**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 | 158 151 151 | Age 18–65 years MDE duration ≥3 months MADRS total score ≥26 |
|  | NCT0115300911 | Placebo Vortioxetine 15 mg Vortioxetine 20 mg | 159 147 154 | Age 18–65 years  MDE duration ≥3 months MADRS total score ≥26 |
|  | NCT0116326612 | Placebo Vortioxetine 10 mg Vortioxetine 20 mg | 157 155 150 | Age 18–65 years  MDE duration ≥3 months MADRS total score ≥26 |
|  | NCT0142221313 | Placebo Vortioxetine 10 mg Vortioxetine 20 mg | 196 195 207 | Age 18–65 years  MDE duration ≥3 months  MADRS total score ≥26 |
|  | NCT0125578714 | Placebo Vortioxetine 5 mg Vortioxetine 10 mg Vortioxetine 20 mg | 151 144 148 150 | Age 20–64 years MDE duration ≥3 months  MADRS total score ≥26 |
|  | NCT0238981615 | Placebo Vortioxetine 10 mg Vortioxetine 20 mg | 161 165 163 | Age 20–75 years MDE duration ≥3 months MADRS total score ≥26 |
| Flexible-dose studiesc | NCT01488071 (REVIVE)16 | Vortioxetine 10–20 mg Agomelatine 25–50 mg | 253 242 | Age 18–75 years  MDE duration ≥3 months MADRS total score ≥22 Inadequate response to SSRI/SNRI |
|  | NCT01564862 (CONNECT)17 | Placebo Vortioxetine 10–20 mg Duloxetine 60 mg | 191 196 207 | Age 18–65 years  MDE duration <12 months MADRS total score ≥26 MADRS item 1 (apparent sadness) score ≥3 |
|  | NCT02272517  ReMIND SWITCH18 | Vortioxetine 10–20 mg Escitalopram 10–20 mg | 50 49 | Age 18–65 years  MADRS total score ≥22 PHQ-9 score ≥14 PDQ-D-20 score >25 Inadequate response to SSRI/SNRI |
|  | NCT03835715 (COMPLETE)19 | Vortioxetine 10–20 mg | 150 | Age 18–65 years  MDE duration <12 months MADRS total score >21 and <29 ODQ score ≥50 Inadequate 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 mg VOR 10 mg VOR 15 mg VOR 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 mg VOR 10 mg VOR 15 mg VOR 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 mg VOR 10 mg VOR 15 mg VOR 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 mg VOR 10 mg VOR 15 mg VOR 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 mg VOR 10 mg VOR 15 mg VOR 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 mg VOR 10 mg VOR 15 mg VOR 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 mg VOR 10 mg VOR 15 mg VOR 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 mg VOR 10 mg VOR 15 mg VOR 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 mg VOR 10 mg VOR 15 mg VOR 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 mg VOR 10 mg VOR 15 mg VOR 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.