

# Effectiveness of Vortioxetine in Patients with Major Depressive Disorder in Real-World Clinical Practice in Italy: Results from the RELIEVE Study

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**Purpose:** Vortioxetine has demonstrated efficacy in randomized controlled trials and is approved for the treatment of major depressive disorder (MDD); however, data are limited concerning its effectiveness when used in routine clinical care. The Real-Life Effectiveness of Vortioxetine in Depression (RELIEVE) study aimed to assess the effectiveness and tolerability of vortioxetine for the treatment of MDD in routine clinical practice in Canada, France, Italy, and the USA. This paper presents findings for the patient cohort in Italy.

**Patients and Methods:** RELIEVE was a 6-month, international, observational, prospective cohort study in outpatients initiating vortioxetine treatment for MDD in routine care settings at their physician's discretion (NCT03555136). Patient functioning was assessed using the Sheehan Disability Scale (SDS). Secondary outcomes included depression severity (9-item Patient Health Questionnaire [PHQ-9]), cognitive symptoms (5-item Perceived Deficits Questionnaire-Depression [PDQ-D-5]), and quality of life (EuroQol 5-Dimensions 5-Levels questionnaire [EQ-5D-5L]). Changes from baseline to month 6 were assessed using mixed models for repeated measures, adjusted for relevant confounders.

**Results:** Data are available for 231 patients enrolled in Italy (mean age, 55.5 years; 27% >65 years). Overall, 69% of patients reported at least one comorbidity, 55% were overweight/obese, and 47% had current anxiety symptoms. Adjusted least-squares mean (standard error) change in SDS score from baseline to week 24 was -6.6 (0.6) points ( $P < 0.001$ ). Respective changes in PHQ-9, PDQ-D-5, and EQ-5D-5L scores were -5.9 (0.5), -3.6 (0.4), and +0.13 (0.01) points (all  $P < 0.0001$ ). Adverse events were reported by 29 patients (13%), most commonly nausea ( $n = 14$ , 6%). Eleven patients (5%) discontinued treatment due to adverse events.

**Conclusion:** Clinically relevant and sustained improvements in overall functioning, symptoms of depression, cognitive symptoms, and health-related quality of life were observed in patients with MDD treated with vortioxetine over a period of 6 months in routine care in Italy, including a high proportion of elderly patients.

**Keywords:** major depressive disorder, vortioxetine, effectiveness, functioning, real-world evidence

## Introduction

Depression is a common illness and a leading cause of disability worldwide.<sup>1</sup> Depressive disorders accounted for over 520,000 million years lived with disability in Italy in 2015.<sup>2</sup> Current estimates suggest that annually depression affects 5.4% of the Italian population aged 15 years or older, with prevalence rising to 11.6% in the elderly (age  $\geq 65$  years).<sup>3</sup> The prevalence of depression in Italy has further increased since the onset of the COVID-19 pandemic.<sup>4-6</sup> Major depressive disorder (MDD) is a multidimensional condition characterized by a range of emotional, cognitive, and physical symptoms that have a significant impact on psychosocial functioning.<sup>7,8</sup> According to the Canadian Network for Mood and Anxiety Treatments (CANMAT) treatment guidelines issued in 2016, restoration of psychosocial functioning

is an important treatment goal in patients with MDD.<sup>9</sup> However, the potential of antidepressant therapies to directly improve functional outcomes has not been extensively evaluated in routine care settings to date.

Vortioxetine is a novel antidepressant with a multimodal mechanism of action.<sup>10</sup> It was first licensed by the European Medicines Agency for the treatment of adult patients with MDD in 2013<sup>11</sup> and has been available in Italy since 2016. Vortioxetine acts as an inhibitor of the serotonin transporter as well as modulating the activity of several serotonin receptor subtypes, thus both directly and indirectly influencing a range of neurotransmitter systems relevant to the neurobiology of MDD.<sup>10,12</sup> Data from randomized controlled clinical trials show vortioxetine to have broad dose-dependent efficacy across the entire spectrum of symptoms experienced by patients with MDD, including functional impairment, with greatest treatment effects seen at a dosage of 20 mg/day.<sup>13–20</sup>

Real-world evidence is useful to support the results of regulatory studies in the more diverse patient populations likely to be encountered in routine care settings. However, data on the real-world effectiveness of vortioxetine in patients with MDD in Italy are currently lacking. The Real-Life Effectiveness of Vortioxetine in Depression (RELIEVE) study aimed to assess the effectiveness and tolerability of vortioxetine for the treatment of MDD in routine clinical practice settings in Canada, France, Italy, and the USA. The overall results of this study have been reported previously.<sup>21</sup> This paper presents the study findings for the patient cohort enrolled in Italy.

## Patients and Methods

### Study Design and Participants

RELIEVE was a multinational, observational, prospective cohort study conducted in outpatients initiating vortioxetine for the treatment of MDD at their physician's discretion (NCT03555136).

The study design has been reported in detail previously.<sup>21</sup> In brief, eligible patients were aged  $\geq 18$  years and were experiencing a major depressive episode (MDE) according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition) criteria.<sup>22</sup> Patients with schizophrenia, bipolar disorder, substance-use disorder, or any neurodegenerative disease significantly affecting cognitive function and those considered at significant risk of suicide or who had attempted suicide within the last 6 months were excluded. As this was a real-world study, participating patients were allowed to use other psychotropic drugs as needed during the study period.

Data were collected at routine clinic visits at baseline and after 12 and 24 weeks of vortioxetine treatment. In response to the COVID-19 pandemic, a critical management plan was implemented that allowed patients to have remote follow-up visits and complete some patient-reported outcome assessments at home if necessary. However, this was not expected to have a significant impact on the study results, as very few patients did not complete their visits or completed their visits remotely (22 patients, ie, 2% of all eligible patients enrolled in the global RELIEVE study).

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Appropriate local ethics committee approval was obtained at all participating sites ([Supplementary Table S1](#)). Patients participated freely and provided written informed consent before study entry.

### Study Outcomes

The primary study outcome was patient functioning assessed using the Sheehan Disability Scale (SDS).<sup>23,24</sup> The SDS assesses functional impairment over the past week across three domains: work/school, family life/home responsibilities, and social/leisure activities. The level of impairment for each domain is rated on a scale from 0 (not at all) to 10 (very severe); scores from the individual domains are combined to generate the SDS total score, ranging from 0 (unimpaired) to 30 (highly impaired). In patients who did not work or study during follow-up for reasons unrelated to MDD, an SDS work/school domain score was imputed for the calculation of SDS total score based on the average of the other two SDS domain scores.<sup>25</sup>

An improvement of  $\geq 4$  points in SDS total score is considered clinically relevant.<sup>24</sup> Response was defined as SDS total score  $\leq 12$  and remission (functional recovery) as SDS score  $\leq 6$ .<sup>24,25</sup> The number of work days lost in the past week (absenteeism) and the number of underproductive work days during the past week (presenteeism) were

derived from the SDS for the working population. Sick/disability leave and healthcare resource utilization were assessed during the past 12 weeks at baseline and since the last visit at weeks 12 and 24.

Secondary outcomes included depressive symptoms, cognitive function, sexual function, and quality of life. Severity of depressive symptoms was assessed by patients using the 9-item Patient Health Questionnaire (PHQ-9)<sup>26</sup> and by clinicians using the Clinical Global Impressions scale.<sup>27,28</sup> Cognitive symptoms were assessed by patients using the 5-item Perceived Deficits Questionnaire-Depression (PDQ-D-5),<sup>29,30</sup> and cognitive performance was evaluated by means of the Digit Symbol Substitution Test (DSST).<sup>31</sup> Sexual function was assessed using the Arizona Sexual Experiences Scale (ASEX),<sup>32</sup> and overall health-related quality of life was assessed using the EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L).<sup>33</sup> An overview of these psychometric assessment scales is provided in [Supplementary Table S2](#).

Any adverse events (AEs) spontaneously reported by the patient or observed by the investigator were reported according to local regulations. AEs were summarized by the lowest level Medical Dictionary for Regulatory Activities (Version 23.1) preferred terms.

## Statistical Analysis

All patients enrolled in Italy who initiated treatment with vortioxetine  $\leq 7$  days before the study baseline visit and who had a valid baseline and at least one post-baseline assessment were included in this analysis (full analysis set). Safety was assessed in all patients who initiated treatment with vortioxetine for MDD. With the exception of the SDS total score as described above, missing data were not imputed.

Changes in psychometric scale scores from baseline at weeks 12 and 24 were estimated using a linear mixed model for repeated measurements, with adjustment for clinically relevant baseline variables: age, sex, educational level, duration of current depressive episode, presence of somatic and psychiatric comorbidities, and depression severity as measured by PHQ-9 score as a continuous variable. Results are reported as estimated least-squares (LS) means, with standard errors (SEs) and *P* values. Change in SDS and PHQ-9 total scores from baseline at weeks 12 and 24 were also analyzed by vortioxetine treatment line (first, second, or third or later line). Changes in measures of work productivity and healthcare resource utilization from baseline at weeks 12 and 24 were analyzed by paired *t* test.

The proportion of patients with sexual dysfunction was calculated at baseline, week 12, and week 24. Sexual dysfunction was defined as ASEX total score  $\geq 19$ , any individual ASEX item score  $\geq 5$ , or a score  $\geq 4$  for any three ASEX items.<sup>32</sup>

All statistical analyses were performed using R version 3.6.1.<sup>34</sup> Significance was set at  $P < 0.05$ .

## Results

### Study Population

This study was conducted at a total of 23 sites (22 psychiatric centers and one neurological center) in Italy between November 2017 and January 2021. Data are available for a total of 231 patients (ie, 31% of all patients included in the full analysis set for the overall RELIEVE study) ([Table 1](#)). Approximately two-thirds (62%) of patients were female. The mean patient age was 55.5 years, and over one-quarter (27%) of the patient cohort in Italy was aged  $>65$  years. Approximately 40% of patients had a full- or part-time occupation. Over half of all patients were overweight or obese (55% of those with available body-mass index data); mean (standard deviation [SD]) body-mass index was 26.0 (4.6) kg/m<sup>2</sup>. Overall, 69% of patients reported at least one comorbid condition and 15% had three or more comorbidities. The most common comorbid medical conditions were cardiovascular diseases (22% of patients), sleep disorders (17%), diabetes (8%), and neurological disorders (7%). Almost half (47%) of all patients reported current anxiety symptoms; of these, 44% reported that they had experienced anxiety symptoms for  $>5$  years. Type of anxiety was unspecified in 38% of patients, 7% had generalized anxiety disorder, and 6% had panic disorder.

Clinical characteristics and psychometric scale scores at baseline are shown in [Table 2](#). The mean duration of MDD was 10.5 years, and most patients (74%) reported at least one previous MDE. The duration of the current MDE was  $>14$  weeks in 42% of patients. Overall, the patient population had moderately severe symptoms and moderate functional impairment at

**Table I** Patient Demographic Characteristics at Baseline (Full Analysis Set)

| Characteristic                                        | Full Analysis Set (N = 231) |
|-------------------------------------------------------|-----------------------------|
| Female, n (%)                                         | 143 (61.9)                  |
| Age (years), mean $\pm$ SD                            | 55.5 $\pm$ 14.4             |
| >65 years, n (%)                                      | 63 (27.3)                   |
| Race/ethnicity                                        |                             |
| White/Caucasian                                       | 226 (97.8)                  |
| Black/African American                                | 1 (0.4)                     |
| Asian                                                 | 1 (0.4)                     |
| Other (unspecified)                                   | 2 (0.9)                     |
| Not reported                                          | 1 (0.4)                     |
| Living status, n (%)                                  |                             |
| Living with others                                    | 195 (84.4)                  |
| Work status, n (%)                                    |                             |
| Full/part-time work or school                         | 93 (40.3)                   |
| Comorbidities, n (%)                                  |                             |
| Overweight/obese (BMI $\geq$ 25.0 kg/m <sup>2</sup> ) | 122 (54.5) <sup>a</sup>     |
| Cardiovascular disease                                | 51 (22.1)                   |
| Sleep disorder                                        | 40 (17.3)                   |
| Diabetes                                              | 19 (8.2)                    |
| Neurologic disorder                                   | 17 (7.4)                    |
| Chronic pain                                          | 11 (4.8)                    |
| Current anxiety, n (%)                                | 109 (47.2)                  |
| Time since onset of current anxiety >5 years          | 47 (43.9) <sup>b</sup>      |
| Type of anxiety symptoms                              |                             |
| Unspecified                                           | 87 (37.7)                   |
| Generalized anxiety disorder                          | 15 (6.5)                    |
| Panic disorder                                        | 14 (6.1)                    |

**Notes:** <sup>a</sup>Percentage based on the number of patients with available BMI data (n = 224). <sup>b</sup>Percentage based on the number of patients with current anxiety symptoms and available data (n = 107).

**Abbreviations:** BMI, body-mass index; SD, standard deviation.

baseline. Of the 93 employed patients, 27 (29%) reported taking sick or disability leave in the previous 12 weeks; this was considered by the investigator to be related to depression in 22 patients (24%). The mean (SD) number of sick/disability leave days taken in the 12 weeks before baseline was 26.6 (28.1) days (median, 15 days; range, 1–84 days). Data are available for all patients concerning healthcare resource use in the 12 weeks before baseline; patients reported a mean (SD) of 3.7 (4.8) healthcare visits during this time (median, 3 visits; range, 0–41), most commonly visits to GPs and psychiatrists.

Vortioxetine was initiated as first-line treatment for the current MDE in 53% of patients. A total of 109 patients had received prior treatment for the current MDE before the study baseline visit. Most of these patients were switching due to the lack of effectiveness of prior antidepressant therapy (75 patients [69%]). Twenty-five patients (23%) were switching due to lack of tolerability of prior therapy, three patients were switching at their own request and the remaining six patients were switching due to non-specified reasons. For the 83 patients known to have received prior antidepressants for the current MDE, the most frequently reported prior antidepressants were escitalopram (26 patients), sertraline (23 patients), paroxetine (21 patients), duloxetine (15 patients), venlafaxine (12 patients), and citalopram (12 patients).

Mean (SD) vortioxetine dosage at baseline was 9.1 (4.5) mg/day. Of the 207 patients with available dose data, just over half (n = 106 [51%]) initiated vortioxetine treatment at a dose of 10 mg/day. The starting dosage of vortioxetine was 5 mg/day in 70 patients (34%), 15 mg/day in 11 patients (5%), and 20 mg/day in 20 patients (10%).

## Effectiveness

Clinically relevant improvement in overall functioning (ie, a decrease in SDS total score  $\geq$ 4 points) was seen after 12 and 24 weeks of vortioxetine treatment (Figure 1A). The adjusted LS mean SDS total score decreased from 17.8 points at

**Table 2** Patient Clinical Characteristics and Psychometric Assessment Scale Scores at Baseline (Full Analysis Set)

| Characteristic                                     | Full Analysis Set (N=231) |
|----------------------------------------------------|---------------------------|
| Time since MDD diagnosis (years), mean $\pm$ SD    | 10.5 $\pm$ 12.8           |
| No. of previous MDEs, n (%)                        |                           |
| 0                                                  | 60 (26.0)                 |
| 1                                                  | 46 (19.9)                 |
| 2+                                                 | 125 (54.1)                |
| Duration of current MDE >14 weeks, n (%)           | 97 (42.2) <sup>a</sup>    |
| Vortioxetine treatment line for current MDE, n (%) |                           |
| 1st line                                           | 122 (52.8)                |
| 2nd line                                           | 79 (34.2)                 |
| $\geq$ 3rd line                                    | 30 (13.0)                 |
| Baseline assessment scores, mean $\pm$ SD          |                           |
| SDS total score                                    | 17.8 $\pm$ 7.6            |
| Work/school domain                                 | 5.7 $\pm$ 3.0             |
| Family life/home responsibilities domain           | 6.1 $\pm$ 2.8             |
| Social life/leisure activities domain              | 6.0 $\pm$ 2.8             |
| Absenteeism (days/week)                            | 1.9 $\pm$ 2.6             |
| Presenteeism (days/week)                           | 3.8 $\pm$ 2.6             |
| PHQ-9                                              | 15.7 $\pm$ 6.0            |
| PDQ-D-5                                            | 9.8 $\pm$ 5.0             |
| DSST                                               | 32.4 $\pm$ 15.8           |
| EQ-5D-5L                                           | 0.60 $\pm$ 0.17           |
| ASEX                                               | 24.0 $\pm$ 6.4            |
| CGI-S                                              | 4.1 $\pm$ 0.9             |

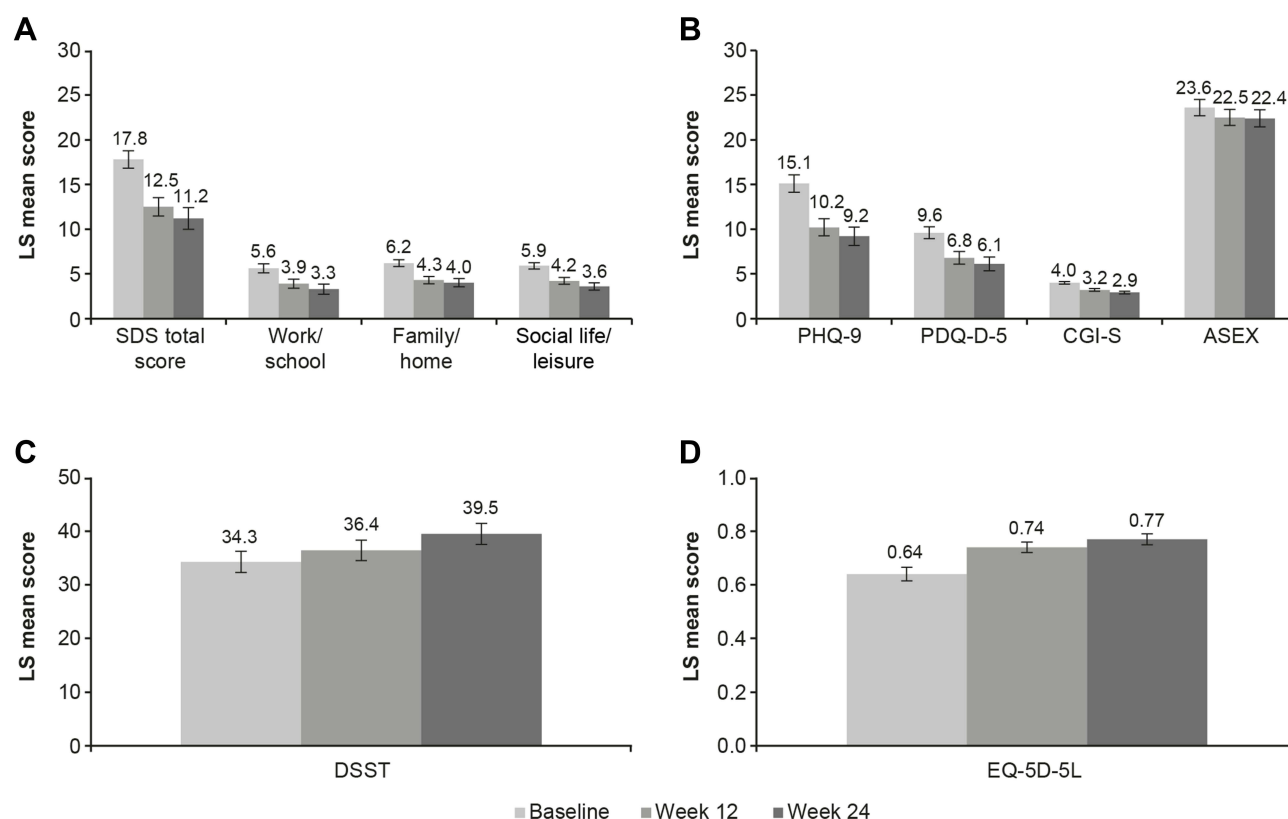
**Notes:** <sup>a</sup>Percentage based on the number of patients with available data (n = 230).

**Abbreviations:** ASEX, Arizona Sexual Experience Scale (score range 5–30); CGI-S, Clinical Global Impression–Severity (score range 1–7); DSST, Digit Symbol Substitution Test (score range 0–133); EQ-5D-5L, EuroQoL 5-Dimensions 5-Levels utility index (score range 0–1); MDD, major depressive disorder; MDE, major depressive episode; PDQ-D-5, 5-item Perceived Deficits Questionnaire–Depression (score range 0–20); PHQ-9, 9-item Patient Health Questionnaire (score range 0–27), SD, standard deviation; SDS, Sheehan Disability Scale (total score range 0–30).

baseline to 12.5 points after 12 weeks of vortioxetine treatment and 11.2 points after 24 weeks. This corresponds to an adjusted LS mean (SE) change from baseline of  $-5.2$  (0.5) points at week 12 and  $-6.6$  (0.6) points after 24 weeks of vortioxetine treatment (both  $P < 0.001$ ) (Table 3). Significant reductions in all SDS domain scores were also observed at both time points ( $P < 0.001$  for all changes at weeks 12 and 24 vs baseline). The proportions of patients with SDS total score  $\leq 12$  (ie, SDS responders) and SDS total score  $\leq 6$  (ie, SDS remission) increased over time. SDS total score was  $\leq 12$  in 58/230 patients (25%) at baseline, 123/226 patients (54%) at week 12 and 111/182 patients (61%) at week 24. SDS total score was  $\leq 6$  in 21/230 patients (9%) at baseline, 54/226 patients (24%) at week 12 and 62/182 patients (34%) at week 24.

Significant improvement in all work productivity measures (sick leave, absenteeism, and presenteeism) was seen in the working population (ie, patients in full/part-time work or education) after 24 weeks of vortioxetine treatment (paired  $t$  test, all differences  $P < 0.05$ ). At week 24, the absolute mean (SD) reduction from baseline in sick/disability leave during the preceding 12 weeks was 3.3 (11.9) days ( $P < 0.05$ ). Respective mean (SD) reductions in absenteeism (work/school days lost) and presenteeism (work/school days underproductive) from baseline after 24 weeks of vortioxetine treatment were 0.6 (2.9) and 1.6 (3.1) days/week ( $P < 0.05$  and  $P < 0.0001$ , respectively). At week 24, the mean (SD) reduction from baseline in healthcare resource utilization during the preceding 12 weeks was 1.6 (5.2) visits (paired  $t$  test,  $P = 0.0001$ ).

Improvements in patient- and clinician-rated measures of depression severity, cognitive function, sexual function, and health-related quality of life were also observed after 12 and 24 weeks of vortioxetine treatment (Figure 1B–D). For all



**Figure 1** Adjusted LS mean (95% CI) score at baseline and after 12 and 24 weeks of vortioxetine treatment for **(A)** SDS total and domain scores, **(B)** PHQ-9, PDQ-D-5, CGI-S and ASEX, **(C)** DSST, and **(D)** EQ-5D-5L scores (full analysis set).

**Notes:** All changes at weeks 12 and 24,  $P < 0.0001$  vs baseline (see Table 3).

**Abbreviations:** ASEX, Arizona Sexual Experience Scale (score range 5–30); CGI-S, Clinical Global Impression–Severity (score range 1–7); CI, confidence interval; DSST, Digit Symbol Substitution Test (score range 0–133); EQ-5D-5L, EuroQol 5-Dimensions 5-level utility index (score range 0–1); LS, least-squares; PDQ-D-5, 5-item Perceived Deficits Questionnaire–Depression (score range 0–20); PHQ-9, 9-item Patient Health Questionnaire (score range 0–27); SDS, Sheehan Disability Scale (total score range 0–30).

effectiveness outcomes, the adjusted LS mean changes from baseline were statistically significant at both week 12 and week 24 (all  $P < 0.0001$ ) (Table 3). The proportion of patients who met the definition for sexual dysfunction decreased over the 24 weeks of vortioxetine treatment, from 84% at baseline to 76% at week 24.

Statistically significant and sustained improvements in patient functioning and depression severity were observed over the 24 weeks of treatment, irrespective of vortioxetine treatment line (Figure 2). However, numerically greater improvements in adjusted LS mean SDS and PHQ-9 total scores from baseline were seen when vortioxetine was used as first-line treatment for the current MDE compared with subsequent treatment lines. At week 24, the adjusted LS mean (SE) change in SDS total score from baseline was  $-8.1$  ( $0.8$ ) points in patients receiving vortioxetine as first-line treatment ( $P < 0.0001$ ),  $-4.9$  ( $1.1$ ) points in those receiving vortioxetine as second-line treatment ( $P < 0.0001$ ), and  $-5.9$  ( $2.2$ ) points in those for whom vortioxetine was third- or later-line treatment ( $P = 0.0128$ ) (Table 4). Corresponding adjusted LS mean (SE) changes in PHQ-9 total score from baseline were  $-6.9$  ( $0.6$ ) points ( $P < 0.0001$ ),  $-4.7$  ( $0.9$ ) points ( $P < 0.0001$ ), and  $-5.2$  ( $1.5$ ) points ( $P = 0.0024$ ), respectively.

## Safety

At least one AE was reported over the 24 weeks of vortioxetine treatment in 29 patients (13%). The most commonly reported AE was nausea (14 patients, 6%). No other AEs were reported by  $>5\%$  of patients. Only 11 patients discontinued treatment with vortioxetine due to AEs (5 patients by the week 12 visit and a further 6 patients by the week 24 visit).



**Table 3** Adjusted Least-Squares Mean Change from Baseline for Primary and Secondary Study Endpoints After 12 and 24 Weeks of Vortioxetine Treatment (Full Analysis Set)

| Variable                          | Adjusted Least-Squares Mean Change (SE) |                |
|-----------------------------------|-----------------------------------------|----------------|
|                                   | Week 12                                 | Week 24        |
| SDS total score                   | −5.2 (0.5)***                           | −6.6 (0.6)***  |
| Work/school                       | −1.7 (0.3)***                           | −2.3 (0.3)***  |
| Family life/home responsibilities | −1.9 (0.2)***                           | −2.2 (0.2)***  |
| Social life/leisure activities    | −1.7 (0.2)***                           | −2.3 (0.2)***  |
| PHQ-9                             | −4.9 (0.4)***                           | −5.9 (0.5)***  |
| CGI-S                             | −0.8 (0.1)***                           | −1.2 (0.1)***  |
| PDQ-D-5                           | −2.9 (0.3)***                           | −3.6 (0.4)***  |
| DSST                              | 2.1 (0.6)***                            | 5.2 (0.6)***   |
| ASEX                              | −1.1 (0.3)***                           | −1.2 (0.4)***  |
| EQ-5D-5L                          | 0.10 (0.01)***                          | 0.13 (0.01)*** |

**Note:** \*\*\* $P < 0.001$  vs baseline.

**Abbreviations:** ASEX, Arizona Sexual Experience Scale (score range 5–30); CGI-S, Clinical Global Impression–Severity (score range 1–7); DSST, Digit Symbol Substitution Test (score range 0–133); EQ-5D-5L, EuroQoL 5-Dimensions 5-Levels utility index (score range 0–1); PDQ-D-5, 5-item Perceived Deficits Questionnaire–Depression (score range 0–20); PHQ-9, 9-item Patient Health Questionnaire (score range 0–27); SDS, Sheehan Disability Scale (total score range 0–30); SE, standard error.

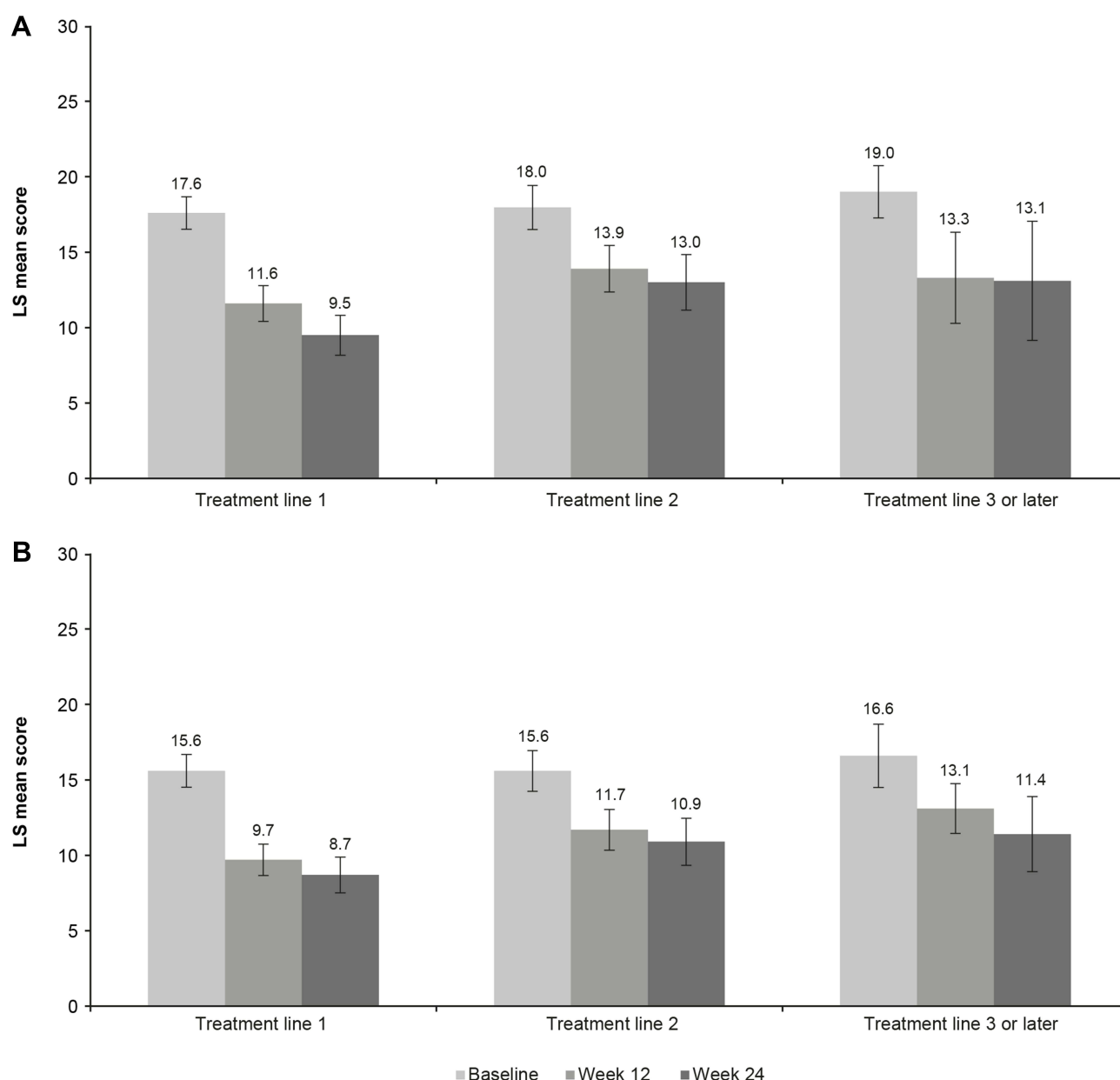
## Discussion

To our knowledge, this is the first study to assess the effectiveness of vortioxetine for the treatment of MDD in routine practice settings in Italy. In line with the global RELIEVE study findings,<sup>21</sup> clinically meaningful and sustained improvements in overall functioning, depressive symptoms, cognitive function, and quality of life were observed in patients with MDD treated with vortioxetine in routine practice settings over a period of 6 months. Significant improvements in all outcome assessments were seen after 3 months of vortioxetine treatment, with further improvements observed after 6 months. This finding confirms the importance of continuing antidepressant treatment for at least 6 months in patients with MDD to achieve maximum therapeutic effects, as recommended in current treatment guidelines.<sup>35</sup>

Improvement in measures of sexual functioning was observed over the 6 months of vortioxetine treatment, including a reduction in both mean ASEX total score and the proportion of patients who met the definition for sexual dysfunction. This is encouraging, as sexual side effects are one of the main reasons for poor adherence and treatment discontinuation in patients receiving selective serotonin reuptake inhibitors.<sup>36,37</sup> Indeed, treatment with vortioxetine was found to be well tolerated in this study. No unexpected AEs were reported and very few patients discontinued treatment due to AEs. While greater adherence to treatment may be expected in a clinical trial setting due to more frequent patient follow-up, it should be noted that in this study patients were receiving treatment in routine practice settings and were only seen at 3-month intervals.

Our findings are particularly noteworthy as the cohort in Italy included a relatively high proportion of elderly patients and patients with medical comorbidities, and almost half of all patients reported current anxiety symptoms. Physicians may have been more likely to prescribe vortioxetine than other antidepressants in these patients due to its established efficacy and tolerability profile.<sup>13,38</sup> In particular, the well-documented lack of weight gain during treatment with vortioxetine may have influenced its use in overweight/obese patients; many other drugs for depression are associated with the potential for weight gain.<sup>39</sup>

These results are consistent with those of other studies in patients with MDD treated with vortioxetine in routine care settings.<sup>40–44</sup> The observed improvement in functioning, as assessed by change in mean SDS total score from baseline at weeks 12 and 24 (approximately 5 and 7 points, respectively), was greater than the threshold considered meaningful for patients (ie,  $\geq 4$  points).<sup>24</sup> Improvements of similar magnitude were observed across all SDS domains (work/school, social life/leisure, and family/home life). Working patients also reported missing significantly fewer days of work and were



**Figure 2** Adjusted LS mean (95% CI) score at baseline and at 12 and 24 weeks according to vortioxetine treatment for (A) SDS total score and (B) PHQ-9 score (full analysis set).

**Notes:** All changes at weeks 12 and 24,  $P < 0.0001$  vs baseline for first- and second-line treatment and  $P < 0.05$  for third-line treatment or later (see Table 4).

**Abbreviations:** CI, confidence interval; LS, least-squares; PHQ-9, 9-item Patient Health Questionnaire (score range 0–27); SDS, Sheehan Disability Scale (total score range 0–30).

more productive while at work during treatment with vortioxetine. A reduction in healthcare resource utilization was also observed over the 6 months of vortioxetine treatment.

The observed improvements in DSST and PDQ-D-5 scores show vortioxetine to be effective for the treatment of objective and subjective cognitive symptoms in patients with MDD, in keeping with the results of earlier randomized controlled trials,<sup>15,45–49</sup> and observational studies.<sup>40–44</sup> DSST scores were lower in the cohort in Italy than in the global RELIEVE study population, both at baseline and at 24 weeks.<sup>21</sup> This may at least in part be due to the high proportion of elderly patients in the Italian cohort; performance on cognitive tests that require rapid processing of information, such as the DSST, tends to decline with age.<sup>50</sup> Obesity has also been shown to be associated with cognitive impairment,<sup>51–53</sup> and over half of all patients in this patient cohort were considered overweight or obese. Nevertheless, the LS mean change in



**Table 4** Adjusted Least-Squares Mean Change from Baseline for SDS and PHQ-9 Total Score After 12 and 24 Weeks of Vortioxetine Treatment According to Treatment-Line (Full Analysis Set)

| Variable            | Adjusted Least-Squares Mean Change (SE) |               |
|---------------------|-----------------------------------------|---------------|
|                     | Week 12                                 | Week 24       |
| SDS total score     |                                         |               |
| First-line          | −5.9 (0.7)***                           | −8.1 (0.8)*** |
| Second-line         | −4.1 (0.9)***                           | −4.9 (1.1)*** |
| Third-line or later | −5.7 (1.6)**                            | −5.9 (2.2)*   |
| PHQ-9               |                                         |               |
| First-line          | −6.0 (0.6)***                           | −6.9 (0.6)*** |
| Second-line         | −3.9 (0.7)***                           | −4.7 (0.9)*** |
| Third-line or later | −3.4 (0.9)***                           | −5.2 (1.5)**  |

Notes: \* $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\* $P < 0.001$  vs baseline.

Abbreviations: PHQ-9, 9-item Patient Health Questionnaire (score range 0–27); SDS, Sheehan Disability Scale (total score range 0–30); SE, standard error.

DSST score from baseline to week 24 in the patient cohort in Italy was similar to that seen in the overall study population (5.2 vs 6.2 points, respectively).<sup>21</sup>

Almost half of all patients in this cohort also had symptoms of anxiety at study baseline. Anxiety symptoms are common in patients with MDD,<sup>54–56</sup> and have been shown to be associated with lower rates of treatment response and remission, increased risk of recurrence, and greater functional impairment.<sup>55–58</sup> Other studies have shown treatment with vortioxetine to be effective in patients with MDD and high levels of concurrent anxiety symptoms,<sup>14,41</sup> and in patients with comorbid anxiety disorders.<sup>59–61</sup> Although the impact of vortioxetine on anxiety was not assessed in the present study, it is possible that a beneficial effect of treatment on anxiety symptoms may have contributed to the improvement seen in functioning and quality of life.

Of note, just over half of all patients were receiving vortioxetine as a first-line antidepressant treatment in real-world clinical practice settings in Italy. As in the global RELIEVE study,<sup>21</sup> the greatest improvements in patient functioning and depressive symptom severity were observed when vortioxetine was used as first-line therapy. However, clinically meaningful improvements were also seen in patients who had received prior antidepressant therapy for the current MDE.

The main strength of this study is that it was conducted in a heterogeneous patient population representative of the patients likely to be encountered in daily clinical practice in Italy, many of whom have clinically relevant comorbidities. In particular, the proportion of elderly patients in the patient cohort was similar to that in the general population in Italy. In 2020, individuals aged  $\geq 65$  years accounted for 23% of the total population in Italy and this proportion is projected to increase further in coming years.<sup>62</sup> A further study strength is the use of patient-reported outcome measures to assess functional impairment and MDD symptoms. This is in keeping with the increased awareness of the importance of addressing patient perspectives when managing mental health disorders such as MDD.<sup>63</sup> Clinician-rated assessments may not fully capture a patient's subjective experience of MDD and antidepressant treatment, and patients' perceptions of symptoms and treatment outcomes in MDD have been shown to differ from those of their physicians.<sup>64–66</sup> Potential limitations include the open-label study design and lack of a placebo or active comparator, and the fact that the patient cohort in Italy almost exclusively comprised White/Caucasian patients (98% of all patients). Due to the relatively infrequent study visits (ie, at baseline and after 3 and 6 months of treatment), collection of vortioxetine dose data was limited, precluding assessment of vortioxetine dosage across the study period.

## Conclusions

In summary, the results of this study demonstrate the real-world effectiveness and good safety profile of vortioxetine in patients with MDD treated in routine practice settings in Italy. Clinically relevant and sustained improvements in overall functioning, work productivity, symptoms of depression, cognitive symptoms, and health-related quality of life were observed in the heterogeneous and representative population of patients with MDD over the 6 months of vortioxetine treatment, including a high proportion of elderly patients.

## Data Sharing Statement

The data supporting the findings of this study are available within the manuscript. The corresponding author may be contacted for further data sharing.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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## Disclosure

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