Supplementary Information

1. Sensitivity analyses primary outcome

Sensitivity analyses of the Hamilton Depression Rating Scale – 17 items ($HDRS_{17}$) total scores provided results that were consistent with the findings of the linear mixed model (LMM) that included a random intercept and fixed effects for time and the cross-level interaction between treatment and time. A per-protocol LMM excluding three participants from the placebo arm and nine from the fixed low-dose esketamine arm (because of dosing reduction of study medication or adjustments of psychopharmacological treatment), revealed no significant interaction between treatment and any of the individual time-dummy variables (Supplementary table 1). An independent samples T-Test comparing the mean changes of the $HDRS_{17}$ total scores from baseline to end-of-treatment between the two arms provided results that were also consistent with the main findings (mean difference -0.7, 95% CI -2.94 to 1.50, p=0.520).

Supplementary table 1: Estimates of per-protocol fixed effects for the cross-level interaction between thrice-daily fixed low-dose oral esketamine and dummy variables for time

	Estimate	Standard error	Degrees of freedom	95% Confidence Interval		p-value
				Lower bound	Upper bound	
$HDRS_{17}$						
Week 2 (visit 3)	-1.1	1.19	220	-3.45	1.26	0.359
Week 4 (visit 4)	-0.1	1.21	225	-2.52	2.23	0.905
Week 6 (visit 5)	0.6	1.22	231	-1.83	2.98	0.636

Data are based on the per-protocol sample (N=99), excluding three participants from the placebo arm and nine from the fixed low-dose esketamine arm. Because a non-linear development over time was assumed, time was modelled as a categorical variable represented by dummy variables (0/1), using the baseline measurement as the reference category. The per-protocol linear mixed model included a random intercept and fixed effects for time and the cross-level interaction between treatment with oral esketamine and time. To adjust for baseline scores, the treatment variable was not part of the model, but its interaction with time was. This way the baseline values for both groups are assumed to be equal and are reflected in the intercept of the model. The treatment effects can be directly obtained from the estimates provided. $HDRS_{17}$ = Hamilton Depression Rating Scale.

2. Inventory of Depressive Symptomatology – Self Report (IDS-SR)

Mean total IDS-SR score decreased from 48.4 points (SD 9.72) to 43.0 points (SD 12.99) in the fixed low-dose esketamine arm and from 47.4 points (SD 8.90) to 41.2 points (SD 14.07) in the placebo arm. The LMM revealed no significant interaction between treatment and any of the individual time-dummy variables (Supplementary table 3), indicating no significant difference in change of depressive symptoms between the esketamine and placebo arm.

3. Clinical Global Impression (CGI)

Mean CGI-severity score decreased from 5.3 (SD 0.78) to 5.1 (SD 0.97) in the fixed low-dose esketamine arm and from 5.4 (SD 0.61) to 5.0 (SD 1.36) in the placebo arm. The LMM revealed no significant interaction between treatment and any of the individual time-dummy variables (Supplementary table 3). After six weeks of treatment, mean CGI-improvement score was 3.8 (SD 1.06) in the esketamine arm and 3.8 (SD 1.08) in the placebo arm, indicating no or minimally improvement in both arms. There was no significant difference in CGI-improvement between the two arms after two weeks (mean difference 0.17, 95% CI -0.19 to 0.52, p=0.353,), four weeks (mean difference -0.06, 95% CI -0.48 to 0.35, p=0.763) or six weeks of treatment (mean difference -0.05, 95% CI -0.48 to 0.38, p=0.809).

4. EuroQol (EQ-5D-5L) index value

There was no significant difference in improvement of health-related quality of life between the fixed low-dose esketamine arm and placebo arm (mean difference 0.02, 95% CI -0.07 to 0.12, p=0.615). Between baseline and end-of-treatment, the mean index value increased from 0.41 (SD 0.24) to 0.46 (SD 0.25) in the fixed low-dose esketamine arm and from 0.39 (SD 0.25) to 0.46 (SD 0.29) in the placebo arm. For comparison, the mean index value of the Dutch population is 0.87 (SD 0.17).

5. Systematic Assessment for Treatment Emergent Events (SAFTEE)

Of the 55 potential adverse events measured by the SAFTEE, only "dizziness or faintness" (26.0% versus 5.0% in the esketamine arm and placebo arm respectively, Fisher exact test value 6.76, p=0.020) and "dizziness when standing up" (13.0% versus 0.0% in the esketamine arm and placebo arm respectively, X^2=5.61, p=0.028) were more often moderately to severely increased in the fixed low-dose esketamine arm compared to the placebo arm (Supplementary table 2).

Supplementary table 2: Systematic Assessment for Treatment Emergent Events (SAFTEE)

	Moderate increase		Severe increase			
Symptom (SAFTEE Item)	**Esketamine**	**Placebo**	**Esketamine**	**Placebo**	**Test value**	**P**
Trouble sleeping	6 (13.0)	6 (15.0)	1 (2.2)	1 (2.5)	0.374[a]	1.000
Sleep disturbance	3 (6.5)	2 (5.0)	1 (2.2)	0 (0.0)	0.994[a]	1.000
Feeling drowsy or sleepy	4 (8.7)	4 (9.5)	0 (0.0)	1 (2.4)	1.135[a]	0.851
Feeling nervous or hyper	5 (10.4)	0 (0.0)	0 (0.0)	0 (0.0)	4.418[b]	0.061
Weakness or fatigue	5 (10.9)	1 (2.5)	0 (0.0)	0 (0.0)	2.309[b]	0.209
Irritable	4 (8.7)	1 (2.5)	0 (0.0)	0 (0.0)	1.500[b]	0.366
Poor memory	3 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	2.764[b]	0.244
Trouble concentrating	2 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	1.821[b]	0.496
Feeling strange or unreal	9 (19.1)	4 (10.0)	1 (2.1)	0 (0.0)	2.266[a]	0.301
Hearing or seeing things	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0.899[b]	1.000
Abnormal sensations	4 (8.5)	3 (7.3)	2 (4.3)	0 (0.0)	1.541[a]	0.619
Numbness or tingling	3 (6.7)	2 (4.9)	0 (0.0)	1 (2.4)	1.218[a]	0.827
Dizziness or faintness	10 (21.7)	2 (5.0)	2 (4.3)	0 (0.0)	6.764[a]	0.020*
Headache	5 (11.1)	5 (12.2)	0 (0.0)	1 (2.4)	1.135[a]	0.864
Blurred vision	4 (8.9)	6 (14.0)	0 (0.0)	0 (0.0)	0.560[b]	0.517
Ringing in ears or trouble hearing	2 (4.3)	3 (7.1)	1 (2.2)	0 (0.0)	1.218[a]	0.827
Stuffy nose	3 (6.7)	0 (0.0)	1 (2.2)	0 (0.0)	3.272[a]	0.244
Dry mouth	3 (6.7)	6 (14.6)	0 (0.0)	0 (0.0)	1.453[b]	0.299
Drooling or increased salivation	0 (0.0)	2 (4.9)	0 (0.0)	0 (0.0)	2.247[b]	0.224
Muscle cramps or stiffness	8 (17.4)	4 (9.8)	0 (0.0)	1 (2.4)	2.001[a]	0.287
Muscle twitching or movements	3 (6.7)	3 (7.5)	0 (0.0)	0 (0.0)	0.022[b]	1.000
Trouble sitting still	2 (4.3)	3 (7.3)	0 (0.0)	0 (0.0)	0.353[b]	0.663
Tremor or shakiness	1 (2.2)	3 (7.5)	0 (0.0)	0 (0.0)	1.315[b]	0.338
Poor coordination or unsteadiness	6 (13.0)	1 (2.5)	1 (2.2)	0 (0.0)	3.946[a]	0.116
Slurred speech	2 (4.4)	2 (5.0)	1 (2.2)	0 (0.0)	0.973[a]	1.000
Rapid or pounding heartbeat	1 (2.2)	3 (7.3)	1 (2.2)	0 (0.0)	1.995[a]	0.344

Trouble catching breath or hyperventilation	6 (13.0)	1 (2.5)	0 (0.0)	1 (2.5)	3.996[a]	0.081
Chest pain	3 (6.7)	1 (2.4)	0 (0.0)	0 (0.0)	0.865[b]	0.618
Nausea or vomiting	1 (2.2)	2 (5.0)	1 (2.2)	0 (0.0)	1.368[a]	0.790
Stomach or abdominal discomfort	4 (8.7)	2 (4.9)	1 (2.2)	1 (2.4)	0.735[a]	0.838
Constipation	2 (4.3)	4 (9.8)	2 (4.3)	1 (2.4)	1.288[a]	0.555
Diarrhea	5 (10.6)	3 (7.1)	1 (2.1)	0 (0.0)	1.222[a]	0.717
Difficulty starting urination	3 (6.7)	3 (7.5)	1 (2.2)	0 (0.0)	0.937[a]	1.000
Frequent need to urinate	6 (12.8)	6 (14.3)	2 (4.3)	2 (4.8)	0.233[a]	1.000
Menstrual irregularities	1 (2.2)	2 (4.9)	1 (2.2)	1 (2.4)	0.779[a]	0.800
Loss of sexual interest	2 (4.4)	3 (7.5)	0 (0.0)	1 (2.5)	1.530[a]	0.502
Problems with sexual arousal	2 (4.4)	2 (5.0)	1 (2.2)	0 (0.0)	0.973[a]	1.000
Delayed or absent orgasm	0 (0.0)	2 (4.9)	2 (4.4)	0 (0.0)	3.269[a]	0.175
Sweating excessively	4 (8.7)	6 (14.6)	0 (0.0)	1 (2.4)	1.905[a]	0.406
Fluid retention or swelling	0 (0.0)	4 (10.0)	1 (2.2)	0 (0.0)	5.150[a]	0.045*
Decreased appetite	4 (8.5)	2 (5.0)	1 (2.1)	0 (0.0)	1.247[a]	0.683
Increased appetite	3 (6.5)	3 (7.1)	0 (0.0)	1 (2.4)	1.148[a]	0.831
Weight gain	4 (8.7)	3 (7.1)	1 (2.2)	2 (4.8)	0.635[a]	0.884
Weight loss	3 (6.7)	4 (10.0	0 (0.0)	0 (0.0)	0.311[b]	0.702
Skin rash or allergy	3 (6.7)	2 (5.0)	0 (0.0)	0 (0.0)	0.106[b]	1.000
Diminished mental capacity	4 (8.9)	3 (7.3)	0 (0.0)	2 (4.9)	1.965[a]	0.398
Difficulty finding words	3 (6.5)	4 (9.8)	0 (0.0)	0 (0.0)	0.307[b]	0.702
Apathy	6 (13.0)	5 (11.9)	1 (2.2)	1 (2.4)	0.314[a]	1.000
Dizziness when standing up	6 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)	5.609[b]	0.028*
Bruising	0 (0.0)	3 (7.5)	0 (0.0)	0 (0.0)	3.498[b]	0.100
Hair thinning or loss	2 (4.3)	1 (2.4)	1 (2.2)	0 (0.0)	1.176[a]	1.000
Hot flashes	3 (6.4)	0 (0.0)	1 (2.1)	1 (2.5)	2.499[a]	0.316
Clenching of teeth at night	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	1.138[b]	0.471
Strange taste in mouth	6 (12.8)	1 (2.5)	0 (0.0)	0 (0.0)	3.078[b]	0.118
Unable to sit still	3 (6.5)	2 (5.0)	0 (0.0)	0 (0.0)	0.090[b]	1.000

The data provided (n (%)) depict how many participants endorsed moderate to severe increases in all 55 specific symptoms of the Systematic Assessment for Treatment Emergent Events (SAFTEE) during the trial. [a] Fishers' Exact Test. [b] Pearson Chi-square.

6. Dissociation Tension Scale (DSS)

Mean total DSS score decreased from 24.1 (SD=24.97) at baseline to 21.6 (SD=19.25) after one week of treatment and 19.5 (SD=17.54) after six weeks of treatment in the fixed low-dose esketamine arm, and from 28.1 (SD=29.19) at baseline to 24.6 (SD=30.33) after one week of treatment and 20.6 (SD=25.94) after six weeks of treatment in the placebo arm, indicating on average a decrease of dissociative symptoms in both arms. There was no significant difference in change of DSS total score between the fixed low-dose esketamine arm and placebo arm after one week of treatment (mean difference 0.51, 95% CI -8.55 to 9.56, p=0.912) or after six weeks of treatment (mean difference -2.76, 95% CI -9.57 to 4.06, p=0.424).

7. Questionnaire for Psychotic Experiences (QPE) and Iowa Sleep Disturbance Inventory (ISDI)

There were no significant differences in psychotic experiences (QPE) or sleep disturbances (ISDI) between the fixed low-dose esketamine arm and placebo arm after one or six weeks of treatment, except for sleep hallucinations (mean difference -0.36, 95% CI -0.71 to -0.00, p=0.048). After one week of treatment, participants in the fixed low-dose esketamine arm experienced an average increase of sleep hallucinations of 0.09 points (SD=0.90) while the participants in the placebo arm experienced an average decrease of sleep hallucinations of 0.26 points (SD=0.86). After six weeks of treatment, there was no longer a difference in report of sleep hallucinations between the two arms.

8. Blood pressure, weight, and liver enzyme levels

The LMM analysis of the systolic blood pressure (SBP) revealed a significant interaction between treatment and the time-dummy variable for day 4 (mean difference 7.2, 95% CI 1.24 to 13.22, p=0.018), but not between treatment and any of the other individual time-dummy variables (Supplementary table 3). Nine participants met the criterion of increased SBP (≥ 30 mmHg) in the first week of treatment: five (9.1%) in the esketamine arm and four (7.5%) in the placebo arm (X^2=0.08, p=1.000). None met the criterion of increased SBP after two or four weeks of treatment; one participant in both arms met the criterion after six weeks of treatment (X^2=0.00, p=1.000). Regarding diastolic blood pressure (DBP) and weight the LMM revealed no significant interaction between treatment and any of the individual time-dummy variables (Supplementary table 3). One participant in the placebo arm met the criterion of increased DBP (≥15 mmHg) in the first week of treatment, none in week 2, 4 or 6. An increase in liver enzyme levels above the reference range was measured in 16 participants, of whom 11 in the esketamine arm (X^2=2.12, p=0.171). Hepatic enzyme activity ≥1.5 times the upper limit of the reference range was measured in one participant in both arms (X^2=0.01, p=1.000). Increase of hepatic enzyme activity of ≥100% was found in three participants in the esketamine arm and one in the placebo arm (X^2=0.86, p=0.617).

9. Supplementary table 3: Estimates of fixed effects for the cross-level interaction between thrice-daily fixed low-dose oral esketamine and dummy variables for time

Supplementary table 3: Estimates of fixed effects for the cross-level interaction between thrice-daily fixed low-dose oral esketamine and dummy variables for time

	Estimate	Standard error	Degrees of freedom	95% Confidence Interval		p-value
				Lower bound	Upper bound	
$HDRS_{17}$						
Week 2 (visit 3)	-1.2	1.11	249	-3.36	1.00	0.286
Week 4 (visit 4)	-0.4	1.12	258	-2.58	1.85	0.748
Week 6 (visit 5)	0.6	1.14	308	-1.65	2.82	0.609
IDS-SR						
Week 2 (visit 3)	-0.0	2.30	191	-4.57	4.51	0.989
Week 4 (visit 4)	2.3	2.36	205	-2.30	6.99	0.320
Week 6 (visit 5)	1.5	2.33	200	-3.06	6.14	0.510
CGI severity						
Week 2 (visit 3)	-0.2	0.19	253	-0.59	0.17	0.272
Week 4 (visit 4)	-0.0	0.20	261	-0.40	0.37	0.954
Week 6 (visit 5)	0.1	0.20	265	-0.32	0.45	0.745
SBP						
Week 1 – day 1	-1.9	3.04	296	-7.84	4.11	0.540
Week 1 – day 2	1.3	3.05	298	-4.66	7.33	0.662
Week 1 – day 3	-0.1	3.05	301	-6.07	5.94	0.982
Week 1 – day 4	7.2	3.05	298	1.24	13.22	0.018*
Week 1 (visit 2)	3.9	3.10	317	-2.23	9.98	0.213
Week 2 (visit 3)	0.7	3.12	323	-5.46	6.82	0.828
Week 4 (visit 4)	3.6	3.13	327	-2.55	9.78	0.250
Week 6 (visit 5)	1.6	3.11	320	-4.51	7.75	0.603
DBP						
Week 1 – day 1	-1.1	2.20	234	-5.39	3.28	0.632
Week 1 – day 2	0.7	2.20	236	-3.61	5.07	0.741
Week 1 – day 3	-0.6	2.21	238	-4.90	3.79	0.802
Week 1 – day 4	1.4	2.20	236	-2.94	5.74	0.526
Week 1 (visit 2)	0.5	2.24	251	-3.87	4.96	0.808
Week 2 (visit 3)	0.9	2.25	253	-3.55	5.31	0.696
Week 4 (visit 4)	-0.1	2.25	256	-4.58	4.30	0.952
Week 6 (visit 5)	0.5	2.24	251	-3.92	4.91	0.825
Weight						
Week 1 (visit 2)	3.7	3.50	110	-3.20	10.66	0.288
Week 2 (visit 3)	4.3	3.50	110	-2.63	11.23	0.221
Week 4 (visit 4)	4.3	3.49	110	-2.65	11.20	0.224
Week 6 (visit 5)	3.7	3.49	110	-3.27	10.58	0.297

Data are based on the intention-to-treat sample (n=111). Because a non-linear development over time was assumed, time was modelled as a categorical variable represented by dummy variables (0/1), using the baseline measurement as the reference category. The intention-to-treat linear mixed models included a random intercept and fixed effects for time and the cross-level interaction between treatment with oral esketamine and time. To adjust for baseline scores, the treatment variable was not part of the model, but its interaction with time was. This way the baseline values for both groups are assumed to be equal and are reflected in the intercept of the model. The treatment effects can be directly obtained from the estimates provided. CGI = Clinical Global Impression. DBP = diastolic blood pressure. $HDRS_{17}$ = Hamilton Depression Rating Scale. IDS-SR = Inventory of Depressive Symptomatology – Self Report. SBP = systolic blood pressure.

10. Response rates open-label treatment

Eighteen participants (25.0% of the intention-to-treat sample of 72 participants) met response criteria, of which 10 (55.6%) descended from the esketamine arm and eight (44.4%) from the placebo arm. None of the 10 participants that descended from the esketamine arm had met response criteria at the end of the RCT treatment phase, but five had met partial-response criteria before. Three of the eight participants that descended from the placebo arm had met response criteria at the end of the RCT treatment phase, and one had met partial-response criteria before.

Nine participants (12.5% of the intention-to-treat sample) met partial-response criteria, of which three (33.3%) descended from the esketamine arm and six (66.7%) from the placebo arm. One of the three participants that descended from the esketamine arm had met response criteria at the end of the RCT treatment phase. Two of the six participants that descended from the placebo arm had met partial-response criteria before.

38 participants (52.8% of the intention-to-treat sample) did not meet response criteria. Of these, two had met response criteria (one in the esketamine arm, one in the placebo arm) and five had met partial-response criteria (two in the esketamine arm, three in the placebo arm) at the end of the RCT treatment phase. Of 7 participants (9.7% of the intention-to-treat sample) data of the effect of open-label treatment is missing. One of these participants had met partial-response criteria at the end of RCT esketamine treatment.