

Online Supplementary Material

Supplementary Table S1. Key Study Characteristics.

Study type	Study	Treatment and dose (per day)	N ^a	Main inclusion criteria ^b
Fixed-dose studies	NCT01140906 ¹⁰	Placebo	158	Age 18–65 years
		Vortioxetine 15 mg	151	MDE duration ≥3 months
		Vortioxetine 20 mg	151	MADRS total score ≥26
	NCT01153009 ¹¹	Placebo	159	Age 18–65 years
		Vortioxetine 15 mg	147	MDE duration ≥3 months
		Vortioxetine 20 mg	154	MADRS total score ≥26
	NCT01163266 ¹²	Placebo	157	Age 18–65 years
		Vortioxetine 10 mg	155	MDE duration ≥3 months
		Vortioxetine 20 mg	150	MADRS total score ≥26
	NCT01422213 ¹³	Placebo	196	Age 18–65 years
		Vortioxetine 10 mg	195	MDE duration ≥3 months
		Vortioxetine 20 mg	207	MADRS total score ≥26
	NCT01255787 ¹⁴	Placebo	151	Age 20–64 years
		Vortioxetine 5 mg	144	MDE duration ≥3 months
		Vortioxetine 10 mg	148	MADRS total score ≥26
		Vortioxetine 20 mg	150	
	NCT02389816 ¹⁵	Placebo	161	Age 20–75 years
		Vortioxetine 10 mg	165	MDE duration ≥3 months
		Vortioxetine 20 mg	163	MADRS total score ≥26
Flexible-dose studies ^c	NCT01488071 (REVIVE) ¹⁶	Vortioxetine 10–20 mg	253	Age 18–75 years
		Agomelatine 25–50 mg	242	MDE duration ≥3 months MADRS total score ≥22 Inadequate response to SSRI/SNRI

NCT01564862 (CONNECT) ¹⁷	Placebo	191	Age 18–65 years
	Vortioxetine 10–20 mg	196	MDE duration <12 months
	Duloxetine 60 mg	207	MADRS total score ≥26 MADRS item 1 (apparent sadness) score ≥3
NCT02272517 ReMIND SWITCH ¹⁸	Vortioxetine 10–20 mg	50	Age 18–65 years
	Escitalopram 10–20 mg	49	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 Studies^{10–15}

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	−0.10	.311	+0.06	.663	−0.11	.432	−0.19	.189
	VOR 10 mg	−0.10	.095	−0.26	< .001	−0.28	< .001	−0.44	< .001
	VOR 15 mg	−0.17	.044	−0.36	< .001	−0.58	.006	−0.50	.127
	VOR 20 mg	−0.16	.013	−0.32	.006	−0.49	< .001	−0.62	< .001
2. Reported sadness	VOR 5 mg	−0.02	.833	−0.00	.986	−0.21	.159	−0.20	.211
	VOR 10 mg	−0.15	.029	−0.26	< .001	−0.32	< .001	−0.45	< .001
	VOR 15 mg	−0.12	.249	−0.34	< .001	−0.48	.053	−0.57	.042
	VOR 20 mg	−0.16	.003	−0.33	< .001	−0.54	< .001	−0.64	< .001
3. Inner tension	VOR 5 mg	+0.08	.429	−0.10	.401	0.00	.983	−0.10	.445
	VOR 10 mg	−0.16	.016	−0.21	< .001	−0.31	< .001	−0.32	< .001
	VOR 15 mg	−0.18	.030	−0.23	.170	−0.36	.095	−0.26	.507
	VOR 20 mg	−0.18	< .001	−0.27	< .001	−0.34	< .001	−0.40	< .001
4. Reduced sleep	VOR 5 mg	+0.08	.530	+0.02	.906	+0.07	.627	+0.12	.471
	VOR 10 mg	+0.06	.388	−0.14	.045	−0.12	.172	−0.27	.011
	VOR 15 mg	−0.13	.368	−0.17	.132	−0.19	.518	−0.29	.305
	VOR 20 mg	+0.01	.866	−0.25	< .001	−0.17	.079	−0.36	< .001
5. Reduced appetite	VOR 5 mg	+0.08	.524	+0.24	.061	+0.12	.366	−0.05	.703
	VOR 10 mg	+0.00	.954	−0.02	.832	−0.08	.335	−0.26	.008
	VOR 15 mg	+0.10	.449	−0.09	.333	−0.16	.238	−0.24	.049
	VOR 20 mg	+0.10	.065	−0.08	.478	−0.15	.133	−0.32	.014
6 .Concentration difficulties	VOR 5 mg	−0.07	.504	−0.01	.918	+0.07	.614	+0.11	.483
	VOR 10 mg	−0.11	.086	−0.08	.206	−0.16	.063	−0.24	.023
	VOR 15 mg	−0.04	.714	−0.11	.252	−0.43	< .001	−0.48	< .001
	VOR 20 mg	−0.09	.086	−0.19	.011	−0.33	< .001	−0.44	< .001
7. Lassitude	VOR 5 mg	−0.03	.801	−0.01	.939	−0.07	.658	−0.02	.902
	VOR 10 mg	−0.09	.179	−0.14	.026	−0.14	.107	−0.27	.016

	VOR 15 mg	-0.06	.483	-0.30	.002	-0.30	.318	-0.37	.200
	VOR 20 mg	-0.10	.055	-0.25	< .001	-0.38	< .001	-0.41	.001
8. Inability to feel	VOR 5 mg	+0.03	.751	+0.02	.878	-0.07	.618	-0.20	.185
	VOR 10 mg	-0.04	.522	-0.14	.030	-0.23	.024	-0.31	< .001
	VOR 15 mg	-0.09	.391	-0.16	.173	-0.31	.031	-0.36	.227
	VOR 20 mg	-0.08	.276	-0.26	< .001	-0.41	< .001	-0.49	< .001
9. Pessimistic thoughts	VOR 5 mg	-0.07	.510	-0.15	.196	-0.15	.236	-0.29	.028
	VOR 10 mg	-0.09	.386	-0.23	.004	-0.33	< .001	-0.34	< .001
	VOR 15 mg	-0.11	.428	-0.19	.033	-0.20	.154	-0.30	.155
	VOR 20 mg	-0.19	< .001	-0.27	< .001	-0.40	< .001	-0.46	< .001
10. Suicidal thoughts	VOR 5 mg	-0.01	.822	-0.03	.718	-0.02	.810	-0.01	.888
	VOR 10 mg	-0.09	.060	-0.11	< .001	-0.11	.020	-0.14	< .001
	VOR 15 mg	-0.11	.480	-0.14	.007	-0.09	.081	-0.17	.002
	VOR 20 mg	-0.08	.066	-0.10	< .001	-0.08	.045	-0.16	< .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

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.

