

Supplementary Material

Efficacy and Safety of Lumateperone and Other Atypical Antipsychotics Approved as Adjunctive Treatment for Major Depressive Disorder in the United States: A Network Meta-Analysis

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Table S1. Key inclusion and exclusion criteria of included registrational trials

Treatment	Trial	Key inclusion criteria	Key exclusion criteria
Lumateperone	NCT04985942	• 18–65 years old • Confirmed diagnosis of MDD per the DSM-5 To enter screening phase • Inadequate response to ADT (<50% improvement) • MADRS score ≥ 24 • CGI-S score ≥ 4 • QIDS-SR-16 > 14 To enter double-blind phase • MADRS score ≥ 24 • CGI-S score ≥ 4 • QIDS-SR-16 > 14	• 25% decrease in MADRS Total or QIDS-SR-16 Total scores between screening and baseline • Significant risk for suicidal behaviour • Lifetime history of treatment resistance (no remission) • No comorbid psychiatric diagnoses
Lumateperone	NCT05061706	• 18–65 years old • Confirmed diagnosis of MDD per the DSM-5 To enter screening phase • Inadequate response to ADT (<50% improvement) • MADRS score ≥ 24 • CGI-S score ≥ 4 • QIDS-SR-16 > 14 To enter double-blind phase • MADRS score ≥ 24 • CGI-S score ≥ 4 • QIDS-SR-16 > 14	• 25% decrease in MADRS Total or QIDS-SR-16 Total scores between screening and baseline • Significant risk for suicidal behaviour • Lifetime history of treatment resistance (no remission) • No comorbid psychiatric diagnoses

Aripiprazole	NCT00095823	• 18–65 years old • Confirmed diagnosis of MDD per the DSM-IV-TR To enter prospective treatment phase • Inadequate response to 1-3 ADTs (<50% reduction in depressive symptoms severity) • HAM-D-17 ≥ 18 To enter double-blind phase • HAM-D-17 total score that represented a <50% reduction in symptoms during prospective treatment • HAM-D total score ≥ 14 • CGI-I score ≥ 3	• Risk of suicidal behaviour • No comorbid psychiatric diagnoses
Aripiprazole	NCT00095758	• 18–65 years old • Confirmed diagnosis of MDD per the DSM-IV-TR To enter prospective treatment phase • Inadequate response to 1-3 ADTs (<50% reduction in depressive symptoms severity) • HAM-D-17 ≥ 18 To enter double-blind phase • HAM-D-17 total score that represented a <50% reduction in symptoms during prospective treatment • HAM-D total score ≥ 14 • CGI-I score ≥ 3	• Risk of suicidal behaviour • No comorbid psychiatric diagnoses
Brexipiprazole	NCT01360645	• 18–65 years old • Confirmed diagnosis of MDD per the DSM-IV-TR To enter prospective treatment phase	• Serious risk of suicide • No comorbid psychiatric diagnoses

		• Inadequate response to 1-3 ADTs (<50% reduction in depressive symptoms severity) • HAM-D-17 score ≥ 18 at screening and first day of prospective treatment To enter double-blind treatment phase • Inadequate response throughout prospective treatment, defined as: HAM-D-17 score ≥ 14; <50% reduction from baseline in HDRS-17, <50% reduction in MADRS total score between start of prospective treatment and each scheduled visit, and CGI-I score ≥ 3 at each scheduled visit	
Brexipiprazole	NCT01360632	• 18–65 years old • Confirmed diagnosis of MDD per the DSM-IV-TR To enter prospective treatment phase • Inadequate response to 1-3 ADTs (<50% reduction in depressive symptoms severity) • HAM-D-17 score ≥ 18 at screening and start of prospective treatment To enter double-blind treatment phase • Inadequate response throughout prospective treatment, defined as: HAM-D-17 score ≥ 14; <50% reduction from baseline in HAM-D-17, <50% reduction in MADRS total score between start of prospective treatment and each scheduled visit, and CGI-I score ≥ 3 at each scheduled visit)	• Serious risk of suicide • No comorbid psychiatric diagnoses
Cariprazine	NCT03738215	• 18–65 years old • Confirmed diagnosis of MDD per the DSM-5 • Inadequate response to 1-3 ADTs (resistance rating score ≥ 3)	• Suicide risk • No comorbid psychiatric diagnoses

		• HAM-D-17 total score ≥ 22 and item 1 (depressed mood) score ≥ 2 at screening and baseline	
Cariprazine	NCT01469377	• 18–65 years old • Confirmed diagnosis of MDD per the DSM-IV-TR • Ongoing inadequate response to ADT defined as resistance rating score ≥ 3 and global confidence score ≥ 3 • MADRS score ≥ 22	• Suicide risk • No comorbid psychiatric diagnoses
Quetiapine XR	NCT00326105	• 18–65 years old • Confirmed diagnosis of MDD per the DSM-IV • Inadequate response to ADT during current depressive episode • HAM-D score ≥ 20 and item 1 (depressed mood) score ≥ 2 at enrollment and randomization	• Suicide risk • No comorbid psychiatric diagnoses
Quetiapine XR	NCT00351910	• 18–65 years old • Confirmed diagnosis of MDD per the DSM-IV-TR • History of inadequate response to ADT during current depressive episode • HAM-D-17 score ≥ 20 and item 1 (depressed mood) score ≥ 2 at enrollment and randomization	• Suicide risk • No comorbid psychiatric diagnoses

ADT: antidepressant therapy; CGI-I: Clinical Global Impression Scale – Improvement; CGI-S: Clinical Global Impression Scale –

Severity; DSM: Diagnostic and Statistical Manual of Mental Disorders; HAM-D-17: Hamilton Depression Rating Scale 17-item;

MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; mg: milligram; NCT: national clinical

trial; QIDS-SR: Quick Inventory of Depressive Symptomatology—Self-Report; SE: standard error; XR: extended-release

Table S2. Patient baseline characteristics of included registrational trials

NCT	Treatment arm	Age (years) mean ± SD	Female n (%)	White n (%)	BMI (kg/m²) mean ± SD	MADRS mean ± SD	CGI-S mean ± SD
NCT04985942	Lumateperone (42 mg/day)	45.0 ± 12.4	158 (65.6)	180 (74.7)	27.7 ± 5.1	30.4 ± 3.8	4.7 ± 0.6
	Placebo+ADT	45.1 ± 12.51	160 (65.8)	191 (78.6)	27.3 ± 5.0	30.1 ± 3.5	4.6 ± 0.6
NCT05061706	Lumateperone (42 mg/day)	45.6 ± 12.8	169 (69.8)	235 (97.1)	27.9 ± 4.9	30.8 ± 3.9	4.6 ± 0.6
	Placebo+ADT	46.4 ± 12.2	165 (69.3)	223 (93.7)	28.2 ± 5.2	31.5 ± 4.0	4.7 ± 0.6
NCT00095823	Aripiprazole (2–20 mg/day)	46.5 ± 10.6	112 (61.5)	159 (87.4)	—	26.0 ± 6.1	4.1 ± 0.0 ¹
	Placebo+ADT	44.2 ± 10.9	113 (64.2)	163 (92.6)	—	25.9 ± 6.5	4.1 ± 0.1 ¹
NCT00095758	Aripiprazole (2–20 mg/day)	44.6 ± 11	126 (66.0)	170 (89.0)	30.7 ± 7.4	25.2 ± 6.2	4.0 ± 0.0
	Placebo+ADT	44.4 ± 10.7	128 (67.4)	169 (88.9)	30.8 ± 7.5	27.0 ± 5.5	4.1 ± 0.0
NCT01360645	Brexpiprazole (2 mg/day)	44.1 ± 11.6	130 (69.1)	163 (86.7)	29.9 ± 6.8	26.6 ± 5.8	4.1 ± 0.6
	Placebo+ADT	45.2 ± 11.3	137 (71.7)	166 (86.9)	29.6 ± 7.1	27.1 ± 5.6	4.2 ± 0.6
NCT01360632	Brexpiprazole (1 mg/day)	45.7 ± 11.6	158 (69.9)	183 (81.0)	29.4 ± 6.7	26.7 ± 5.6	4.2 ± 0.6
	Brexpiprazole (3 mg/day)	44.5 ± 11.2	156 (67.8)	201 (87.4)	29.9 ± 7.0	26.4 ± 5.2	4.1 ± 0.6
	Placebo+ADT	46.6 ± 11	146 (66.1)	188 (85.1)	29.6 ± 7.0	26.3 ± 5.3	4.1 ± 0.5
NCT03738215	Cariprazine (1.5 mg/day)	43.3 ± 13.6	191 (75.8)	205 (81.3)	30.1 ± 7.6	32.8 ± 5.0	4.6 ± 0.6
	Cariprazine (3.0 mg/day)	44.8 ± 13.3	180 (71.4)	215 (85.3)	29.0 ± 7.0	32.7 ± 4.9	4.6 ± 0.6
	Placebo+ADT	46.4 ± 11.9	184 (72.7)	203 (80.2)	30.5 ± 7.9	31.9 ± 5.7	4.6 ± 0.6

NCT01469377	Cariprazine (1–2 mg/day)	45.5 ± 11.9	187 (68.5)	234 (85.7)	28.2 ± 5.5	29.0 ± 4.3	4.4 ± 0.5
	Cariprazine (2–4.5 mg/day)	45.1 ± 11.4	201 (73.6)	242 (88.6)	29.1 ± 5.6	29.3 ± 4.1	4.4 ± 0.6
	Placebo+ADT	46.4 ± 11.6	190 (71.4)	230 (86.5)	28.9 ± 5.1	28.9 ± 4.3	4.4 ± 0.5
NCT00326105	Quetiapine XR (150 mg/day)	45.9 ± 11.0	109 (76.2)	128 (89.5)	—	27.2 ± 5.2	4.4 ± 0.6
	Quetiapine XR (300 mg/day)	44.3 ± 11.3	106 (72.6)	133 (91.1)	—	27.6 ± 5.0	4.5 ± 0.7
	Placebo+ADT	46.2 ± 10.9	98 (68.5)	128 (89.5)	—	27.6 ± 5.5	4.4 ± 0.7
NCT00351910	Quetiapine XR (150 mg/day)	46.0 ± 10.1	115 (69.3)	165 (99.4)	—	28.6 ± 5.4	4.6 ± 0.7
	Quetiapine XR (300 mg/day)	45.5 ± 11.1	110 (68.3)	156 (96.9)	—	28.4 ± 5.5	4.7 ± 0.7
	Placebo+ADT	44.8 ± 10.4	104 (65.0)	157 (98.1)	—	28.2 ± 5.6	4.6 ± 0.8

¹ Values are at randomization, not baseline.

ADT: antidepressant therapy; BMI: body mass index; CGI-S: Clinical Global Impression Scale – Severity; kg: kilogram; m: meter;

MADRS: Montgomery-Åsberg Depression Rating Scale; mg: milligram; NCT: national clinical trial; SD: standard deviation; XR: extended-release

Table S3. Trial-level data used in the NMA for efficacy outcomes

Trial	Treatment regimen	Sample size	MADRS change from baseline mean (SE)	MADRS remission n (%)	MADRS response n (%)	CGI-S change from baseline mean (SE)
NCT04985942	Lumateperone (42 mg/day)	216	-14.70 (0.54)	62 (25.9) ¹	109 (45.6) ¹	-1.60 (0.07)
	Placebo+ADT	229	-9.80 (0.53)	33 (13.6) ¹	58 (24.0) ¹	-0.90 (0.07)
NCT05061706	Lumateperone (42 mg/day)	203	-14.70 (0.56)	58 (25.0) ²	93 (40.1) ²	-1.50 (0.07)
	Placebo+ADT	221	-10.20 (0.54)	32 (13.5) ²	60 (25.3) ²	-1.00 (0.07)
NCT00095823	Aripiprazole (2-20 mg/day)	181	-8.80 (0.39)	47 (26.0)	61 (33.7)	-1.03 (0.08)
	Placebo+ADT	172	-5.80 (0.43)	27 (15.7)	41 (23.8)	-0.64 (0.08)
NCT00095758	Aripiprazole (2-20 mg/day)	185	-8.50 (0.64)	47 (25.4)	60 (32.4)	-1.10 (0.08)
	Placebo+ADT	184	-5.70 (0.70)	28 (15.2)	32 (17.4)	-0.60 (0.08)
NCT01360645	Brexipiprazole (2 mg/day)	175	-8.36 (0.64)	26 (14.9)	41 (23.4)	-0.91 (0.07)
	Placebo+ADT	178	-5.15 (0.63)	16 (9.0)	28 (15.7)	-0.57 (0.07)
NCT01360632	Brexipiprazole (1 mg/day)	211	-7.64 (0.52)	31 (14.7)	49 (23.2)	-0.87 (0.06)
	Brexipiprazole (3 mg/day)	213	-8.29 (0.53)	30 (14.1)	49 (23.0)	-0.92 (0.06)
	Placebo+ADT	203	-6.33 (0.53)	22 (10.8)	29 (14.3)	-0.72 (0.06)
NCT03738215	Cariprazine (1.5 mg/day)	250	-14.10 (0.70)	63 (25.2)	110 (44.0)	-1.40 (0.10)
	Cariprazine (3.0 mg/day)	252	-13.10 (0.70)	42 (16.7)	99 (39.3)	-1.30 (0.10)
	Placebo+ADT	249	-11.50 (0.70)	58 (23.3)	87 (34.9)	-1.10 (0.10)

NCT01469377	Cariprazine (1-2 mg/day)	273	-12.10 (0.63)	87 (31.9)	116 (42.5)	-1.50 (0.10)
	Cariprazine (2-4.5 mg/day)	271	-13.20 (0.63)	87 (32.1)	112 (41.3)	-1.60 (0.10)
	Placebo+ADT	264	-11.00 (0.63)	79 (29.9)	84 (31.8)	-1.40 (0.10)
NCT00326105	Quetiapine XR (150 mg/day)	143	-13.60 (0.80)	60 (42.0)	74 (51.7)	-1.47 (0.08)
	Quetiapine XR (300 mg/day)	146	-14.70 (0.80)	77 (52.7)	86 (58.9)	-1.52 (0.08)
	Placebo+ADT	143	-11.70 (0.80)	47 (32.9)	66 (46.2)	-1.23 (0.08)
NCT00351910	Quetiapine XR (150 mg/day)	166	-15.26 (0.70)	69 (41.6)	92 (55.4)	-1.72 (0.08)
	Quetiapine XR (300 mg/day)	161	-14.94 (0.70)	65 (40.4)	93 (57.8)	-1.64 (0.08)
	Placebo+ADT	160	-12.21 (0.70)	50 (31.3)	74 (46.3)	-1.25 (0.08)

¹ In the lumateperone NCT04985942 trial, MADRS remission and MADRS response were assessed out of N=239 in the lumateperone 42 mg/day arm and N=242 in the placebo arm.

² In the lumateperone NCT05061706 trial, MADRS remission and MADRS response were assessed out of N=232 in the lumateperone 42 mg/day arm and N=237 in the placebo arm.

ADT: antidepressant therapy; CGI-S: Clinical Global Impression Scale – Severity; MADRS: Montgomery-Åsberg Depression Rating Scale; mg: milligram; NCT: national clinical trial; NMA: network meta-analysis; SE: standard error; XR: extended-release

Table S4. Trial-level data used in the NMA for safety outcomes

Trial	Treatment regimen	Sample size	Weight change from baseline mean (SE)	≥7% weight increase n (%)	Akathisia n (%)	Somnolence n (%)
NCT04985942	Lumateperone (42 mg/day)	237	0.07 (0.11)	1 (0.4)	3 (1.2) ¹	10 (4.1) ¹
	Placebo+ADT	242	0.02 (0.10)	2 (0.8)	1 (0.4) ¹	3 (1.2) ¹
NCT05061706	Lumateperone (42 mg/day)	230	-0.19 (0.12)	1 (0.4)	1 (0.4) ²	39 (16.1) ²
	Placebo+ADT	237	0.06 (0.11)	4 (1.7)	1 (0.4) ²	7 (2.9) ²
NCT00095823	Aripiprazole (2-20 mg/day)	182	2.01 (0.17)	13 (7.1)	42 (23.1)	—
	Placebo+ADT	176	0.34 (0.18)	2 (1.1)	8 (4.5)	—
NCT00095758	Aripiprazole (2-20 mg/day)	189	1.47 (0.16)	6 (3.2)	49 (25.9)	13 (6.9)
	Placebo+ADT	190	0.42 (0.17)	0 (0.0)	8 (4.2)	7 (3.7)
NCT01360645	Brexpiprazole (2 mg/day)	188	1.64 (0.15)	9 (4.8)	14 (7.4)	8 (4.3)
	Placebo+ADT	191	0.36 (0.15)	5 (2.6)	2 (1.0)	1 (0.5)
NCT01360632	Brexpiprazole (1 mg/day)	226	1.40 (0.15)	11 (4.9)	10 (4.4)	9 (4.0)
	Brexpiprazole (3 mg/day)	229	1.57 (0.15)	4 (1.7)	31 (13.5)	13 (5.7)
	Placebo+ADT	220	0.24 (0.15)	2 (0.9)	5 (2.3)	1 (0.5)
NCT03738215	Cariprazine (1.5 mg/day)	252	0.68 (0.15)	10 (4.0)	13 (5.2)	13 (5.2)
	Cariprazine (3.0 mg/day)	252	0.78 (0.18)	3 (1.2)	20 (7.9)	11 (4.4)
	Placebo+ADT	253	0.11 (0.12)	2 (0.8)	2 (0.8)	7 (2.8)

NCT01469377	Cariprazine (1-2 mg/day)	273	0.90 (0.12)	4 (1.5) ³	18 (6.6) ³	24 (8.8) ³
	Cariprazine (2-4.5 mg/day)	271	0.90 (0.13)	9 (3.3) ³	61 (22.3) ³	27 (9.9) ³
	Placebo+ADT	264	0.00 (0.12)	5 (1.9) ³	6 (2.3) ³	13 (4.9) ³
NCT00326105	Quetiapine XR (150 mg/day)	148	0.80 (0.19)	2 (1.4)	2 (1.4)	43 (29.1)
	Quetiapine XR (300 mg/day)	149	1.60 (0.20)	11 (7.4)	4 (2.7)	43 (28.9)
	Placebo+ADT	148	0.30 (0.21)	3 (2.0)	1 (0.7)	6 (4.1)
NCT0035191	Quetiapine XR (150 mg/day)	167	0.90 (0.17)	7 (4.2)	3 (1.8)	28 (16.8)
	Quetiapine XR (300 mg/day)	163	1.00 (0.18)	7 (4.3)	4 (2.5)	38 (23.3)
	Placebo+ADT	161	0.00 (0.20)	2 (1.2)	2 (1.2)	5 (3.1)

¹ In the lumateperone NCT04985942 trial, akathisia and somnolence were assessed out of N=241 in the lumateperone arm 42 mg/day and N=243 in the placebo arm.

² In the lumateperone NCT05061706 trial, akathisia and somnolence were assessed out of N=242 in the lumateperone arm 42 mg/day, and N=238 in the placebo arm.

³ In the cariprazine NCT01469377 trial, $\geq 7\%$ weight increase, akathisia, and somnolence were assessed out of N=273 in the cariprazine 1-2 mg/day and 2-4.5 mg/day arm, and N=266 in the placebo arm.

ADT: antidepressant therapy; mg: milligram; NCT: national clinical trial; NMA: network meta-analysis; SE: standard error; XR: extended release

Table S5. Pairwise probabilities of treatment superiority and treatment comparisons for MADRS response¹⁻³

Pairwise probabilities Pairwise treatment	Lumateperone 42 mg/day	Aripiprazole 2-20 mg/day	Brexipiprazole 1 mg/day	Brexipiprazole 2 mg/day	Brexipiprazole 3 mg/day	Cariprazine 1-2 mg/day	Cariprazine 1.5 mg/day	Cariprazine 2-4.5 mg/day	Cariprazine 3 mg/day	Quetiapine XR 150 mg/day	Quetiapine XR 300 mg/day
Lumateperone 42 mg/day	—	80%	78%	86%	79%	95%	98%	97%	100%	99%	95%
Aripiprazole 2-20 mg/day	1.21 (0.78, 1.86)	—	55%	67%	57%	77%	86%	82%	97%	93%	76%
Brexipiprazole 1 mg/day	1.25 (0.70, 2.23)	1.04 (0.57, 1.89)	—	61%	52%	68%	77%	73%	91%	84%	66%
Brexipiprazole 2 mg/day	1.39 (0.76, 2.57)	1.15 (0.62, 2.18)	1.12 (0.53, 2.34)	—	40%	55%	64%	60%	84%	74%	52%
Brexipiprazole 3 mg/day	1.27 (0.71, 2.28)	1.05 (0.58, 1.92)	1.01 (0.64, 1.60)	0.91 (0.43, 1.90)	—	66%	75%	71%	91%	84%	64%
Cariprazine 1-2 mg/day	1.45 (0.92, 2.27)	1.20 (0.74, 1.97)	1.16 (0.62, 2.15)	1.04 (0.55, 1.98)	1.14 (0.62, 2.14)	—	63%	60%	86%	75%	47%
Cariprazine 1.5 mg/day	1.58 (1.00, 2.49)	1.31 (0.80, 2.15)	1.26 (0.68, 2.33)	1.13 (0.59, 2.17)	1.25 (0.67, 2.29)	1.09 (0.65, 1.82)	—	44%	86%	63%	33%
Cariprazine 2-4.5 mg/day	1.52 (0.97, 2.38)	1.26 (0.78, 2.05)	1.21 (0.65, 2.26)	1.09 (0.57, 2.06)	1.19 (0.65, 2.22)	1.05 (0.74, 1.47)	0.96 (0.58, 1.59)	—	82%	69%	39%
Cariprazine 3 mg/day	1.92 (1.22, 3.04)	1.60 (0.97, 2.62)	1.54 (0.82, 2.85)	1.38 (0.71, 2.64)	1.52 (0.82, 2.80)	1.33 (0.80, 2.21)	1.22 (0.85, 1.74)	1.27 (0.76, 2.09)	—	32%	11%
Quetiapine XR 150 mg/day	1.72 (1.11, 2.60)	1.42 (0.89, 2.26)	1.37 (0.75, 2.50)	1.22 (0.66, 2.28)	1.35 (0.74, 2.46)	1.18 (0.73, 1.90)	1.08 (0.67, 1.75)	1.13 (0.70, 1.80)	0.89 (0.55, 1.44)	—	13%
Quetiapine XR 300 mg/day	1.42 (0.93, 2.17)	1.18 (0.74, 1.87)	1.13 (0.62, 2.08)	1.02 (0.54, 1.90)	1.12 (0.62, 2.05)	0.98 (0.61, 1.58)	0.90 (0.55, 1.46)	0.94 (0.58, 1.51)	0.74 (0.45, 1.21)	0.83 (0.60, 1.14)	—

¹ Outcomes were reported at Week 6.

² The upper triangle presents the pairwise probability that the treatment row is superior to treatment in column based on posterior distributions from the Bayesian NMA. Probabilities are expressed as percentages (0%–100%), with higher values indicating greater likelihood that the treatment row has a favorable outcome. Probabilities >99.5% are listed as 100% due to rounding.

³ The lower triangle presents the pairwise treatment comparisons, reported as the odds ratios (95% credible intervals) for the treatment in column versus the treatment in row. Values >1 favor the column treatment (greater improvement in depressive symptoms) while values <1 favor the row treatment.

MADRS: Montgomery-Åsberg Depression Rating Scale; mg: milligram; XR: extended release

Table S6. Pairwise probabilities of treatment superiority and treatment comparisons for MADRS remission¹⁻⁴

Pairwise probabilities Pairwise treatment	Lumateperone 42 mg/day	Aripiprazole 2-20 mg/day	Brexpiprazole 1 mg/day	Brexpiprazole 2 mg/day	Brexpiprazole 3 mg/day	Cariprazine 1-2 mg/day	Cariprazine 1.5 mg/day	Cariprazine 2-4.5 mg/day	Cariprazine 3 mg/day	Quetiapine XR 150 mg/day	Quetiapine XR 300 mg/day
Lumateperone 42 mg/day	—	71%	89%	70%	91%	100%	99%	100%	100%	93%	77%
Aripiprazole 2-20 mg/day	1.15 (0.70, 1.89)	—	79%	57%	83%	98%	97%	98%	100%	81%	56%
Brexpiprazole 1 mg/day	1.53 (0.77, 3.02)	1.33 (0.66, 2.68)	—	31%	58%	77%	75%	76%	98%	42%	23%
Brexpiprazole 2 mg/day	1.22 (0.58, 2.56)	1.06 (0.50, 2.27)	0.80 (0.33, 1.94)	—	73%	90%	89%	89%	99%	66%	47%
Brexpiprazole 3 mg/day	1.61 (0.80, 3.20)	1.40 (0.69, 2.83)	1.05 (0.61, 1.81)	1.32 (0.54, 3.19)	—	72%	71%	71%	97%	36%	19%
Cariprazine 1-2 mg/day	1.98 (1.21, 3.23)	1.72 (1.03, 2.90)	1.29 (0.64, 2.62)	1.62 (0.77, 3.47)	1.23 (0.61, 2.49)	—	49%	48%	96%	10%	2%
Cariprazine 1.5 mg/day	1.96 (1.16, 3.34)	1.71 (0.99, 3.01)	1.28 (0.62, 2.65)	1.60 (0.74, 3.53)	1.22 (0.59, 2.51)	0.99 (0.57, 1.72)	—	50%	99%	12%	3%
Cariprazine 2-4.5 mg/day	1.96 (1.19, 3.21)	1.71 (1.02, 2.88)	1.28 (0.64, 2.62)	1.60 (0.76, 3.43)	1.22 (0.60, 2.47)	0.99 (0.69, 1.41)	1.00 (0.57, 1.73)	—	96%	10%	2%
Cariprazine 3 mg/day	3.32 (1.92, 5.83)	2.89 (1.63, 5.29)	2.17 (1.04, 4.60)	2.72 (1.22, 6.13)	2.06 (0.99, 4.35)	1.67 (0.95, 3.02)	1.69 (1.09, 2.63)	1.69 (0.95, 3.08)	—	0%	0%
Quetiapine XR 150 mg/day	1.43 (0.89, 2.31)	1.24 (0.75, 2.06)	0.94 (0.47, 1.85)	1.17 (0.56, 2.48)	0.89 (0.44, 1.76)	0.72 (0.44, 1.18)	0.73 (0.43, 1.24)	0.73 (0.44, 1.18)	0.43 (0.24, 0.75)	—	13%
Quetiapine XR 300 mg/day	1.19 (0.74, 1.91)	1.04 (0.63, 1.71)	0.78 (0.39, 1.54)	0.97 (0.46, 2.07)	0.74 (0.37, 1.47)	0.60 (0.37, 0.98)	0.61 (0.36, 1.03)	0.61 (0.37, 0.99)	0.36 (0.20, 0.63)	0.83 (0.61, 1.15)	—

¹ Outcomes were reported at Week 6, unless otherwise specified.

² The upper triangle presents the pairwise probability that the treatment row is superior to treatment in column based on posterior distributions from the Bayesian NMA. Probabilities are expressed as percentages (0%–100%), with higher values indicating greater likelihood that the treatment row has a favorable outcome. Probabilities >99.5% are listed as 100% due to rounding.

³ The lower triangle presents the pairwise treatment comparisons, reported as the odds ratios (95% credible intervals) for the treatment in column versus the treatment in row. Values >1 favor the column treatment (greater improvement in depressive symptoms) while values <1 favor the row treatment.

⁴ For cariprazine (NCT01469377; 1–2 mg/day and 2–4.5 mg/day) Week 8 data was used given Week 6 data were not available.

MADRS: Montgomery-Åsberg Depression Rating Scale; mg: milligram; NCT: national clinical trial; XR: extended release

Table S7. Pairwise probabilities of treatment superiority and treatment comparisons for CGI-S change from baseline¹⁻⁵

Pairwise probabilities Pairwise treatment	Lumateperone 42 mg/day	Aripiprazole 2-20 mg/day	Brexiprazole 1 mg/day	Brexiprazole 2 mg/day	Brexiprazole 3 mg/day	Cariprazine 1-2 mg/day	Cariprazine 1.5 mg/day	Cariprazine 2-4.5 mg/day	Cariprazine 3 mg/day	Quetiapine XR 150 mg/day	Quetiapine XR 300 mg/day
Lumateperone 42 mg/day	—	93%	100%	99%	100%	100%	97%	99%	99%	99%	99%
Aripiprazole 2-20 mg/day	-0.15 (-0.37, 0.05)	—	99%	80%	98%	98%	81%	93%	93%	79%	82%
Brexiprazole 1 mg/day	-0.45 (-0.66, -0.23)	-0.29 (-0.52, -0.07)	—	7%	28%	62%	18%	38%	38%	4%	5%
Brexiprazole 2 mg/day	-0.26 (-0.50, -0.03)	-0.11 (-0.36, 0.14)	0.19 (-0.07, 0.44)	—	85%	91%	58%	79%	78%	45%	50%
Brexiprazole 3 mg/day	-0.40 (-0.61, -0.18)	-0.24 (-0.47, -0.01)	0.05 (-0.12, 0.22)	-0.14 (-0.39, 0.12)	—	73%	27%	50%	50%	9%	12%
Cariprazine 1-2 mg/day	-0.50 (-0.81, -0.19)	-0.35 (-0.66, -0.03)	-0.05 (-0.37, 0.28)	-0.24 (-0.57, 0.10)	-0.10 (-0.43, 0.23)	—	16%	24%	31%	6%	7%
Cariprazine 1.5 mg/day	-0.30 (-0.60, 0.02)	-0.14 (-0.46, 0.18)	0.15 (-0.17, 0.48)	-0.03 (-0.37, 0.30)	0.10 (-0.22, 0.43)	0.20 (-0.19, 0.60)	—	70%	76%	38%	41%
Cariprazine 2-4.5 mg/day	-0.40 (-0.70, -0.09)	-0.24 (-0.56, 0.07)	0.05 (-0.27, 0.37)	-0.14 (-0.47, 0.20)	-0.00 (-0.32, 0.32)	0.10 (-0.18, 0.38)	-0.10 (-0.50, 0.29)	—	50%	17%	19%
Cariprazine 3 mg/day	-0.40 (-0.71, -0.08)	-0.24 (-0.56, 0.08)	0.05 (-0.27, 0.38)	-0.14 (-0.47, 0.20)	0.00 (-0.32, 0.33)	0.10 (-0.29, 0.49)	-0.10 (-0.38, 0.18)	0.00 (-0.39, 0.39)	—	18%	20%
Quetiapine XR 150 mg/day	-0.24 (-0.45, -0.04)	-0.09 (-0.31, 0.13)	0.20 (-0.02, 0.43)	0.02 (-0.23, 0.26)	0.15 (-0.08, 0.38)	0.25 (-0.07, 0.57)	0.05 (-0.27, 0.37)	0.15 (-0.16, 0.47)	0.15 (-0.17, 0.47)	—	57%
Quetiapine XR 300 mg/day	-0.26 (-0.47, -0.05)	-0.11 (-0.32, 0.12)	0.19 (-0.04, 0.41)	0.00 (-0.25, 0.25)	0.14 (-0.09, 0.37)	0.24 (-0.08, 0.56)	0.04 (-0.28, 0.36)	0.14 (-0.18, 0.46)	0.14 (-0.18, 0.46)	-0.01 (-0.17, 0.14)	—

¹ Outcomes were reported at Week 6, unless otherwise specified.

² The upper triangle presents the pairwise probability that the treatment row is superior to treatment in column based on posterior distributions from the Bayesian NMA. Probabilities are expressed as percentages (0%–100%), with higher values indicating greater likelihood that the treatment row has a favorable outcome. Probabilities >99.5% are listed as 100% due to rounding.

³ The lower triangle presents the pairwise treatment comparisons, reported as the median difference (95% credible intervals) for the treatment in column versus the treatment in row. A median difference less than 0 indicates that the treatment in the column has a larger change in CGI-S compared to the treatment in the row.

⁴ For CGI-S change from baseline, the missing SE values in the quetiapine XR trials (NCT00326105 and NCT00351910; 150 mg/day and 300 mg/day) were imputed using the mean SE from other trials.

⁵ For cariprazine (NCT01469377; 1–2 mg/day and 2–4.5 mg/day) Week 8 data was used given Week 6 data were not available.

CGI-S: Clinical Global Scale – Severity; mg: milligram; NCT: national clinical trial; XR: extended release

Table S8. Pairwise probabilities of treatment superiority and treatment comparisons for weight change from baseline¹⁻⁵

Pairwise probabilities Pairwise treatment	Lumateperone 42 mg/day	Aripiprazole 2-20 mg/day	Brexpiprazole 1 mg/day	Brexpiprazole 2 mg/day	Brexpiprazole 3 mg/day	Cariprazine 1-2 mg/day	Cariprazine 1.5 mg/day	Cariprazine 2-4.5 mg/day	Cariprazine 3 mg/day	Quetiapine XR 150 mg/day	Quetiapine XR 300 mg/day
Lumateperone 42 mg/day	—	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Aripiprazole 2-20 mg/day	-1.42 (-1.82, -1.03)	—	25%	42%	48%	3%	0%	4%	1%	1%	21%
Brexpiprazole 1 mg/day	-1.24 (-1.72, -0.76)	0.18 (-0.36, 0.72)	—	66%	78%	18%	2%	18%	5%	6%	47%
Brexpiprazole 2 mg/day	-1.36 (-1.83, -0.89)	0.06 (-0.48, 0.60)	-0.13 (-0.73, 0.48)	—	55%	8%	1%	9%	2%	3%	31%
Brexpiprazole 3 mg/day	-1.40 (-1.89, -0.93)	0.01 (-0.53, 0.56)	-0.17 (-0.60, 0.25)	-0.04 (-0.65, 0.56)	—	6%	0%	7%	2%	2%	26%
Cariprazine 1-2 mg/day	-0.98 (-1.38, -0.57)	0.44 (-0.03, 0.91)	0.26 (-0.29, 0.80)	0.38 (-0.16, 0.92)	0.43 (-0.12, 0.98)	—	10%	50%	20%	24%	82%
Cariprazine 1.5 mg/day	-0.64 (-1.08, -0.21)	0.78 (0.27, 1.28)	0.59 (0.03, 1.17)	0.72 (0.14, 1.29)	0.76 (0.19, 1.34)	0.33 (-0.18, 0.84)	—	89%	67%	72%	98%
Cariprazine 2-4.5 mg/day	-0.98 (-1.39, -0.56)	0.44 (-0.04, 0.92)	0.26 (-0.30, 0.82)	0.38 (-0.16, 0.95)	0.43 (-0.12, 0.99)	-0.00 (-0.35, 0.35)	-0.33 (-0.86, 0.19)	—	21%	25%	81%
Cariprazine 3 mg/day	-0.75 (-1.22, -0.27)	0.68 (0.14, 1.21)	0.49 (-0.11, 1.09)	0.62 (0.02, 1.21)	0.66 (0.05, 1.26)	0.23 (-0.31, 0.77)	-0.10 (-0.56, 0.36)	0.23 (-0.32, 0.78)	—	57%	95%
Quetiapine XR 150 mg/day	-0.80 (-1.23, -0.37)	0.62 (0.13, 1.12)	0.44 (-0.12, 1.00)	0.56 (-0.00, 1.12)	0.61 (0.04, 1.17)	0.18 (-0.33, 0.68)	-0.16 (-0.68, 0.37)	0.18 (-0.34, 0.69)	-0.05 (-0.61, 0.51)	—	99%
Quetiapine XR 300 mg/day	-1.21 (-1.65, -0.77)	0.21 (-0.30, 0.71)	0.02 (-0.55, 0.59)	0.15 (-0.42, 0.72)	0.19 (-0.38, 0.76)	-0.24 (-0.75, 0.27)	-0.57 (-1.11, -0.03)	-0.24 (-0.75, 0.28)	-0.47 (-1.04, 0.10)	-0.42 (-0.77, -0.05)	—

¹ Outcomes were reported at Week 6, unless otherwise specified.

² The upper triangle presents the pairwise probability that the treatment row is superior to treatment in column based on posterior distributions from the Bayesian NMA. Probabilities are expressed as percentages (0%–100%), with higher values indicating greater likelihood that the treatment row has a favorable outcome. Probabilities >99.5% are listed as 100% due to rounding.

³ The lower triangle presents the pairwise treatment comparisons, reported as the median difference (95% credible intervals) for the treatment in column versus the treatment in row. A median difference larger than 0 indicates that the treatment in the column has a larger change in weight compared to the treatment in the row.

⁴ For weight change from baseline, the missing SE values in the brexpiprazole trials (NCT01360645 and NCT01360632; 1 mg/day, 2 mg/day and 3 mg/day) were imputed using the mean SE from other trials.

⁵ For cariprazine (NCT01469377; 1–2 mg/day and 2–4.5 mg/day) Week 8 data was used given Week 6 data were not available.

mg: milligram; NCT: national clinical trial; XR: extended release

Table S9. Pairwise probabilities of treatment superiority and treatment comparisons for $\geq 7\%$ weight increase¹⁻⁴

Pairwise probabilities Pairwise treatment	Lumateperone 42 mg/day	Aripiprazole 2-20 mg/day	Brexpiprazole 1 mg/day	Brexpiprazole 2 mg/day	Brexpiprazole 3 mg/day	Cariprazine 1-2 mg/day	Cariprazine 1.5 mg/day	Cariprazine 2-4.5 mg/day	Cariprazine 3 mg/day	Quetiapine XR 150 mg/day	Quetiapine XR 300 mg/day
Lumateperone 42 mg/day	—	100%	100%	97%	96%	81%	100%	97%	91%	97%	100%
Aripiprazole 2-20 mg/day	0.02 (0.00, 0.19)	—	31%	3%	9%	0%	27%	2%	5%	2%	12%
Brexpiprazole 1 mg/day	0.04 (0.00, 0.36)	1.79 (0.15, 18.57)	—	10%	3%	2%	45%	8%	13%	9%	29%
Brexpiprazole 2 mg/day	0.15 (0.01, 1.02)	6.15 (1.00, 52.25)	3.50 (0.50, 31.96)	—	54%	14%	87%	46%	43%	48%	82%
Brexpiprazole 3 mg/day	0.13 (0.01, 1.39)	5.52 (0.42, 72.85)	3.07 (1.00, 11.70)	0.89 (0.08, 7.78)	—	17%	79%	43%	40%	45%	71%
Cariprazine 1-2 mg/day	0.39 (0.03, 3.24)	16.32 (2.25, 161.13)	9.32 (1.25, 94.98)	2.64 (0.45, 17.14)	2.99 (0.32, 34.77)	—	98%	93%	73%	85%	97%
Cariprazine 1.5 mg/day	0.05 (0.00, 0.42)	2.03 (0.19, 20.07)	1.14 (0.09, 13.25)	0.33 (0.04, 2.22)	0.37 (0.02, 4.54)	0.12 (0.01, 0.92)	—	11%	2%	12%	34%
Cariprazine 2-4.5 mg/day	0.16 (0.01, 1.12)	6.63 (1.06, 57.35)	3.77 (0.58, 33.60)	1.08 (0.21, 5.79)	1.22 (0.15, 12.19)	0.42 (0.11, 1.33)	3.32 (0.50, 31.25)	—	45%	52%	85%
Cariprazine 3 mg/day	0.18 (0.01, 2.20)	7.69 (0.62, 99.48)	4.40 (0.30, 65.37)	1.23 (0.12, 12.24)	1.41 (0.08, 22.75)	0.47 (0.04, 4.90)	3.72 (1.07, 18.36)	1.14 (0.10, 10.75)	—	56%	79%
Quetiapine XR 150 mg/day	0.15 (0.01, 1.06)	6.47 (1.00, 54.71)	3.60 (0.55, 32.34)	1.04 (0.21, 5.40)	1.16 (0.14, 12.11)	0.39 (0.06, 2.30)	3.20 (0.47, 29.41)	0.96 (0.18, 5.09)	0.84 (0.09, 8.94)	—	97%
Quetiapine XR 300 mg/day	0.07 (0.01, 0.45)	2.98 (0.50, 24.14)	1.70 (0.28, 14.40)	0.49 (0.10, 2.33)	0.55 (0.07, 5.29)	0.19 (0.03, 1.00)	1.49 (0.23, 13.01)	0.45 (0.09, 2.16)	0.39 (0.04, 4.04)	0.47 (0.20, 1.05)	—

¹ Outcomes were reported at Week 6, unless otherwise specified.

² The upper triangle presents the pairwise probability that the treatment row is superior to treatment in column based on posterior distributions from the Bayesian NMA. Probabilities are expressed as percentages (0%–100%), with higher values indicating greater likelihood that the treatment row has a favorable outcome. Probabilities >99.5% are listed as 100% due to rounding.

³ The lower triangle presents the pairwise treatment comparisons, reported as the odds ratios (95% credible intervals) for the treatment in column versus the treatment in row. Values >1 indicate that the column treatment has a greater risk of weight increase while values <1 indicate that the row treatment has a greater risk of weight increase.

⁴ For cariprazine (NCT01469377; 1–2 mg/day and 2–4.5 mg/day) Week 8 data was used given Week 6 data were not available.

mg: milligram; NCT: national clinical trial; XR: extended release

Table S10. Pairwise probabilities of treatment superiority and treatment comparisons for akathisia¹⁻⁴

Pairwise probabilities Pairwise treatment	Lumateperone 42 mg/day	Aripiprazole 2-20 mg/day	Brexipiprazole 1 mg/day	Brexipiprazole 2 mg/day	Brexipiprazole 3 mg/day	Cariprazine 1-2 mg/day	Cariprazine 1.5 mg/day	Cariprazine 2-4.5 mg/day	Cariprazine 3 mg/day	Quetiapine XR 150 mg/day	Quetiapine XR 300 mg/day
Lumateperone 42 mg/day	—	88%	47%	87%	86%	64%	86%	95%	93%	42%	60%
Aripiprazole 2-20 mg/day	0.30 (0.05, 2.47)	—	3%	59%	48%	8%	56%	88%	76%	5%	12%
Brexipiprazole 1 mg/day	1.09 (0.14, 11.03)	3.63 (0.97, 12.58)	—	94%	100%	73%	93%	99%	98%	44%	66%
Brexipiprazole 2 mg/day	0.24 (0.02, 2.98)	0.82 (0.11, 3.61)	0.22 (0.03, 1.42)	—	40%	13%	48%	67%	64%	7%	15%
Brexipiprazole 3 mg/day	0.31 (0.04, 2.89)	1.03 (0.30, 3.13)	0.29 (0.13, 0.59)	1.27 (0.22, 10.31)	—	13%	56%	83%	75%	6%	15%
Cariprazine 1-2 mg/day	0.68 (0.09, 6.81)	2.27 (0.70, 6.86)	0.62 (0.14, 2.81)	2.80 (0.47, 23.05)	2.21 (0.54, 9.17)	—	84%	100%	94%	24%	45%
Cariprazine 1.5 mg/day	0.26 (0.02, 3.09)	0.87 (0.11, 4.11)	0.24 (0.02, 1.53)	1.06 (0.09, 11.64)	0.85 (0.09, 4.94)	0.38 (0.04, 2.26)	—	68%	90%	8%	17%
Cariprazine 2-4.5 mg/day	0.16 (0.02, 1.54)	0.55 (0.18, 1.50)	0.15 (0.04, 0.64)	0.67 (0.12, 5.45)	0.53 (0.14, 2.10)	0.24 (0.14, 0.42)	0.62 (0.11, 6.25)	—	49%	1%	4%
Cariprazine 3 mg/day	0.16 (0.01, 1.93)	0.55 (0.07, 2.48)	0.15 (0.01, 0.94)	0.66 (0.06, 7.17)	0.54 (0.05, 3.03)	0.24 (0.02, 1.36)	0.63 (0.30, 1.28)	1.02 (0.10, 5.44)	—	3%	8%
Quetiapine XR 150 mg/day	1.27 (0.13, 15.29)	4.23 (0.78, 20.23)	1.16 (0.18, 7.49)	5.32 (0.61, 54.46)	4.08 (0.64, 24.77)	1.86 (0.29, 11.12)	4.97 (0.54, 62.24)	7.71 (1.28, 44.97)	7.88 (0.89, 96.48)	—	82%
Quetiapine XR 300 mg/day	0.75 (0.08, 8.60)	2.50 (0.49, 10.36)	0.69 (0.11, 3.95)	3.11 (0.38, 28.90)	2.41 (0.42, 12.77)	1.10 (0.18, 5.70)	2.91 (0.34, 33.21)	4.57 (0.81, 22.84)	4.64 (0.56, 51.71)	0.60 (0.17, 1.84)	—

¹ Outcomes were reported at Week 6, unless otherwise specified.

² The upper triangle presents the pairwise probability that the treatment row is superior to treatment in column based on posterior distributions from the Bayesian NMA. Probabilities are expressed as percentages (0%–100%), with higher values indicating greater likelihood that the treatment row has a favorable outcome. Probabilities >99.5% are listed as 100% due to rounding.

³ The lower triangle presents the pairwise treatment comparisons, reported as the odds ratios (95% credible intervals) for the treatment in column versus the treatment in row. Values >1 indicate that the column treatment has a greater risk of akathisia while values <1 indicate that the row treatment has a greater risk of akathisia.

⁴ For cariprazine (NCT01469377; 1–2 mg/day and 2–4.5 mg/day) Week 8 data was used given Week 6 data were not available.

mg: milligram; NCT: national clinical trial; XR: extended release

Table S11. Pairwise probabilities of treatment superiority and treatment comparisons for somnolence¹⁻⁴

Pairwise probabilities Pairwise treatment	Lumateperone 42 mg/day	Aripiprazole 2-20 mg/day	Brexpiprazole 1 mg/day	Brexpiprazole 2 mg/day	Brexpiprazole 3 mg/day	Cariprazine 1-2 mg/day	Cariprazine 1.5 mg/day	Cariprazine 2-4.5 mg/day	Cariprazine 3 mg/day	Quetiapine XR 150 mg/day	Quetiapine XR 300 mg/day
Lumateperone 42 mg/day	—	4%	79%	73%	88%	2%	4%	3%	2%	79%	88%
Aripiprazole 2-20 mg/day	2.85 (0.86, 9.32)	—	96%	94%	99%	48%	49%	56%	39%	99%	100%
Brexpiprazole 1 mg/day	0.40 (0.02, 3.19)	0.14 (0.01, 1.27)	—	46%	81%	3%	4%	4%	3%	33%	39%
Brexpiprazole 2 mg/day	0.48 (0.01, 3.70)	0.17 (0.00, 1.52)	1.16 (0.03, 36.43)	—	63%	4%	6%	6%	4%	39%	45%
Brexpiprazole 3 mg/day	0.27 (0.01, 2.13)	0.09 (0.00, 0.82)	0.68 (0.27, 1.61)	0.57 (0.02, 23.13)	—	1%	1%	1%	1%	21%	27%
Cariprazine 1-2 mg/day	2.95 (1.09, 8.35)	1.04 (0.32, 3.55)	7.59 (0.89, 134.22)	6.20 (0.79, 223.86)	11.23 (1.37, 194.19)	—	52%	66%	40%	100%	100%
Cariprazine 1.5 mg/day	2.87 (0.88, 9.61)	1.01 (0.26, 3.87)	7.40 (0.81, 139.05)	6.01 (0.71, 212.21)	10.96 (1.23, 206.44)	0.98 (0.29, 3.19)	—	56%	33%	99%	100%
Cariprazine 2-4.5 mg/day	2.60 (0.98, 7.30)	0.91 (0.29, 3.10)	6.63 (0.80, 118.73)	5.49 (0.70, 199.57)	9.85 (1.22, 174.22)	0.88 (0.49, 1.57)	0.91 (0.28, 2.97)	—	32%	100%	100%
Cariprazine 3 mg/day	3.47 (1.03, 11.81)	1.22 (0.31, 4.76)	8.93 (0.97, 165.13)	7.21 (0.83, 255.53)	13.21 (1.47, 243.73)	1.17 (0.34, 3.88)	1.20 (0.52, 2.83)	1.33 (0.39, 4.42)	—	100%	100%
Quetiapine XR 150 mg/day	0.67 (0.25, 1.87)	0.24 (0.07, 0.76)	1.70 (0.20, 31.27)	1.39 (0.18, 46.84)	2.51 (0.31, 46.80)	0.23 (0.08, 0.59)	0.23 (0.07, 0.74)	0.26 (0.10, 0.67)	0.19 (0.06, 0.63)	—	84%
Quetiapine XR 300 mg/day	0.55 (0.21, 1.55)	0.20 (0.06, 0.63)	1.40 (0.17, 26.21)	1.16 (0.15, 38.82)	2.08 (0.26, 38.29)	0.19 (0.07, 0.49)	0.19 (0.06, 0.61)	0.21 (0.08, 0.55)	0.16 (0.05, 0.53)	0.83 (0.57, 1.21)	—

¹ Outcomes were reported at Week 6, unless otherwise specified.

² The upper triangle presents the pairwise probability that the treatment row is superior to treatment in column based on posterior distributions from the Bayesian NMA. Probabilities are expressed as percentages (0%–100%), with higher values indicating greater likelihood that the treatment row has a favorable outcome.

³ The lower triangle presents the pairwise treatment comparisons, reported as the odds ratios (95% credible intervals) for the treatment in column versus the treatment in row. Values >1 indicate that the column treatment has a greater risk of somnolence while values <1 indicate that the row treatment has a greater risk of somnolence.

⁴ For cariprazine (NCT01469377; 1–2 mg/day and 2–4.5 mg/day) Week 8 data was used given Week 6 data were not available.

mg: milligram; NCT: national clinical trial; XR: extended release

Table S12. Surface under the cumulative ranking curve (SUCRA) values for efficacy and safety outcomes in the first set of sensitivity analyses¹⁻²

	Lumateperone 42 mg/day	Brexpiprazole 2 mg/day	Aripiprazole 2-20 mg/day	Quetiapine XR 300 mg/day	Cariprazine 1-4.5 mg/day	Quetiapine XR 150 mg/day	Brexpiprazole 3 mg/day	Cariprazine 3 mg/day	Brexpiprazole 1 mg/day	Placebo + ADT
MADRS change from baseline	97.2%	69.8%	64.5%	62.8%	56.0%	53.4%	38.8%	29.9%	22.5%	1.1%
MADRS response	89.6%	54.6%	72.7%	55.1%	42.5%	31.1%	64.2%	20.3%	65.8%	2.9%
MADRS remission	86.7%	68.2%	75.2%	73.6%	27.9%	52.7%	45.0%	1.0%	50.2%	17.8%
CGI-S change from baseline	98.3%	63.3%	78.8%	NA	55.3%	NA	37.9%	36.8%	26.8%	2.0%
Weight change from baseline	96.2%	NA	3.9%	14.4%	56.0%	45.0%	NA	47.8%	NA	87.1%
≥7% weight increase from baseline	96.9%	57.3%	10.1%	32.8%	22.7%	60.2%	55.3%	63.2%	20.5%	81.6%
Akathisia	66.8%	25.3%	30.7%	59.1%	31.0%	76.3%	31.6%	13.1%	72.4%	93.9%
Somnolence	46.4%	26.5%	75.7%	22.8%	75.6%	34.2%	14.3%	81.9%	27.3%	96.3%

¹ In the first set of sensitivity analyses, the 8-week cariprazine trial (NCT01469377) was excluded and no imputation of SE was conducted.

² SUCRA values summarize each treatment-node's network-wide ranking for an outcome on a 0–100% scale. Values are derived by ranking all treatment-nodes at each Markov Chain Monte Carlo iteration and computing the area under the cumulative ranking curve of those ranks. Higher values indicate a better average rank.

ADT: antidepressant therapy; Clinical Global Impression Scale – Severity; MADRS: Montgomery-Åsberg Depression Rating Scale; mg: milligram, NCT: national clinical trial; SE: standard error; SUCRA: surface under the curve; XR: extended release

Table S13. Surface under the cumulative ranking curve (SUCRA) values for efficacy and safety outcomes in the second set of sensitivity analyses¹⁻²

	Lumateperone 42 mg/day	Aripiprazole 2-20 mg/day	Quetiapine XR 150-300 mg/day	Brexiprazole 1-3 mg/day	Cariprazine 1-4.5 mg/day	Placebo+ADT
MADRS change from baseline	99.6%	67.2%	59.3%	41.4%	31.4%	0.0%
MADRS response	94.0%	73.1%	39.1%	61.0%	33.8%	0.1%
MADRS remission	90.0%	73.9%	61.3%	52.5%	10.7%	10.5%
CGI-S change from baseline	98.7%	77.2%	59.8%	34.9%	29.6%	0.2%
Weight change from baseline	95.3%	8.1%	42.5%	14.1%	55.3%	84.7%
≥7% weight increase from baseline	98.0%	2.4%	32.2%	38.1%	49.8%	80.0%
Akathisia	65.7%	21.1%	63.8%	36.0%	18.0%	94.7%
Somnolence	34.7%	70.0%	15.9%	11.0%	70.1%	98.3%

¹ In the second sensitivity analysis, treatments were pooled across doses to evaluate the NMA at the comparator rather than the treatment-dose level resulting in a star-shaped five-node network (one node per treatment).

² SUCRA values summarize each treatment-node's network-wide ranking for an outcome on a 0–100% scale. Values are derived by ranking all treatment-nodes at each Markov Chain Monte Carlo iteration and computing the area under the cumulative ranking curve of those ranks. Higher values indicate a better average rank.

ADT: antidepressant therapy; Clinical Global Impression Scale – Severity; MADRS: Montgomery-Åsberg Depression Rating Scale; mg: milligram; NCT: national clinical trial; NMA: network meta-analysis; SE: standard error; SUCRA: surface under the curve; XR: extended release

Table S14. Pairwise treatment comparisons for lumateperone vs comparators across efficacy and safety outcomes in the second set of sensitivity analyses¹⁻⁷

Lumateperone 42 mg/day vs	Placebo+ADT	Aripiprazole 2-20 mg/day	Brexpiprazole 1-3 mg/day	Cariprazine 1-4.5 mg/day	Quetiapine XR 150-300 mg/day
MADRS change from baseline	-4.71 (-5.78, -3.65)	-1.77 (-3.20, -0.32)	-2.54 (-4.02, -1.04)	-2.87 (-4.44, -1.29)	-2.01 (-3.66, -0.36)
MADRS response	2.31 (1.77, 3.05)	1.20 (0.78, 1.87)	1.32 (0.84, 2.09)	1.60 (1.13, 2.29)	1.55 (1.05, 2.30)
MADRS remission	2.19 (1.57, 3.07)	1.15 (0.70, 1.90)	1.43 (0.83, 2.42)	2.20 (1.45, 3.31)	1.30 (0.84, 2.02)
CGI-S change from baseline	-0.60 (-0.74, -0.46)	-0.16 (-0.36, 0.05)	-0.37 (-0.55, -0.19)	-0.40 (-0.62, -0.18)	-0.25 (-0.45, -0.06)
Weight change from baseline	-0.08 (-0.30, 0.13)	-1.42 (-1.82, -1.03)	-1.34 (-1.70, -0.98)	-0.86 (-1.17, -0.54)	-1.01 (-1.40, -0.61)
≥7% weight increase from baseline	0.30 (0.04, 1.42)	0.03 (0.00, 0.21)	0.11 (0.01, 0.69)	0.15 (0.02, 0.91)	0.10 (0.01, 0.61)
Akathisia	2.19 (0.40, 17.17)	0.30 (0.05, 2.54)	0.40 (0.06, 3.52)	0.28 (0.04, 2.52)	0.91 (0.09, 10.07)
Somnolence	5.46 (2.86, 11.50)	2.78 (0.84, 9.22)	0.45 (0.05, 2.04)	2.83 (1.21, 6.87)	0.61 (0.23, 1.58)

¹ In the second sensitivity analysis, treatments were pooled across doses to evaluate the NMA at the comparator rather than the treatment-dose level resulting in a star-shaped five-node network (one node per treatment).

² Outcomes were reported at Week 6, unless otherwise specified.

³ The table presents the pairwise comparisons of lumateperone 42 mg/day versus the column comparators. Results are reported as median difference (95% CrI) for continuous outcomes (MADRS change from baseline, CGI-S change from baseline, and weight change from baseline), and as odds ratios (ORs; 95% CrI) for binary outcomes (MADRS response, MADRS remission, $\geq 7\%$ weight increase from baseline, akathisia, and somnolence). For MADRS and CGI-S change from baseline, a median difference < 0 indicates greater improvement with lumateperone versus the comparator. For MADRS response and remission, an OR > 1 indicates a higher probability of response or remission with lumateperone versus the comparator. For $\geq 7\%$ weight increase, akathisia, and somnolence, an OR < 1 indicates a lower probability of the event with lumateperone versus the comparator.

⁴ For cariprazine (NCT01469377; 1–2 mg/day and 2–4.5 mg/day) Week 8 data was used for MADRS remission, CGI-S change from baseline, and all safety outcomes given Week 6 data were not available.

⁵ For MADRS change from baseline, the missing SE values in cariprazine (NCT01469377; 1–2 mg/day and 2–4.5 mg/day) were imputed using the mean SE from other trials.

⁶ For CGI-S change from baseline, the missing SE values in the quetiapine XR trials (NCT00326105 and NCT00351910; 150 mg/day and 300 mg/day) were imputed using the mean SE from other trials.

⁷ For weight change from baseline, the missing SE values in the brexpiprazole trials (NCT01360645 and NCT01360632; 1 mg/day, 2 mg/day and 3 mg/day) were imputed using the mean SE from other trials.

CGI-S: Clinical Global Impressions–Severity; CrI: credible interval; MADRS: Montgomery–Åsberg Depression Rating Scale; mg: milligram; NCT: national clinical trial; NMA: network meta-analysis; OR: odds ratio; SE: standard error; XR: extended release

Table S15. Pairwise probabilities of treatment superiority for lumateperone vs comparators across efficacy and safety outcomes in the second set of sensitivity analyses¹⁻⁷

Lumateperone 42 mg/day vs	Placebo+ADT	Aripiprazole 2-20 mg/day	Brexipiprazole 1-3 mg/day	Cariprazine 1-4.5 mg/day	Quetiapine XR 150-300 mg/day
MADRS change from baseline	100%	99%	100%	100%	99%
MADRS response	100%	80%	89%	100%	99%
MADRS remission	100%	72%	91%	100%	88%
CGI-S change from baseline	100%	93%	100%	100%	99%
Weight change from baseline	77%	100%	100%	100%	100%
≥7% weight increase from baseline	94%	100%	99%	98%	99%
Akathisia	19%	88%	81%	88%	53%
Somnolence	0%	5%	83%	1%	85%

¹ In the second sensitivity analysis, treatments were pooled across doses to evaluate the NMA at the comparator rather than the treatment-dose level resulting in a star-shaped five-node network (one node per treatment).

² Outcomes were reported at Week 6, unless otherwise specified.

³ The table presents the pairwise probabilities of superiority of lumateperone 42 mg/day versus the column comparators based on posterior distributions from the Bayesian NMA. Probabilities are expressed as percentages (0%–100%), with higher values indicating greater likelihood that lumateperone has a favorable outcome. Probabilities >99.5% are listed as 100% due to rounding.

⁴ For cariprazine (NCT01469377; 1–2 mg/day and 2–4.5 mg/day) Week 8 data was used for MADRS remission, CGI-S change from baseline, and all safety outcomes given Week 6 data were not available.

⁵ For MADRS change from baseline, the missing SE values in cariprazine (NCT01469377; 1–2 mg/day and 2–4.5 mg/day) were imputed using the mean SE from other trials.

⁶ For CGI-S change from baseline, the missing SE values in the quetiapine XR trials (NCT00326105 and NCT00351910; 150 mg/day and 300 mg/day) were imputed using the mean SE from other trials.

⁷ For weight change from baseline, the missing SE values in the brexpiprazole trials (NCT01360645 and NCT01360632; 1 mg/day, 2 mg/day and 3 mg/day) were imputed using the mean SE from other trials.

CGI-S: Clinical Global Impressions–Severity; CrI: credible interval; MADRS: Montgomery–Åsberg Depression Rating Scale; mg: milligram; NCT: national clinical trial; NMA: network meta-analysis; SE: standard error; XR: extended release