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The MEMORY Study: An Effectiveness Study of Vortioxetine in Patients With Major Depressive Disorder and Early Dementia

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BACKGROUND

- Major depressive disorder (MDD) is one of the most prevalent psychiatric diseases, affecting approximately 350 million people worldwide. The recurrence rate of MDD is high, associated with cognitive impairment, reduced functioning, and poor quality of life (QoL)[1,2]
- Dementia is also a condition with a high rate of occurrence of around 55 million cases worldwide.[3] Risk of dementia increases with age, doubling every 5 years after the age of 65 years[4]
- Depression and depressive episodes can be a reaction to early-onset cognitive deficit, which can advance to dementia. Comorbid dementia and depressive conditions, such as MDD, often share a symbiotic relationship, with each one indicating a poor prognosis for the other[4,5]
- Vortioxetine is a multimodal antidepressant, approved in more than 80 countries for the treatment of MDD,[6] demonstrating efficacy, tolerability, and safety in adults as well as elderly patients with MDD and comorbid Alzheimer's disease, and showing improvement in depressive symptoms including cognitive performance.[6–9] The direct effect of vortioxetine on cognitive function improvement is profound[10]
- The MEMORY study investigated the effectiveness of vortioxetine in patients with MDD and early-onset comorbid dementia in improving depressive symptoms and cognitive performance

OBJECTIVES

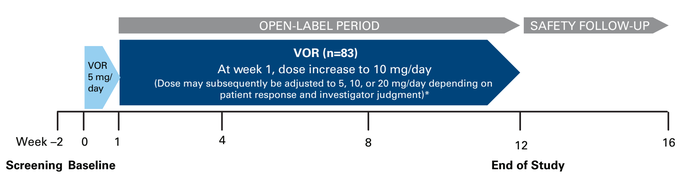
- To evaluate the effectiveness of vortioxetine flexible dose 10–20 mg, with a starting dose of 5 mg, during 12 weeks of acute treatment on depressive symptoms in patients with MDD and comorbid dementia
- To assess the effectiveness of vortioxetine treatment on cognitive performance, global clinical impression, severity in relation to daily functioning, and health-related QoL

METHODS

Study Design and Patients

- In this interventional, open-label, flexible-dose, single-group study, vortioxetine was administered orally at a starting dose of 5 mg once daily from baseline to week 1 and increased to 10 mg once daily at week 1 visit. After week 1, the dose could be increased to 20 mg or decreased to 5 mg, based on investigator judgment and patient response (**Figure 1**)
- Duration of the study included a 2-week screening period and a 12-week treatment period, with a safety follow-up visit 4 weeks after the last treatment or withdrawal
- Patients were enrolled in the study based on the following eligibility criteria:
  - Patients aged 55–85 years diagnosed with recurrent MDD (onset before age 55 years) who experienced an episode within the past 6 months and with comorbid dementia ≥6 months prior to screening
  - Eligible patients required a baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score of ≥26 (moderate to severe depression) and a Mini-Mental State Examination, 2nd Edition, total score of 20–24 (mild dementia)
- Patients were excluded based on the following criteria:
  - Patients with dementia and vitamin B12 or folate deficiency, patients with significant risk of suicide, and patients with diagnosis of a psychiatric disorder other than MDD
  - Patients treated with anti–amyloid-beta or anti–tau protein monoclonal antibodies within 1 year of the study
- Concomitant medications disallowed or allowed with restrictions:
  - Patients on acetylcholinesterase (AChE) inhibitors, like donepezil, were allowed to participate only if they were on a stable dose, without any change in dose at least 3 months prior to the screening visit
  - The use of other antidepressants was not allowed within 2 weeks prior to baseline and throughout the study, except for selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), which were allowed until baseline. Fluoxetine was not allowed within 5 weeks prior to baseline or throughout the study

Figure 1. MEMORY Study Design



*Dose may be adjusted at either scheduled or unscheduled visits.
VOR, vortioxetine.

Endpoints and Assessments

- The primary endpoint was change from baseline to week 12 in MADRS total score, to assess the severity of symptoms in depressive illness. MADRS was administered at screening, baseline, week 1, week 4, week 8, and week 12
- Secondary endpoint assessments measured the following:
  - Cognitive performance using change from baseline to week 12 Digit Symbol Substitution Test (DSST) scores and Rey Auditory Verbal Learning Test (RAVLT) scores
  - Health-related QoL using change from baseline to week 12 Bath Assessment of Subjective Quality of Life in Dementia (BASQID) scores
  - Global clinical impression using Clinical Global Impression–Improvement (CGI-S) at week 12 (CGI-I) and change from baseline to week 12 CGI-Severity scores. Both the CGI-S and CGI-I scales evaluate symptoms in relation to daily functioning
  - Depression using response (defined as a ≥50% decrease from baseline in MADRS total score) and remission (MADRS ≤10) measures
- The safety endpoints were adverse events (AEs) and withdrawals due to AEs, assessed at week 12

Statistical Analysis

- Analyses were performed using an all-patients-enrolled set (APES), an all-patients-treated set (APTS) consisting of those who took ≥1 dose of vortioxetine, and a full-analysis set (FAS), including those in the APTS with a valid baseline assessment and ≥1 valid post-baseline assessment of MADRS total score. Effectiveness and safety analyses were based on FAS and APTS, respectively
- For primary endpoint analysis, estimates and associated CIs of the change from baseline to week 12 in MADRS total score were obtained from a mixed model for repeated measurements (MMRM), with week and site as fixed factors and baseline MADRS score as a covariate using an unstructured covariance matrix. Interaction between baseline MADRS score and week were also included in the analysis
- The continuous secondary efficacy endpoints will be analyzed using a similar MMRM model as the primary endpoint, other than for CGI-I where a baseline score of CGI-S was used, and response and remission were summarized by timepoint with 95% CIs

RESULTS

Patient Disposition

- In total, 83 patients were enrolled across 6 countries and from 24 study sites
- The APTS and FAS consisted of 82 (98.8%) patients, of whom 69 (83.1%) completed treatment and 13 (15.7%) discontinued treatment

Demographic and Baseline Characteristics

- The majority of patients were female (n=54 [65.9%]) and White/Caucasian (n=78 [95.1%]), and mean age was 70.3 (n=82) years (**Table 1**)

Table 1. Baseline Characteristics

Demographic Characteristics, n (%)	N=82
Sex	
Male	28 (34.1)
Female	54 (65.9)
Type of Dementia	
Alzheimer's disease	35 (42.7)
Mixed-type dementia	22 (26.8)
Vascular dementia	12 (14.6)
Other type of dementia	11 (13.4)
Frontotemporal dementia	2 (2.4)
Baseline Efficacy Variables , Mean (SD)	
MADRS	30.4 (3.85)
CGI-S	4.6 (0.65)
MMSE-2	21.9 (1.27
BASQID Percentage (Total)	31.3 (12.38)
Life satisfaction	29.5 (12.90)
Feeling of positive QoL	33.8 (15.33)
	n=81
DSST	23.3 (12.81)
RAVLT (Total)	28.7 (9.31)
Short recall	4.5 (2.41)
Delayed recall	4.1 (2.61)

BASQID, Bath Assessment of Subjective Quality of Life in Dementia; CGI-S, Clinical Global Impression–Improvement; DSST, Digit Symbol Substitution Test; MADRS, Montgomery-Åsberg Depression Rating Scale; MMSE-2, Mini-Mental State Examination, second edition; QoL, quality of life; RAVLT, Rey Auditory Verbal Learning Test.

Study Drug Exposure

- The mean daily oral dose of vortioxetine was 12.3 mg (n=82)
- All 82 patients received vortioxetine 5 mg/day between baseline to week 1 and between weeks 1 to 4, 79 (100%) of patients received vortioxetine 10 mg/day. Between weeks 4 to 8, vortioxetine was increased to 20 mg/day for 52.6% (n=40/76) of patients. From weeks 8 to 12, 47.2% (n=34/72) of patients remained on vortioxetine 20 mg/day (**Table 2**)

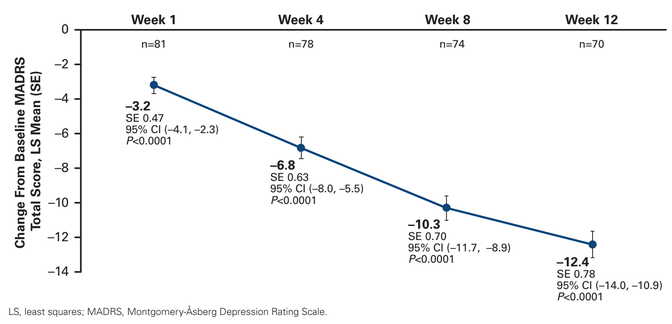
Table 2. Vortioxetine Exposure Throughout the Study

	Change in dosage, Yes/No	Vortioxetine 5 mg/day, n (%)	Vortioxetine 10 mg/day, n (%)	Vortioxetine 20 mg/day, n (%)
Baseline to week 1 (n=82)	No	82 (100)		
Weeks 1 to 4 (n=79)	Yes	2 (2.5)	79 (100)	1 (1.3)
Weeks 4 to 8 (n=76)	No	2 (2.6)	31 (40.8)	1 (1.3)
	Yes	3 (3.9)	3 (3.9)	40 (52.6)
Weeks 8 to 12 (n=72)	No	4 (5.6)	28 (38.9)	34 (47.2)
	Yes		3 (4.2)	3 (4.2)

Primary Outcome

- The mean (SE) change from baseline to week 12 (n=70) of the MADRS total score was –12.4 (0.78), indicating significant improvement in severity of symptoms (P<0.0001) (**Figure 2**)

Figure 2. LS Mean of MADRS Total Score Change From Baseline to Weeks 1, 4, 8, and 12



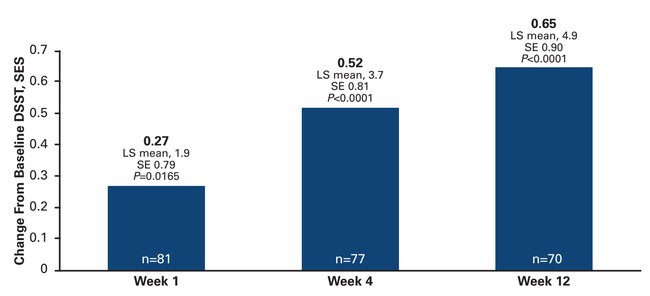
LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale.

Secondary Outcomes

Cognitive Outcomes

- The standardized effect size (SES) for change from baseline to week 12 DSST total score was 0.65, exceeding the minimum clinically important difference of 0.2 (**Figure 3**)

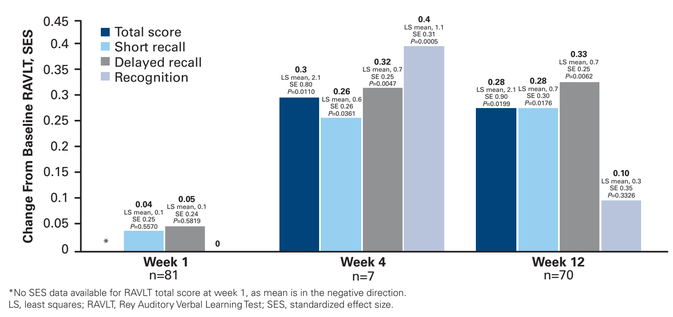
Figure 3. SES of Change From Baseline DSST at Weeks 1, 4, and 12



DSST, Digit Symbol Substitution Test; LS, least squares; SES, standardized effect size.

- At week 12 (n=70), a SES of 0.28 was observed for both change from baseline RAVLT total score and "short recall" and the SES for "delayed recall" was 0.33, exceeding the minimum clinically important difference of 0.2 (**Figure 4**)
- The SES for change from baseline RAVLT "recognition" at week 12 (n=70) was 0.10 (**Figure 4**)

Figure 4. SES of Change From Baseline RAVLT Scores at Weeks 1, 4, and 12

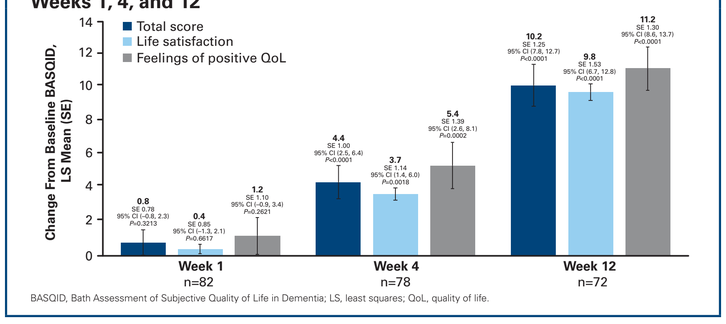


*No SES data available for RAVLT total score at week 1, as mean is in the negative direction.
LS, least squares; RAVLT, Rey Auditory Verbal Learning Test; SES, standardized effect size.

Health-Related QoL

- A significant improvement (P<0.0001) in subjective QoL was observed through the change from baseline to week 12 (n=72) mean (SE) of percentages of BASQID total score (10.2 [1.25]) (**Figure 5**)
- The mean (SE) of percentages for change from baseline to week 12 (n=72) BASQID subscores were 9.8 (1.53) and 11.2 (1.30), indicating significant improvement in patients' life satisfaction and feelings of positive QoL, respectively (P<0.0001) (**Figure 5**)

Figure 5. LS Mean of BASQID Percentages for Total Score, Life Satisfaction, and Feelings of Positive QoL Change From Baseline to Weeks 1, 4, and 12



BASQID, Bath Assessment of Subjective Quality of Life in Dementia; LS, least squares; QoL, quality of life.

- When answering the BASQID additional questions, 67 patients reported their memory as "very poor" or "poor" at baseline; only 39 patients answered questions at week 12. Yet, only 15 patients reported their memory as "fair" at baseline, which increased to 32 patients at week 12. One patient reported their memory as being "good" at week 12

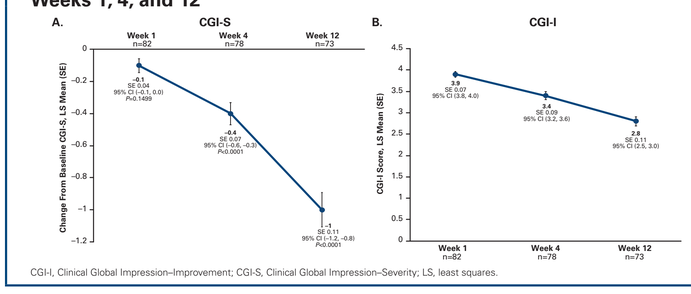
Correlation Analysis

- Change in MADRS total score significantly correlates with change in BASQID total score (–0.57, P<0.0001) and subscores (Life satisfaction: –0.56, P<0.0001; Positive QoL: –0.40, P=0.0007), indicating that the lower the depression, the greater overall health-related QoL

Severity and Improvement

- A significant reduction in MDD severity was observed, as indicated by the change from baseline to week 12 (n=73) CGI-S mean (SE) of –1.0 (0.11) (P<0.0001) (**Figure 6A**)
- Overall improvement in patients' condition was observed, through the CGI-I score at week 12 (n=73) mean (SE) of 2.8 (0.11) (**Figure 6B**)

Figure 6. LS Mean of CGI-S Change From Baseline and CGI-I Score at Weeks 1, 4, and 12

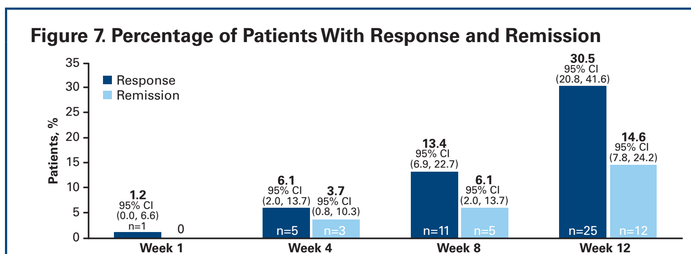


CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity; LS, least squares.

Response and Remission

- A response was observed in 30.5% (n=25) of patients showing at least a ≥50% reduction of MADRS score from baseline at week 12 (**Figure 7**)
- Overall, 14.6% (n=12) of patients' MADRS score reduced to ≤10 at week 12 from baseline, indicating remission (**Figure 7**)

Figure 7. Percentage of Patients With Response and Remission



Response defined as ≥50% reduction in MADRS total score from baseline. Remission defined as MADRS total score ≤10 at week 12.
MADRS, Montgomery-Åsberg Depression Rating Scale.

- At week 12, response as assessed using the CGI-I score (≤2) was observed in 42.4% (n=31) of patients and remission as assessed using the CGI-S score (≤2) was observed in 9.7% (n=8) of patients

Safety Outcomes

- The 5 mg, 10 mg, and 20 mg doses of vortioxetine were well tolerated
- Throughout the study, a total of 39 (47.6%) patients reported 60 occurrences of AEs (**Table 3**). Most commonly reported AEs were abdominal pain (n=9 [11%]) and nausea (n=9 [11%])

Table 3. Incidence of Adverse Events

Total AEs, n	60
Number of patients with AEs, n (%)	39 (47.6)
AEs leading to withdrawal, n (%)	6 (7.3)
Total TEAEs, n	58
Number of patients with TEAEs, n (%)	38 (46.3)
TEAEs leading to withdrawal, n (%)	6 (7.3)
Study drug–related TEAEs, n	34
Number of patients with study drug–related TEAEs, n (%)	26 (31.7)
Total SAEs, n (%)	1 (1.2)

AEs, adverse events; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events.

CONCLUSIONS

- In this study, vortioxetine 10-20 mg/day, starting dose 5 mg/day for the first week, demonstrated effectiveness in significantly reducing symptoms of depression as well as improving cognitive performance in patients with MDD and comorbid early dementia, and was well tolerated. A considerable improvement in severity was seen, with many patients being assessed as "very much improved" at week 12
- Cognitive performance assessed by DSST showed clinically relevant improvement from week 1 through week 12, and memory as assessed by RAVLT showed clinically relevant improvement from week 4 onward. Self-reported memory showed substantial improvement, with many patients shifting from "very poor" at baseline to "fair" at week 12
- Reduced symptoms of depression contributed to a significant and broad improvement in health-related QoL, which was observed as early as week 4 and was clinically meaningful at the end of the study
- The safety profile of vortioxetine was in line with the established profile, across all dosages (5–20 mg/day), with the possibility for an increased dosage to achieve optimal therapeutic benefit

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DISCLOSURES

MCC and SNS are employees of H. Lundbeck A/S. IG is an advisor, consultant, and/or speaker for Lundbeck, Otsuka, ADAMED, Angelini, CasenRecordati, Ferrer, and Janssen Cilag, and has received research funding from the Institut de Salud Carlos III, Ministry of Economy and Competitiveness, Spain.
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