Supplemental Table 1.

Key Inclusion criteria
• Male or female outpatients 18 to 65 years of age, inclusive, at time of consent
• Met DSM-IV-TR criteria for a principal diagnosis of bipolar I or II disorder (without psychotic features)
• A current major depressive episode ≥4 weeks and not exceeding 12 months
• Fewer than 8 episodes of a mood disturbance (depression, mania, hypomania, or mixed state) in the previous 12 months
• Verified lifetime history of at least one bipolar manic or mixed episode (bipolar I disorder patients) or hypomanic or mixed episode (bipolar II disorder patients)
• Scores ≥20 on the $HAMD_{17}$ and ≥2 on Item 1 of the $HAMD_{24}$
• Women of childbearing potential with a negative serum β-human chorionic gonadotropin pregnancy test
• Normal physical examination findings, clinical laboratory test results, and ECG results or abnormal results that were judged not clinically significant by the investigator
• Body mass index between 18 and 40, inclusive
Key Exclusion criteria
• YMRS score >12
• Principal DSM-IV-TR-based diagnosis of an axis I disorder other than bipolar disorder or any axis I disorder other than bipolar disorder that was the primary focus of treatment within 6 months
• History of meeting DSM-IV-TR criteria for cognitive disorder (eg, delirium, dementia, amnesia), psychotic disorder (eg, schizophrenia, schizoaffective disorder) or mental retardation
• DSM-IV-TR–based diagnosis of borderline or antisocial personality disorder or other axis II disorder of sufficient severity to interfere with study participation
• History of meeting DSM-IV-TR criteria for alcohol or substance abuse or dependence within the 6 months of the study
• Positive drug screen for any prohibited medication
• Patients at imminent risk of injuring self or others or causing significant damage to property (investigator judged)
• Suicide risk (any of the following criteria: suicide attempt within the past year, significant risk based on the psychiatric interview and/or information collected in the Columbia–Suicide Severity Rating Scale [investigator judged]; score ≥5 on item 10 of the MADRS)
• Pregnant, breastfeeding, plan to become pregnant/breastfeed during the study, not at least 2 years postmenopausal, surgically sterile, abstinent, or practicing a reliable method of contraception
• A concurrent medical condition that may have interfered with the conduct of the study, confounded the interpretation of the study results, or endangered the patient's well-being
• Patients requiring concomitant treatment with any prohibited medication; psychotropic drugs were prohibited except for eszopiclone, zolpidem, zolpidem extended-release, or zaleplon for sleep;

lorazepam for severe anxiety; or diphenhydramine, benztropine, or propranolol for EPS
• History of nonresponse to two or more adequate treatment trials (≥4 weeks at an adequate dose based on Package Insert recommendations) with fluoxetine + olanzapine combination, quetiapine, or a mood stabilizer (lithium, valproate, lamotrigine, carbamazepine, or oxycarbamazepine) in combination with an antidepressant used to treat the current depressive episode
• Use of any antipsychotic, antidepressant, anticonvulsant/mood stabilizer, anxiolytic, sedative/hypnotic medication, or investigational drug within 1 week or 5 half-lives; history of being treated with clozapine (within 5 years)

HAMD=Hamilton Depression Rating Scale (17- or 24-item version); MADRS=Montgomery-Åsberg Depression Rating Scale; YMRS=Young Mania Rating Scale.

Supplemental Table 2. Change from baseline to the end of the study in clinical laboratory and vital sign parameters in the safety population

			Cariprazine			
Serum chemistry	**Number assessed**	**Placebo mean (SD) n=77**	**Number assessed**	**0.25-0.75 mg/d mean (SD) n=75**	**Number assessed**	**1.5-3.0 mg/d mean (SD) n=75**
Total cholesterol, mmol/L	70	-0.107 (0.69)	64	-0.042 (0.72)	65	-0.124 (0.78)
HDL cholesterol, mmol/L	70	-0.038 (0.21)	64	-0.014 (0.19)	65	-0.020 (0.22)
LDL cholesterol, mmol/L	70	-0.085 (0.53)	64	-0.061 (0.65)	65	-0.226 (0.59)
Triglycerides, mmol/L	70	-0.114 (0.85)	64	-0.022 (0.68)	65	0.200 (0.99)
Fasting glucose, mmol/L	59	0.028 (0.64)	58	-0.136 (0.74)	56	0.022 (0.71)
ALT, U/L	70	0.2 (8.9)	64	1.4 (11.2)	65	2.8 (10.9)
AST, U/L	70	0.3 (5.9)	64	-0.1 (7.9)	65	1.0 (7.8)
Alkaline phosphatase, U/L	70	-2.5 (9.3)	64	0.2 (10.9)	65	0.1 (9.8)
Creatine phosphokinase, U/L	70	27.40 (126.15)	64	-1.20 (279.61)	65	75.72 (422.58)
Prolactin, ng/mL	70	0.39 (4.25)	64	2.36 (3.49)	65	3.16 (4.95)
Total bilirubin, mmol/L	70	-0.538 (4.69)	64	-0.748 (4.29)	65	-0.816 (2.79)
Vital signs						
Supine systolic blood pressure, mm Hg	76	0.8 (12.3)	75	-1.3 (10.8)	74	0.5 (10.2)
Supine diastolic blood pressure, mm Hg	76	0.9 (8.9)	75	-0.1 (8.7)	74	0.1 (6.4)
Supine pulse, bpm	76	0.4 (10.7)	75	3.6 (11.3)	74	1.4 (11.6)

Body weight change, kg	76	0.30 (2.16)	75	0.62 (2.76)	74	1.42 (2.93)
Weight gain ≥7%	0/76	0.0%	4/75	5.3%	5/74	6.8%
Body mass index, kg/m^2	76	0.11 (0.74)	75	0.21 (0.94)	74	0.50 (1.05)
Orthostatic hypotension	16/76	21.1%	17/72	23.6%	7/73	9.6%
Electrocardiogram parameters						
Ventricular heart rate, bpm	76	3.2 (11.5)	75	3.7 (11.2)	74	5.4 (12.2)
QRS interval, msec	76	0.1 (6.2)	75	-0.8 (6.7)	74	0.6 (7.0)
PR interval, msec	76	-1.0 (10.8)	75	1.6 (11.6)	74	0.9 (12.7)
QT interval, msec	76	-5.8 (22.7)	75	-6.4 (25.7)	74	-12.2 (27.6)
QTcB interval, msec	76	3.1 (21.9)	75	3.9 (19.7	74	3.4 (19.4)
QTcF interval, msec	76	-0.1 (15.8)	75	0.4 (16.2)	74	-2.1 (15.9)

Data are mean (SD) except for body weight increase ≥7% and orthostatic hypotension (≥20 mm Hg reduction in systolic blood pressure or ≥10 mm Hg reduction in diastolic blood pressure while changing from a supine to standing position), which are reported as percentages. Baseline is defined as the last assessment before the start of the double-blind treatment phase. ALT=alanine aminotransferase; AST=aspartate aminotransferase, QTcB= QT interval corrected for heart rate using the Bazett formula; QTcF= QT interval corrected for heart rate using the Fridericia formula.