**Online Supplementary Material**

**Supplementary Table S1.** Key Study Characteristics.

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| --- | --- | --- | --- | --- |
| **Study type** | **Study** | **Treatment and dose (per day)** | **Na** | **Main inclusion criteriab** |
| Fixed-dose studies | NCT0114090610 | Placebo Vortioxetine 15 mg Vortioxetine 20 mg | 158151151 | Age 18–65 yearsMDE duration ≥3 monthsMADRS total score ≥26 |
|  | NCT0115300911 | PlaceboVortioxetine 15 mgVortioxetine 20 mg | 159147154 | Age 18–65 years MDE duration ≥3 monthsMADRS total score ≥26 |
|  | NCT0116326612 | PlaceboVortioxetine 10 mgVortioxetine 20 mg | 157155150 | Age 18–65 years MDE duration ≥3 monthsMADRS total score ≥26 |
|  | NCT0142221313 | PlaceboVortioxetine 10 mgVortioxetine 20 mg | 196195207 | Age 18–65 years MDE duration ≥3 months MADRS total score ≥26 |
|  | NCT0125578714 | PlaceboVortioxetine 5 mgVortioxetine 10 mgVortioxetine 20 mg | 151144148150 | Age 20–64 yearsMDE duration ≥3 months MADRS total score ≥26 |
|  | NCT0238981615 | PlaceboVortioxetine 10 mgVortioxetine 20 mg | 161165163 | Age 20–75 yearsMDE duration ≥3 monthsMADRS total score ≥26 |
| Flexible-dose studiesc | NCT01488071(REVIVE)16 | Vortioxetine 10–20 mgAgomelatine 25–50 mg | 253242 | Age 18–75 years MDE duration ≥3 monthsMADRS total score ≥22Inadequate response to SSRI/SNRI |
|  | NCT01564862(CONNECT)17 | PlaceboVortioxetine 10–20 mgDuloxetine 60 mg | 191196207 | Age 18–65 years MDE duration <12 monthsMADRS total score ≥26MADRS item 1 (apparent sadness) score ≥3 |
|  | NCT02272517 ReMIND SWITCH18 | Vortioxetine 10–20 mgEscitalopram 10–20 mg | 5049 | Age 18–65 years MADRS total score ≥22PHQ-9 score ≥14PDQ-D-20 score >25Inadequate response to SSRI/SNRI |
|  | NCT03835715 (COMPLETE)19 | Vortioxetine 10–20 mg | 150 | Age 18–65 years MDE duration <12 monthsMADRS total score >21 and <29ODQ score ≥50Inadequate response to SSRI/SNRI |

Abbreviations: DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Text revision; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode (confirmed by MINI); MINI, Mini International Neuropsychiatric Interview; ODQ, Oxford Depression Questionnaire; PDQ-D-20, 20-item Perceived Deficits Questionnaire–Depression; PHQ-9, 9-item Patient Health Questionnaire; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor
aNumber of randomized patients who received at least one dose of study medication (all patients treated set)
bIn all studies, patients had a diagnosis of MDD according to the current DSM criteria at the time of the study (DSM-IV-TR or DSM-V), and current MDE was confirmed using the MINI cAll patients received vortioxetine 10 mg/d for 1 week, followed by vortioxetine 10–20 mg/d flexible dose

**Supplementary Table S2.** Meta-Analysis of the Change from Baseline in MADRS Individual Item Score Difference vs Placebo Over Time (Full Analysis Set, MMRM) in Fixed-Dose Studies10–15

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| --- | --- | --- | --- | --- | --- |
| **MADRS item** | **Treatment and dose (per day)** | **Week 2** | **Week 4** | **Week 6** | **Week 8** |
| **Difference vs PBO** | ***P* value** | **Difference vs PBO** | ***P* value** | **Difference vs PBO** | ***P* value** | **Difference vs PBO** | ***P* value** |
| 1. Apparent sadness | VOR 5 mgVOR 10 mgVOR 15 mgVOR 20 mg | −0.10−0.10−0.17−0.16 | .311.095**.044.013** | +0.06−0.26−0.36−0.32 | .663**< .001< .001.006** | −0.11−0.28−0.58−0.49 | .432**< .001.006< .001** | −0.19−0.44−0.50−0.62 | .189**< .001**.127**< .001** |
| 2. Reported sadness | VOR 5 mgVOR 10 mgVOR 15 mgVOR 20 mg | −0.02−0.15−0.12−0.16 | .833**.029**.249**.003** | −0.00−0.26−0.34−0.33 | .986**< .001< .001< .001** | −0.21−0.32−0.48−0.54 | .159**< .001**.053**< .001** | −0.20−0.45−0.57−0.64 | .211**< .001.042< .001** |
| 3. Inner tension | VOR 5 mgVOR 10 mgVOR 15 mgVOR 20 mg | +0.08−0.16−0.18−0.18 | .429**.016.030< .001** | −0.10−0.21−0.23−0.27 | .401**< .001**.170**< .001** | 0.00−0.31−0.36−0.34 | .983**< .001**.095**< .001** | −0.10−0.32−0.26−0.40 | .445**< .001**.507**< .001** |
| 4. Reduced sleep | VOR 5 mgVOR 10 mgVOR 15 mgVOR 20 mg | +0.08+0.06−0.13+0.01 | .530.388.368.866 | +0.02−0.14−0.17−0.25 | .906**.045**.132**< .001** | +0.07−0.12−0.19−0.17 | .627.172.518.079 | +0.12−0.27−0.29−0.36 | .471**.011**.305**< .001** |
| 5. Reduced appetite | VOR 5 mgVOR 10 mgVOR 15 mgVOR 20 mg | +0.08+0.00+0.10+0.10 | .524.954.449.065 | +0.24−0.02−0.09−0.08 | .061.832.333.478 | +0.12−0.08−0.16−0.15 | .366.335.238.133 | −0.05−0.26−0.24−0.32 | .703**.008.049.014** |
| 6 .Concentration difficulties | VOR 5 mgVOR 10 mgVOR 15 mgVOR 20 mg | −0.07−0.11−0.04−0.09 | .504.086.714.086 | −0.01−0.08−0.11−0.19 | .918.206.252**.011** | +0.07−0.16−0.43−0.33 | .614.063**< .001****< .001** | +0.11−0.24−0.48−0.44 | .483**.023< .001****< .001** |
| 7. Lassitude | VOR 5 mgVOR 10 mgVOR 15 mgVOR 20 mg | −0.03−0.09−0.06−0.10 | .801.179.483.055 | −0.01−0.14−0.30−0.25 | .939**.026****.002****< .001** | −0.07−0.14−0.30−0.38 | .658.107.318**< .001** | −0.02−0.27−0.37−0.41 | .902**.016**.200**.001** |
| 8. Inability to feel | VOR 5 mgVOR 10 mgVOR 15 mgVOR 20 mg | +0.03−0.04−0.09−0.08 | .751.522.391.276 | +0.02−0.14−0.16−0.26 | .878**.030**.173**< .001** | −0.07−0.23−0.31−0.41 | .618**.024****.031****< .001** | −0.20−0.31−0.36−0.49 | .185**< .001**.227**< .001** |
| 9. Pessimistic thoughts | VOR 5 mgVOR 10 mgVOR 15 mgVOR 20 mg | −0.07−0.09−0.11−0.19 | .510.386.428**< .001** | −0.15−0.23−0.19−0.27 | .196**.004.033< .001** | −0.15−0.33−0.20−0.40 | .236**< .001**.154**< .001** | −0.29−0.34−0.30−0.46 | **.028< .001**.155**< .001** |
| 10. Suicidal thoughts | VOR 5 mgVOR 10 mgVOR 15 mgVOR 20 mg | −0.01−0.09−0.11−0.08 | .822.060.480.066 | −0.03−0.11−0.14−0.10 | .718**< .001****.007****< .001** | −0.02−0.11−0.09−0.08 | .810**.020**.081**.045** | −0.01−0.14−0.17−0.16 | .888**< .001****.002****< .001** |

Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures; PBO, placebo; VOR, vortioxetine

**Supplementary Table S3.** Overview of Dose Adjustments in the Open-Label, Flexible-Dose COMPLETE Study of Vortioxetine 10–20 mg/d in Patients with Major Depressive Disorder19

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| --- | --- |
| **Vortioxetine Dose, mg/d** | **Patients, n (%)****(N = 142)** |
| **Baseline** | **Week 1** | **Week 8** |
| 10 | 20  | 20  | 33 (23.2) |
| 10  | 20  | 10  | 3 (2.1) |
| 10  | 20  | – | 2 (1.4) |
| 10  | 10  | 20  | 38 (26.8) |
| 10  | 10  | 10  | 62 (43.7) |
| 10  | 10  | – | 4 (2.8) |

**Supplementary Figure S1.** Mean difference in change from baseline for vortioxetine (VOR 5, 10, 15, or 20 mg/d) vs placebo in Montgomery–Åsberg Depression Rating Scale (MADRS) item scores at week 8 (full analysis set; mixed model for repeated measures analysis of six fixed-dose studies).10–15 \**P* < .05, \*\**P* < .01, \*\*\**P* < .001 vs placebo.