adverse event was reported (COVID-19 pneumonia considered by the investigator to be unrelated to treatment with vortioxetine). Only six patients withdrew from the overall study population due to TEAEs. The only TEAEs leading to study withdrawal in more than a single patient were headache and nausea (each reported by two patients).

## Discussion

Results of these subgroup analyses support and extend those of the primary analysis of the MEMORY study of vortioxetine in patients with MDD and early-stage dementia.<sup>42</sup> The clinically significant beneficial effects observed in the overall patient population in terms of improvement in depressive symptoms, cognitive performance, and health-related quality of life during treatment with vortioxetine were also evident in patients with two of the most common forms of dementia (Alzheimer's disease and mixed-type dementia), those receiving concomitant treatment with drugs for dementia, and patients who had severe depression (ie, MADRS total score  $\geq 30$ ) at baseline.

Improvement in the severity of core depressive symptoms, including anhedonia, was seen from week 1 onwards in all patient subgroups. After 12 weeks of vortioxetine treatment, the mean improvement in MADRS total and anhedonia scores across the different patient subgroups was 12–14 points and 6–8 points, respectively. In patients with MDD alone, a reduction in MADRS total score of 8–10 points is considered clinically meaningful.<sup>43–45</sup> For MADRS anhedonia factor, the proposed minimum clinically important change in patients with MDD is approximately 5 points.<sup>46</sup> In another study in outpatients with MDD and comorbid Alzheimer's disease receiving treatment with vortioxetine in routine care settings in South Korea ( $n = 207$ ), the mean change in MADRS total score from baseline was  $-11.5$  points at week 24.<sup>37</sup>

The improvements in cognitive performance, ability to perform activities of daily living, health-related quality of life, and overall disease severity and global functioning seen across all patient subgroups over the 12 weeks of vortioxetine are noteworthy given the progressive decline over time in these domains usually seen in patients with dementia. The observed improvement in cognitive performance assessed using the DSST in this study (ie, approximately 3–6 points across the four patient subgroups at week 12) is consistent with the proposed minimum clinically important change in older adults with a history of falls (3–5 points),<sup>47</sup> and appears greater than that reported in studies of vortioxetine for the treatment of MDD in elderly patients without a diagnosis of dementia (approximately 2–3 points).<sup>48,49</sup> The reported mean change in DSST score from baseline in outpatients with MDD and comorbid Alzheimer's disease after 24 weeks of vortioxetine treatment was approximately 4 points.<sup>37</sup>

Improvements in RAVLT scores were also seen in all patient subgroups after 12 weeks of vortioxetine treatment, except those receiving concomitant treatment for dementia. It is possible that greater improvement in RAVLT scores may have been observed across all patient subgroups over longer term therapy. In another recent study in patients with MDD and Alzheimer's disease treated with vortioxetine, the mean improvement in RAVLT total score increased from approximately 2 points after 4 months of vortioxetine treatment to 7 points after 12 months.<sup>38</sup>

Vortioxetine was well tolerated in all patient subgroups, including those receiving concomitant treatment for dementia (mostly, donepezil). Safety results were consistent with those observed in the overall study population<sup>42</sup> and with the known tolerability profile of vortioxetine in patients with MDD.<sup>50,51</sup> The safety profile of vortioxetine has been established over a post-authorization period of more than 10 years. Previous studies have shown vortioxetine to be efficacious and well tolerated for the treatment of MDD in older patients with MDD,<sup>48,49</sup> including those with comorbid medical conditions taking a variety of concomitant medications.<sup>52</sup> The pharmacokinetic and pharmacodynamic profile of vortioxetine is well characterized.<sup>53</sup> Of note, vortioxetine does not significantly impact cytochrome P450 enzyme activity, reducing the risk of clinically significant drug–drug interactions.<sup>53</sup> This is an important consideration in older patients with dementia in whom polypharmacy is common.

Potential limitations include the open-label study design, the lack of a placebo or comparator group, and the post-hoc nature of these analyses. In addition, the MEMORY study was not powered to investigate treatment effectiveness and tolerability in the different patient subgroups, resulting in a relatively small number of patients in some subgroups, and individual patients may have been included in more than one subgroup; this may limit generalization of the study findings. As such, our findings should be considered exploratory and should be interpreted with caution.

A further consideration is the potential contribution of learning effects to the observed improvements in measures of cognitive performance over time. However, attempts were undertaken to mitigate against such effects in this study. First,

as the DSST is not widely used in routine practice settings, participants undertook familiarity training with this scale at the screening visit to minimize the impact of any potential learning effects on early on-treatment assessments. The magnitude of the improvements in DSST and RAVLT scores observed at the week 1 visit in both the overall study population and the individual patient subgroups suggests that any learning effects due to the familiarity training were minimal. Secondly, neither the DSST nor RAVLT were assessed at week 8, resulting in an interval of 2 months between the final two on-treatment assessments of cognitive performance. In an elderly patient population with a confirmed diagnosis of dementia and MDD, this time interval between neuropsychological tests should be sufficient to minimize any learning effects.

Furthermore, treatment duration was only 12 weeks and both MDD and dementia require long-term treatment. While our findings do not provide information on long-term MDD and dementia treatment outcomes in the patient subgroups analyzed, results of other studies show the beneficial effects of vortioxetine on depressive symptoms, cognitive performance, patient functioning, and health-related quality of life in patients with MDD and dementia to be sustained over treatment periods of up to 12 months.<sup>36–40</sup>

Finally, dementia-specific assessment scales were not used in the present study; however, significant improvements in mood symptoms assessed using the Cornell Scale for Depression in Dementia and the Geriatric Depression Scale and cognitive function assessed using the MMSE and the Neuropsychiatric Inventory have been reported in other studies in patients with MDD and Alzheimer's disease treated with vortioxetine.<sup>36,38–40</sup>

## Conclusion

In summary, our findings further support the use of vortioxetine for the treatment of patients with MDD and early-stage dementia. Clinically significant improvement in core depressive symptoms (including anhedonia), cognitive performance, health-related quality of life, and overall disease severity was seen in patients with Alzheimer's disease and those with mixed-type dementia, patients receiving concomitant treatment with drugs for dementia, and patients with severe depressive symptoms at baseline. Treatment with vortioxetine was well tolerated in all patient subgroups, with reported adverse effects consistent with the established tolerability profile.

## Abbreviations

BASQID, Bath Assessment of Subjective Quality of Life in Dementia scale; CGI, Clinical Global Impression scale; CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity of Illness; CI, confidence intervals; DSST, Digit Symbol Substitution Test; IADL, Instrumental Activities of Daily Living scale; LS, least-squares; MMRM, mixed model for repeated measurements; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; MMSE-2, Mini-Mental State Examination-2; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; SE, standard error; TEAEs, treatment-emergent adverse events.

## Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article. For information about clinical data sharing policy and processes, please visit: <https://www.lundbeck.com/global/our-science/clinical-data-sharing>.

## Ethics Approval and Informed Consent

The MEMORY study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the appropriate ethics committee(s)/institutional review board(s) in each country: Estonia (Research Ethics Committee of the National Institute for Health Development, Tallinn); France (Comité de Protection des Personnes QUEST III, Poitiers Cedex); Italy (Comitato Etico di Brescia, Brescia; Comitato Etico Indipendente Fondazione Santa Lucia, Rome; Comitato Etico Regionale dell'Umbria, Perugia; and Comitato Etico Della Province Di Chieti e Pescara, Chieti); Poland (Komisja Bioetyczna, Warsaw); and Spain (Ethics Committee for Research with Medicines, Madrid). Written informed consent was obtained from all patients or their legal representatives prior to study participation.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors report no other conflicts of interest in this work.

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