An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar I Depression

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Objective: The authors evaluated the efficacy, safety, and tolerability of cariprazine, an atypical antipsychotic candidate, in adult patients with acute bipolar I depression.

Method: This was an 8-week multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in adult patients with bipolar I disorder experiencing a current major depressive episode. Patients were randomly assigned (1:1:1:1) to receive placebo or cariprazine at 0.75, 1.5, or 3.0 mg/day. The primary and secondary efficacy parameters were change from baseline to week 6 on the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impressions severity subscale (CGI-S), respectively, analyzed using a mixed-effects model for repeated measures on the modified intent-to-treat population.

Results: The intent-to-treat population comprised 571 patients (141 in the placebo group and 140, 145, and 145 in the cariprazine 0.75-, 1.5-, and 3.0-mg/day groups). Cariprazine at 1.5 mg/day showed significantly greater improvement on MADRS total score change from baseline to week 6 compared with placebo; the least squares mean difference was −4.0 (95% CI=−6.3, −1.6; significant after adjustment for multiple comparisons). Cariprazine at 3.0 mg/day showed greater MADRS score reduction than placebo (−2.5, 95% CI=−4.9, −0.1; not significant when adjusted for multiple comparisons). The 0.75 mg/day dosage was similar to placebo. A similar pattern for significance was observed on the CGI-S (1.5 mg/day: least squares mean difference=−0.4, 95% CI=−0.6, −0.1; 3.0 mg/day: −0.3, 95% CI=−0.5, −0.0). The most common adverse events (≥10%) in cariprazine-treated patients were akathisia and insomnia; weight gain was slightly higher with cariprazine than with placebo.

Conclusions: Cariprazine at 1.5 mg/day demonstrated consistent efficacy compared with placebo across outcomes and was generally well tolerated, suggesting efficacy for the treatment of bipolar I depression.

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Although manic or hypomanic episodes are distinguishing diagnostic characteristics of bipolar disorder, depressive episodes and symptoms are the most enduring and disabling features of the disorder (1). The majority of time spent unwell for a patient with bipolar disorder is accounted for by syndromal or subsyndromal depressive symptoms (2), partly because there are few proven and approved treatments available for managing depressive symptoms in bipolar disorder. Although most atypical antipsychotics are approved by the U.S. Food and Drug Administration (FDA) for acute manic/mixed episodes in bipolar disorder, quetiapine and lurasidone are the only FDA-approved antipsychotics for bipolar depression (3, 4); lurasidone has not been assessed in bipolar mania and is not indicated for its treatment. Despite the substantial burden of illness, bipolar depression has not been as widely studied as mania, and treatment options remain limited.

Cariprazine is a potent dopamine D_3 and D_2 receptor partial-agonist atypical antipsychotic with preferential binding to D_3 receptors (5). At antipsychotic-like effective dosages, cariprazine shows high and balanced occupancy of D_3 and D_2 receptors (5, 6); other atypical antipsychotics display high occupancy at D_2 receptors, but low or negligible occupancy at D_3 receptors (6–8). In a positron emission tomography study in schizophrenia patients, 4- to 5-day dosing with cariprazine at 1 mg/day resulted in occupancies of 70% for D_2 receptors and 86% for D_3 receptors (9).

Several lines of evidence, including reduced CSF levels of homovanillic acid in depressed patients, depressogenic

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effects of alpha-methyl-paratyrosine, and antidepressant efficacy of dopaminergic agonists (e.g., bupropion and pramipexole), implicate a role for the dopaminergic system in depression (10). Dopamine D_3 receptors, expressed in brain regions that regulate motivation and reward-related behavior, may present a new pharmacological target for treating depression (11), as D_3 knockout mice display depressive symptoms (12). In rodents, cariprazine has shown antidepressant-like activity in anhedonia models (13, 14); these effects were absent in D_3-receptor knockout mice, suggesting that the effects were mediated by the D_3 receptor (13). Additionally, cariprazine has high affinity for serotonin 5-HT_{1A} receptors, which may contribute to antidepressant efficacy (15). Collectively, the pharmacological profile of cariprazine suggests potential utility in treating bipolar I depression.

The efficacy of cariprazine in manic or mixed/manic states of bipolar I disorder has been demonstrated in phase II and III clinical trials (16–18). In a previous phase II study of cariprazine in bipolar I depression, improvement compared with placebo did not reach significance on the primary assessment (19); high placebo response may have contributed to the outcome. The present study further evaluated the efficacy, safety, and tolerability of cariprazine in bipolar I depression; cariprazine dosages were selected based on results from the phase II trial.

METHOD

This phase II study was conducted from July 2011 to March 2014 at 88 locations in the United States, Canada, Colombia, the Russian Federation, and Ukraine in compliance with the International Conference on Harmonisation Guidances on General Considerations for Clinical Trials and Good Clinical Practice and the Declaration of Helsinki. The study was approved by institutional review boards (U.S. sites) or ethics committees and government agencies (non-U.S. sites). Participants provided written informed consent after receiving a complete description of the study. Randomization to treatment groups was done by computer-generated numbers. Medications and placebo were delivered in identically appearing capsules.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in adult patients with bipolar I depression. The study comprised a screening period (up to 14 days, including a no-drug 1-week washout), 8-week double-blind treatment, and 1-week safety follow-up. The primary analysis endpoint was week 6; patients continued double-blind treatment through week 8 to assess the persistence of efficacy. Patients were randomly assigned (1:1:1:1) to receive placebo or cariprazine at 0.75, 1.5, or 3.0 mg/day. All cariprazine patients initiated treatment at 0.5 mg/day, and the dosage was increased to 0.75 mg/day on day 3. In the 1.5- and 3.0-mg/day groups, the dosage was increased to 1 and 1.5 mg/day on days 5 and 8, respectively; in the 3.0-mg/day group, the dosage was increased to 3.0 mg/day on day 15. Patients unable to tolerate the fixed dose were discontinued. Patients could be hospitalized during screening and for up to 2 weeks of double-blind treatment.

Patients

Patients were 18–65 years of age and currently met DSM-IV-TR criteria for bipolar I disorder (confirmed by the Structured Clinical Interview for DSM-IV-TR), with a current major depressive episode without psychotic features that had lasted at least 4 weeks and no more than 12 months; a previous manic or mixed episode was verified. Patients had a total score ≥20 on the 17-item Hamilton Depression Rating Scale (HAM-D) (20), a score ≥2 on item 1 of the HAM-D, and a score ≥4 on the Clinical Global Impressions severity subscale (CGI-S) (21). Physical examination, clinical laboratory, and ECG findings were either normal or included abnormal results that were not considered clinically significant; women of childbearing potential had negative serum β-human chorionic gonadotropin pregnancy testing.

Typical exclusion criteria were applied, including history or current diagnoses of various axis I disorders other than bipolar I disorder, suicide risk, or risk of injury to self or others (see Table S1 in the data supplement that accompanies the online edition of this article). Concurrent medical conditions that may interfere with study participation, confound interpretation of results, or endanger the patient's well-being were exclusionary. Psychotropic drug use was prohibited except for eszopiclone, zolpidem, zopiclone, chloral hydrate, or zaleplon (for insomnia), lorazepam (for agitation), or diphenhydramine, benztropine, or propranolol (for extrapyramidal symptoms).

Efficacy Evaluations

Efficacy was assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) (22), the CGI-S, and the HAM-D, all of which were administered at screening, at baseline, and at weeks 1, 2, 4, 6, and 8.

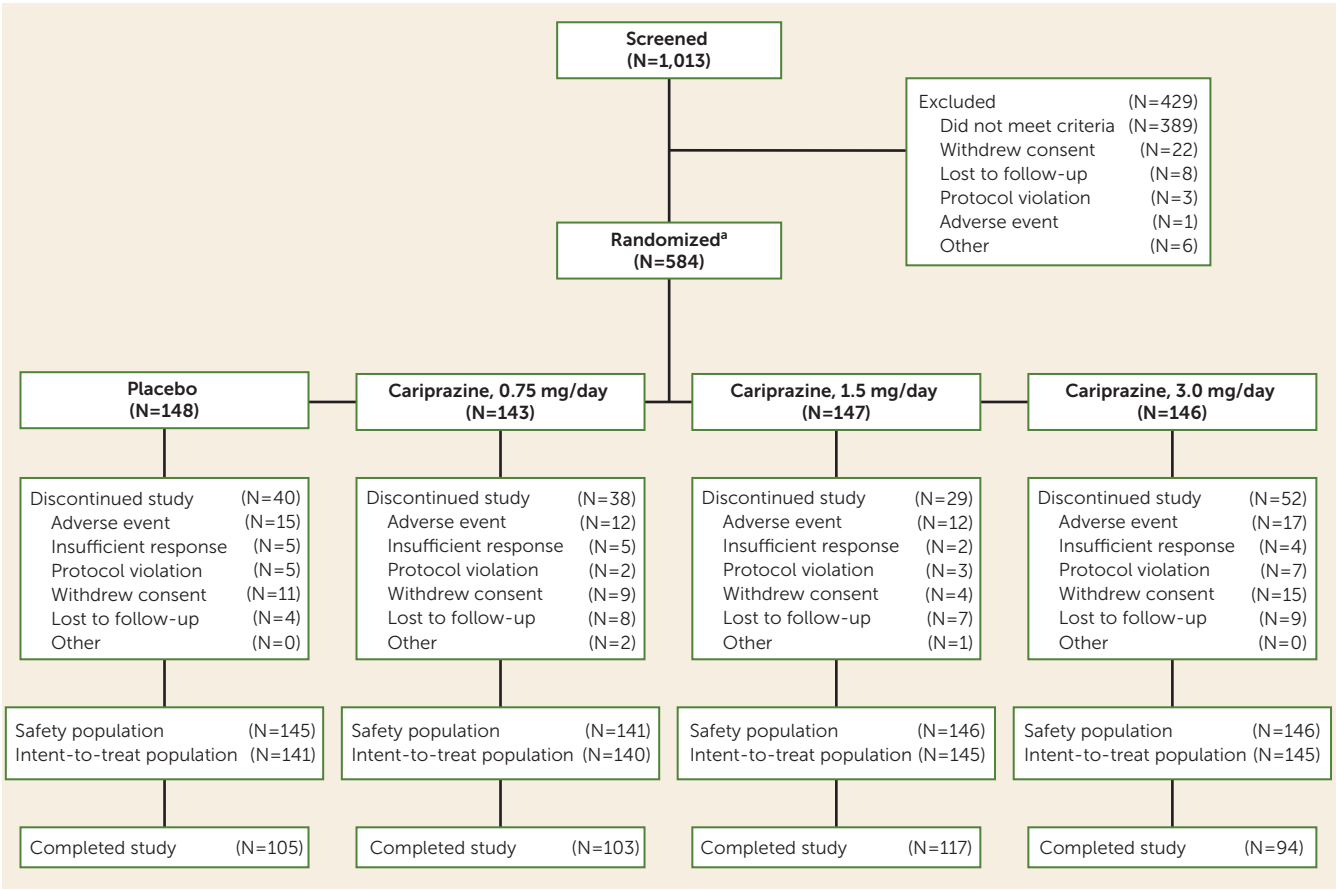
Safety Evaluations

Physical examination and clinical laboratory monitoring were conducted at screening and at week 8. Adverse events and vital sign parameters were recorded at each study visit; ECG was performed at screening and at weeks 1, 4, and 8. The Young Mania Rating Scale (YMRS) (23) was administered at screening and at all study visits. The Columbia–Suicide Severity Rating Scale (24) and extrapyramidal symptom scales (the Barnes Akathisia Rating Scale [25], the Abnormal Involuntary Movement Scale [AIMS] [26], and the Simpson-Angus Scale [27]) were administered at all study visits. The Columbia–Suicide Severity Rating Scale was also administered at follow-up.

Statistical Analysis

Safety and efficacy analyses were based on the safety population (randomized patients who took at least one dose of double-blind medication) and the modified intent-to-treat population (patients in the safety population with a baseline and at least one postbaseline MADRS assessment),

FIGURE 1. CONSORT Flow Diagram for a Study of Cariprazine in Patients With Bipolar I Depression[a]



[a] Six patients who were randomized were not included in the safety population: three patients were lost to follow-up (two in the placebo group, one in the cariprazine 0.75 mg/day group); two withdrew consent (one in the placebo group and one in the cariprazine 0.75 mg/day group); and one (in the cariprazine 1.5 mg/day group) was withdrawn from the study because of a protocol violation.

respectively. The primary efficacy parameter, MADRS total score change from baseline to week 6, was analyzed using a mixed-effects model for repeated measures with treatment group, study center, visit, and treatment group-by-visit interaction as fixed effects and baseline value and baseline-by-visit interaction as covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores; the Kenward-Roger approximation was used to estimate denominator degrees of freedom. Sensitivity analysis using a pattern-mixture model based on non-future dependent missing value restrictions (28) was performed. The secondary efficacy parameter, CGI-S score change from baseline to week 6, was analyzed using a mixed-effects model for repeated measures similar to that of the primary analysis.

MADRS, CGI-S, and HAM-D score changes by week were evaluated using a mixed-effects model for repeated measures and an analysis of covariance (ANCOVA) approach with treatment group and study center as factors and the baseline value as the covariate with last-observation-carried-forward imputation for missing values. Response (≥50% MADRS total score reduction) and remission (MADRS total score ≤10; HAM-D total score ≤7) were determined by logistic regression with last observation carried forward. Post hoc analyses were conducted to estimate MADRS effect size (Cohen's d), numbers needed to treat, and change from baseline on MADRS single items and the MADRS-6 subscale (29), which measures the core symptoms of depression (using six items: apparent sadness, reported sadness, inner tension, lassitude, inability to feel, and pessimistic thoughts) (mixed-effects model for repeated measures; ANCOVA with last observation carried forward). Post hoc analyses evaluated efficacy in patients who continued treatment for the full 8 weeks (MADRS total score change for patients with assessments at baseline and week 8 [completer population]).

All statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, N.C.). Assuming effect sizes of at least 0.30, 0.36, and 0.40 for cariprazine at 0.75, 1.5, and 3.0 mg/day, respectively, it was determined that 150 patients per group would provide 90% power to detect at least one of the effect sizes with multiplicity adjustment. All statistical hypothesis tests were performed at a significance threshold of 5% (two-sided); all confidence intervals (CIs) were two-sided 95% CIs. For primary and secondary efficacy analyses, a matched parallel gatekeeping procedure (30) was used to control the overall type I error rate (alpha=0.05) for multiple comparisons; significance of the secondary endpoint was not claimed

TABLE 1. Patient Characteristics in a Study of Cariprazine in Patients With Bipolar I Depression (Safety Population)

Characteristic	Placebo		Cariprazine 0.75 mg/day		Cariprazine 1.5 mg/day		Cariprazine 3.0 mg/day	
	N	%	N	%	N	%	N	%
Female	89	61.4	91	64.5	92	63.0	88	60.3
Race								
White	110	75.9	111	78.7	109	74.7	113	77.4
Black or African American	30	20.7	26	18.4	30	20.5	26	17.8
Other	5	3.5	4	2.8	7	4.8	7	4.8
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)[a]	43.6	12.0	40.1	11.2	40.9	11.4	42.8	10.8
Weight (kg)	80.0	17.1	80.8	18.4	81.4	16.8	81.5	17.9
BMI	27.8	5.3	28.4	5.7	28.4	5.4	28.3	5.6
Age at onset of original episode (years)	28.4	11.4	26.0	10.2	25.4	10.2	28.1	11.0
Duration of bipolar disorder (years)	15.3	10.2	14.1	9.7	15.5	10.3	14.6	9.5
Duration of current depressive episode (months)	3.3	2.3	3.8	2.6	3.7	2.7	3.5	2.4
Number of lifetime depressive episodes	6.2	5.8	5.7	5.2	7.2	8.0	6.8	7.0

[a] Significant difference between groups (p=0.016) based on an analysis-of-variance model.

unless the corresponding primary outcome was significant. A kappa analysis showed high interrater reliability (kappa values >0.90). Additional, post hoc, and by-week efficacy analyses were not controlled for multiplicity; statistical significance was defined as a p value <0.05.

Safety analyses included the incidence of treatment-emergent adverse events, mania (a postbaseline YMRS total score ≥16), or extrapyramidal symptoms during double-blind treatment. Treatment-emergent parkinsonism was defined as a score ≤3 on the Simpson-Angus Scale at baseline and a score >3 after baseline; akathisia was defined as a score ≤2 on the Barnes Akathisia Rating Scale at baseline and a score >2 after baseline. Descriptive statistics were computed for laboratory values and vital signs.

RESULTS

Patient Disposition and Demographic Characteristics

A total of 584 patients were randomly assigned to double-blind treatment (Figure 1). Approximately 73% of patients completed the study; the most frequent reason for discontinuation was adverse events. Baseline demographic and clinical characteristics were generally well matched across treatment groups (Table 1). Baseline MADRS and HAM-D total scores were similar across groups (Table 2) and indicated symptomatic depression (31).

Efficacy Outcomes

Primary, secondary, and additional efficacy outcomes. The primary analysis point was week 6 of double-blind treatment; double-blind treatment was continued through week 8 to assess efficacy persistence. The least squares mean difference in MADRS score change from baseline to week 6 was statistically significant in favor of cariprazine at 1.5 mg/day compared with placebo (adjusted p=0.003) (Table 2). Cariprazine at 3.0 mg/day demonstrated greater MADRS score reduction than placebo (p=0.037), but the difference was not significant when adjusted for multiplicity; cariprazine at 0.75 mg/day was not significantly different from placebo. Improvement in MADRS score was significantly greater in all cariprazine groups compared with the placebo group using ANCOVA with last observation carried forward. Pattern-mixture model analysis confirmed the robustness of the mixed-effects model for repeated-measures results. MADRS effect sizes were 0.20, 0.42, and 0.26 for the 0.75-, 1.5-, and 3.0-mg/day groups, respectively.

There was significant improvement in CGI-S score from baseline to week 6 with cariprazine at 1.5 mg/day compared with placebo (adjusted p=0.013) (Table 2); a greater score reduction was observed for cariprazine at 3.0 mg/day compared with placebo (p=0.049), but the difference was not significant when adjusted for multiplicity. Statistically significant improvements were observed for cariprazine 1.5 and 3.0 mg/day compared with placebo using ANCOVA with last observation carried forward.

Statistically significant improvement occurred in all cariprazine groups compared with placebo (without multiplicity adjustment) as early as week 1 on the MADRS (Figure 2A) and week 2 on the CGI-S (Figure 2B). In the 1.5- and 3.0-mg/day groups, a significant difference compared with placebo persisted through week 8 on the MADRS; on the CGI-S, a significant difference persisted through week 8 in the 1.5-mg/day group and through week 6 in the 3.0-mg/day group.

Additional efficacy parameters are presented in Table 2. At week 6, cariprazine at 1.5 mg/day compared with placebo had significantly greater rates of MADRS response (p<0.05; number needed to treat, 6 [95% CI=4, 16]), and MADRS and HAM-D remission (p<0.01 for both; number needed to treat, 6 [95% CI=4, 16] for MADRS remission and 7 [95% CI=5, 20] for HAM-D remission). Cariprazine at 3.0 mg/day was significantly superior to placebo only on MADRS response (p<0.05; number needed to treat, 8 [95% CI=5, 58]).

Post hoc efficacy analyses. Analysis of MADRS single-item change from baseline to week 6 showed significant improvement with cariprazine at 1.5 mg/day compared with placebo on six of 10 items using mixed-effects model for repeated-measures analysis (Figure 2C) and on nine of 10 items using ANCOVA with last observation carried forward (data not shown). A significant improvement with cariprazine at 1.5 mg/day was also seen on the MADRS-6 (mixed-effects model

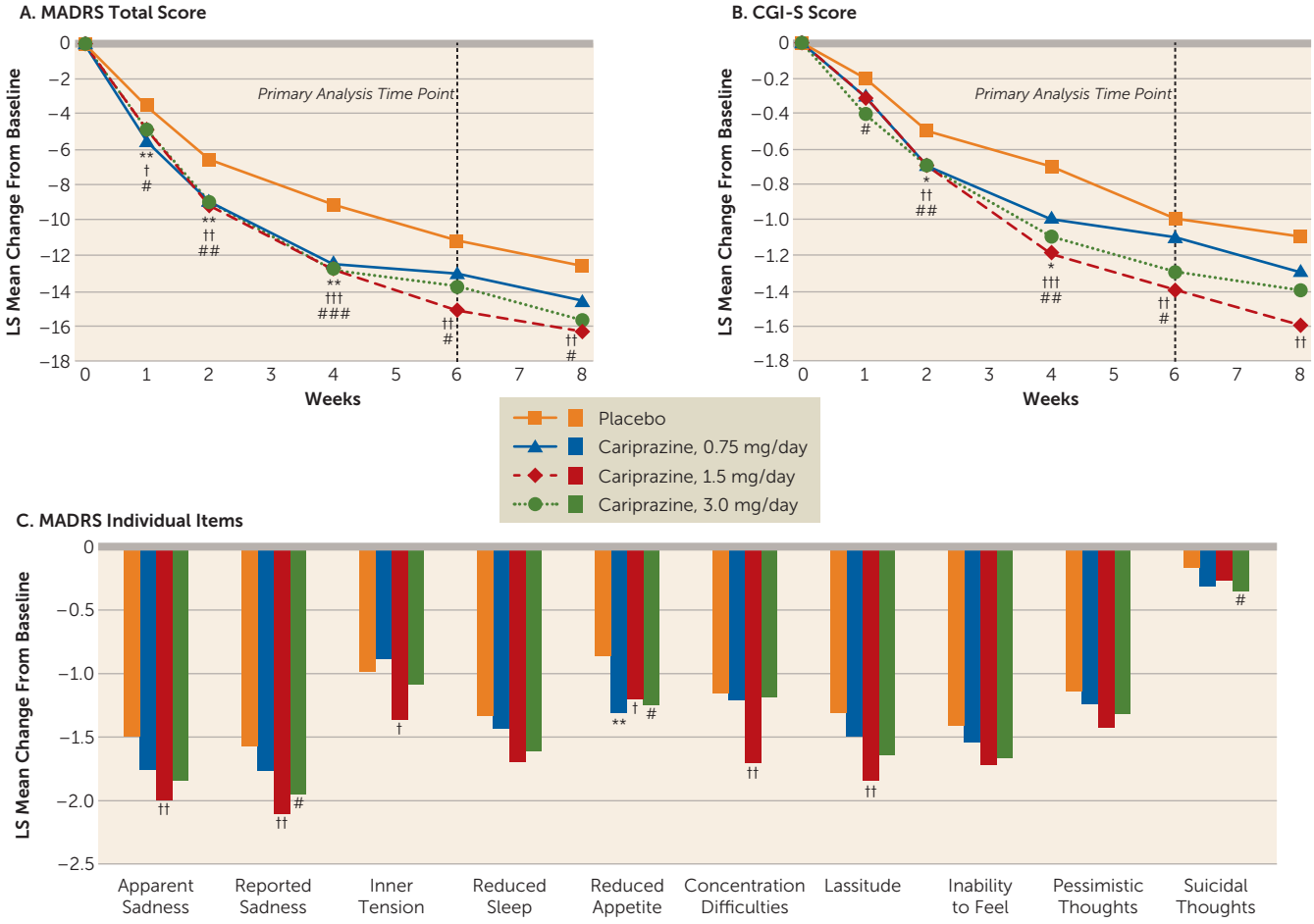
TABLE 2. Efficacy Parameters, Response, and Remission in a Study of Cariprazine in Patients With Bipolar I Depression (Intent-to-Treat Population)[a]

Measure, Model, and Group	Analyses								
		Baseline score		Change		Difference versus placebo			
	N	Mean	SD	LS mean	SE	LSMD	95% CI	p	Adjusted p
Primary Efficacy Parameter: MADRS									
Mixed-effects model for repeated measures									
Placebo	141	30.4	4.6	−11.1	0.9				
Cariprazine 0.75 mg/day	140	31.1	4.7	−13.0	0.9	−1.9	−4.3, 0.5	0.129	0.129
Cariprazine 1.5 mg/day	145	30.3	4.4	−15.1	0.8	−4.0	−6.3, −1.6	0.001	0.003
Cariprazine 3.0 mg/day	145	30.6	4.7	−13.7	0.9	−2.5	−4.9, −0.1	0.037	0.112
ANCOVA with last observation carried forward									
Placebo	141	30.4	4.6	−10.1	0.8				
Cariprazine 0.75 mg/day	140	31.1	4.7	−12.4	0.8	−2.3	−4.6, −0.1	0.041	
Cariprazine 1.5 mg/day	145	30.3	4.4	−14.2	0.8	−4.1	−6.3, −1.9	<0.001	
Cariprazine 3.0 mg/day	145	30.6	4.7	−12.8	0.8	−2.7	−4.9, −0.5	0.017	
Secondary Efficacy Parameter: CGI-S									
Mixed-effects model for repeated measures									
Placebo	141	4.4	0.5	−1.0	0.1				
Cariprazine 0.75 mg/day	140	4.4	0.5	−1.1	0.1	−0.1	−0.4, 0.1	0.303	0.303
Cariprazine 1.5 mg/day	145	4.4	0.5	−1.4	0.1	−0.4	−0.6, −0.1	0.004	0.013
Cariprazine 3.0 mg/day	145	4.4	0.5	−1.3	0.1	−0.3	−0.5, −0.0	0.049	0.112
ANCOVA with last observation carried forward									
Placebo	141	4.4	0.5	−0.9	0.1				
Cariprazine 0.75 mg/day	140	4.4	0.5	−1.0	0.1	−0.2	−0.4, 0.1	0.198	
Cariprazine 1.5 mg/day	145	4.4	0.5	−1.3	0.1	−0.4	−0.6, −0.2	0.001	
Cariprazine 3.0 mg/day	145	4.4	0.5	−1.2	0.1	−0.3	−0.5, −0.0	0.024	
Additional Efficacy Parameters									
HAM-D									
Mixed-effects model for repeated measures									
Placebo	141	24.1	2.8	−9.1	0.6				
Cariprazine 0.75 mg/day	140	24.6	3.4	−10.3	0.6	−1.1	−2.9, 0.6	0.199	
Cariprazine 1.5 mg/day	145	23.9	3.2	−11.8	0.6	−2.7	−4.4, −1.0	0.002	
Cariprazine 3.0 mg/day	145	24.0	3.1	−11.3	0.6	−2.2	−3.9, −0.5	0.013	
ANCOVA with last observation carried forward									
Placebo	141	24.1	2.8	−8.4	0.6				
Cariprazine 0.75 mg/day	140	24.6	3.4	−9.7	0.6	−1.4	−3.1, 0.3	0.098	
Cariprazine 1.5 mg/day	145	23.9	3.2	−11.2	0.6	−2.9	−4.5, −1.2	0.001	
Cariprazine 3.0 mg/day	145	24.0	3.1	−10.6	0.6	−2.2	−3.9, −0.6	0.007	

			Odds Ratio Versus Placebo		
	n	%	Odds Ratio	95% CI	p
Response at week 6 (≥50% score reduction on MADRS)[b]					
Placebo	45	31.9			
Cariprazine 0.75 mg/day	54	38.6	1.35	0.83, 2.22	0.227
Cariprazine 1.5 mg/day	72	49.7	2.10	1.30, 3.41	0.002
Cariprazine 3.0 mg/day	65	44.8	1.74	1.07, 2. 82	0.024
Remission at week 6 (score ≤10 on MADRS)[b]					
Placebo	28	19.9			
Cariprazine 0.75 mg/day	33	23.6	1.32	0.74, 2.36	0.340
Cariprazine 1.5 mg/day	53	36.6	2.38	1.38, 4.09	0.002
Cariprazine 3.0 mg/day	40	27.6	1.59	0.91, 2.78	0.105
HAM-D remitters (score ≤7)[b]					
Placebo	22	15.6			
Cariprazine 0.75 mg/day	28	20.0	1.44	0.77, 2.67	0.254
Cariprazine 1.5 mg/day	44	30.3	2.34	1.31, 4.18	0.004
Cariprazine 3.0 mg/day	31	21.4	1.46	0.80, 2.69	0.219

[a] ANCOVA=analysis of covariance; CGI-S=Clinical Global Impressions severity scale; HAM-D=17-item Hamilton Depression Rating Scale; LSMD=least squares mean difference; MADRS=Montgomery-Åsberg Depression Rating Scale.
[b] Analyses based on logistic regression model with last observation carried forward.

FIGURE 2. Mean Change From Baseline in Efficacy Parameters in a Study of Cariprazine in Patients With Bipolar I Depression[a]



[a] Mixed-effects model for repeated measures, intent-to-treat population; p values were not adjusted for multiple comparisons. Cariprazine 0.75 mg/day compared with placebo: *p<0.05; **p<0.01; ***p<0.001. Cariprazine 1.5 mg/day compared with placebo: †p<0.05; ††p<0.01; †††p<0.001. Cariprazine 3.0 mg/day compared with placebo: #p<0.05; ##p<0.01; ###p<0.001.

for repeated measures: p=0.003; ANCOVA with last observation carried forward: p=0.022).

Analyses of patients who completed the full 8-week treatment (the completer population) demonstrated significant reductions from baseline in MADRS score (least squares mean difference compared with placebo) for the cariprazine 1.5- and 3.0-mg/day groups at week 6 (1.5 mg/day: −3.0 [95% CI=−5.4, −0.6], p=0.013; 3.0 mg/day: −2.8 [95% CI=−5.3, −0.3], p=0.028) and at week 8 (1.5 mg/day: −3.0 [95% CI=−5.5, −0.5], p=0.021; 3.0 mg/day: −3.2 [95% CI=−5.8, −0.5], p=0.019) (see Figure S1 in the online data supplement).

Safety Outcomes

Extent of exposure. Mean treatment duration for the placebo and cariprazine 0.75-, 1.5-, and 3.0-mg/day groups was 46.2 (SD=18.2), 48.0 (SD=15.2), 49.3 (SD=14.7), and 46.0 (SD=16.5) days, respectively; length of exposure was 18.3, 18.5, 19.7, and 18.4 patient-years, respectively.

Adverse events. A summary of adverse events is presented in Table 3. The incidence of adverse events leading to discontinuation was similar across groups; the only adverse events that led to discontinuation in ≥2% of patients were akathisia (3%), agitation (2%), and anxiety (2%) in the cariprazine 3.0-mg/day group and depression (2%) in the placebo and cariprazine 0.75- and 1.5-mg/day groups. Most cases of akathisia (94%) were considered by the investigator to be mild or moderate in intensity and did not result in study discontinuation. Excluding akathisia and restlessness, the incidence of treatment-emergent extrapyramidal symptom-related adverse events was generally low (placebo group: N=2 [1%]; cariprazine 0.75 mg/day group: N=2 [1%]; 1.5 mg/day group: N=4 [3%]; 3.0 mg/day group: N=7 [5%]).

Serious adverse events were reported in 10 patients (placebo group: N=5 [hemiparesis, depression, mania, suicidal ideation, and chronic obstructive pulmonary disorder in one patient each]; cariprazine, 0.75 mg/day group: N=1 [depression]; 1.5 mg/day group: N=2 [injury and hypomania in one patient each]; 3.0 mg/day group: N=2 [lower limb fracture and vertigo in one patient each]). The only serious adverse events considered related to study drug were depression and hypomania (one patient each in the cariprazine 0.75-mg/day and 1.5-mg/day groups).

The use of rescue medications for agitation and restlessness was generally low, with rates ranging from 1% to 9% (diazepam: 3%, 3%, 3%, and 1% for the placebo and cariprazine 0.75-, 1.5-, and 3.0-mg/day groups, respectively; lorazepam: 5%, 6%, 9%, and 8%, respectively).

Laboratory values, vital signs, and other safety parameters. Changes from baseline in laboratory values, vital signs, and other safety outcomes were generally small and similar across groups; change in weight was slightly higher in all three cariprazine groups compared with placebo (Table 4). Potentially clinically significant body weight increases (≥7%) occurred in five patients (4%) in the placebo group and three (2%), 10 (7%), and seven (5%) in the cariprazine 0.75-, 1.5-, and 3.0-mg/day groups, respectively. In patients with clinically meaningful changes in fasting glucose levels, shifts from normal (<100 mg/dL) to high (≥126 mg/dL) occurred in three (3%) patients in the placebo group and five (6%), one (1%), and three (4%) in the cariprazine 0.75-, 1.5-, and 3.0-mg/day groups, respectively. No potentially clinically significant changes were noted for triglyceride levels. None of the patients met Hy's law criteria (ALT or AST ≥3 × upper limit of normal [ULN], with total bilirubin ≥2×ULN and alkaline phosphatase <2×ULN).

TABLE 3. Summary of Adverse Events in a Study of Cariprazine in Patients With Bipolar I Depression (Safety Population)

			Cariprazine					
	Placebo (N=145)		0.75 mg/day (N=141)		1.5 mg/day (N=146)		3.0 mg/day (N=146)	
Measure	N	%	N	%	N	%	N	%
Overall adverse event summary								
Patients with any treatment-emergent adverse event	79	54.5	80	56.7	91	62.3	91	62.3
Patients with serious adverse event	5	3.4	1	0.7	2	1.4	2	1.4
Deaths	0	0.0	0	0.0	0	0.0	0	0.0
Patients who discontinued due to adverse events	15	10.3	12	8.5	12	8.2	17	11.6
Patients with newly emergent adverse events[a]	6	4.1	2	1.4	5	3.4	3	2.1
Adverse events during double-blind treatment period (≥5% in any treatment group)								
Akathisia	2	1.4	4	2.8	7	4.8	21	14.4
Insomnia	12	8.3	16	11.3	10	6.8	17	11.6
Nausea	7	4.8	12	8.5	12	8.2	12	8.2
Headache	16	11.0	11	7.8	10	6.8	10	6.8
Somnolence	6	4.1	6	4.3	9	6.2	10	6.8
Restlessness	5	3.4	4	2.8	4	2.7	9	6.2
Diarrhea	8	5.5	2	1.4	9	6.2	3	2.1
Irritability	1	0.7	7	5.0	3	2.1	2	1.4

[a] Newly emergent adverse events occurred during the safety follow-up period and within 30 days after the last dose of double-blind study drug.

Treatment-emergent parkinsonism occurred infrequently. Treatment-emergent akathisia occurred with greater frequency in the cariprazine 3.0-mg/day group than in the placebo or cariprazine 0.75- or 1.5-mg/day groups. Treatment-emergent mania was similar across groups. The incidence of orthostatic hypotension was greater in the placebo and cariprazine 0.75-mg groups than in the cariprazine 1.5- and 3.0-mg groups (Table 4). None of the patients had a postbaseline QTcB or QTcF interval >500 ms.

Suicidality. There was no suicidal behavior, as assessed with the Columbia–Suicide Severity Rating Scale, in any treatment group. Suicidal ideation was less in the cariprazine 1.5-mg/day group (N=8 [6%]) than the placebo (N=15 [10%]) or cariprazine 0.75- (N=15 [11%]) or 3.0-mg/day (N=13 [9%]) groups. Treatment-emergent suicidal ideation occurred at an incidence ≥2% only in the placebo group (N=3 [2%]); one event was a serious adverse event, and two patients discontinued.

DISCUSSION

This phase II study evaluated three dosages of cariprazine for the treatment of bipolar I depression. Efficacy for cariprazine at 1.5 mg/day compared with placebo was demonstrated by significant improvement on every efficacy measure. An efficacy signal was detected for the 3.0-mg/day dosage, but this dosage was not significantly superior to placebo when adjusted for multiplicity. The 0.75-mg/day dosage was not significantly different from placebo on most measures.

The 4-point mean difference in MADRS total score at week 6 for the cariprazine 1.5-mg/day group compared with the placebo group was within the range of mean drug-placebo differences in MADRS scores observed in bipolar depression trials of other atypical antipsychotics (quetiapine, 3.55–6.47 [32–36], lurasidone, 4.7 [37] [both approved for bipolar depression], and olanzapine, 2.15–3.13 [38, 39]). Furthermore, improvements at week 6 for the 1.5- and 3.0-mg/day groups were sustained through week 8. In post hoc analyses, significantly greater improvements were seen on most MADRS individual items for cariprazine at 1.5 mg/day compared with placebo, suggesting potential benefit for cariprazine across a range of depression symptoms; improvement with cariprazine at 1.5 mg/day compared with placebo on the MADRS-6 subscale supports the potential of cariprazine in treating the core symptoms of depression.

On the CGI-S, which measures overall illness severity, the pattern of statistical significance compared with placebo was similar to that observed on the MADRS. Overall, significant improvement with cariprazine began early in treatment, and the 1.5- and 3.0-mg/day dosages remained significantly better than placebo through week 6 (on the CGI-S) or through week 8 (on the MADRS and the HAM-D). MADRS response was

TABLE 4. Changes in Clinical Laboratory Values and Safety Outcomes From Baseline to End of Double-Blind Treatment in a Study of Cariprazine in Patients With Bipolar I Depression (Safety Population)

Parameter	Placebo			Cariprazine								
				0.75 mg/day			1.5 mg/day			3.0 mg/day		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Liver function												
ALT (U/L)	131	0.4	11.1	120	0.1	16.8	132	1.4	9.4	125	1.7	21.6
AST (U/L)	131	−0.8	7.1	120	−0.1	11.1	132	0.6	7.1	124	0.2	6.9
Total bilirubin (mg/dL)	131	−0.03	0.24	119	−0.01	0.20	132	0.00	0.24	125	−0.02	0.25
Metabolic parameters												
Cholesterol												
HDL (mg/dL)	131	0.73	13.69	120	0.88	12.10	132	0.46	10.33	124	−1.64	9.49
LDL (mg/dL)[a]	131	−3.41	23.48	120	−2.78	21.96	132	−3.18	23.40	124	−6.40	23.86
Total (mg/dL)	131	−2.50	30.12	120	−3.93	29.13	132	−2.56	28.83	125	−6.76	27.00
Triglycerides (mg/dL)	115	1.97	64.38	105	−5.27	90.14	119	−2.36	61.26	106	7.51	74.44
Fasting glucose (mg/dL)	115	3.63	13.91	105	1.97	18.90	119	1.45	13.17	106	8.08	20.31
Chemistry parameters												
Prolactin (ng/mL)	131	−1.00	15.50	119	0.59	8.35	131	0.25	14.29	123	1.54	15.22
Creatine kinase (U/L)	131	−2.3	94.9	120	13.0	66.2	132	27.3	191.6	124	9.4	70.8
Vital signs												
Blood pressure[b]												
Systolic (mmHg)	142	−0.7	10.4	140	−1.4	8.3	145	1.3	8.7	145	−0.6	12.0
Diastolic (mmHg)	142	−0.1	8.0	140	−0.7	7.8	145	0.8	6.5	145	−0.4	7.5
Pulse[b]	142	0.2	10.4	140	−0.6	10.0	145	1.4	10.8	145	2.2	10.2
Body weight (kg)	142	0.10	2.28	140	0.84	2.50	145	1.10	2.64	145	0.63	2.26
Waist circumference (cm)	142	0.08	4.07	140	0.77	3.48	145	0.23	3.33	145	0.53	3.54
	N	n	%	N	n	%	N	n	%	N	n	%
Other safety outcomes												
Orthostatic hypotension[c]	142	17	12.0	139	19	13.7	145	12	8.3	143	13	9.1
Treatment-emergent parkinsonism[d]	142	0	0	140	2	1.4	145	2	1.4	145	3	2.1
Treatment-emergent akathisia[e]	142	6	4.2	140	8	5.7	145	12	8.3	145	25	17.2
Treatment-emergent mania[f]	142	5	3.5	140	6	4.3	145	4	2.8	145	4	2.8

[a] LDL direct and LDL calculated are combined.
[b] Measured in the supine position.
[c] Defined as a reduction of ≥20 mmHg in systolic or ≥10 mmHg reduction in diastolic blood pressure after changing from a supine to a standing position.
[d] Based on a Simpson-Angus Scale score ≤3 at baseline and >3 after baseline.
[e] Based on a Barnes Akathisia Rating Scale score ≤2 at baseline and >2 after baseline.
[f] Based on a Young Mania Rating Scale score ≥16 at any visit.

significantly higher for cariprazine at 1.5 and 3.0 mg/day compared with placebo; MADRS and HAM-D remission were also significantly higher for cariprazine at 1.5 mg/day compared with placebo. The numbers needed to treat based on MADRS response for cariprazine (1.5 mg/day: number needed to treat=6; 3.0 mg/day: number needed to treat=8) were comparable to those of pooled atypical antipsychotics (number needed to treat=8), quetiapine (300 mg/day: number needed to treat=6; 600 mg/day: number needed to treat=7), olanzapine (number needed to treat=12) (40), and lurasidone 20–60 mg and 80–120 mg (both dosage ranges: number needed to treat=5) (37). Similarly, numbers needed to treat based on MADRS remission were comparable for cariprazine at 1.5 mg/day (number needed to treat=6), quetiapine (300 mg/day: number needed to treat=7; 600 mg/day: number needed to treat=6) (40), and lurasidone (20–60 mg/day: number needed to treat=6; 80–120 mg/day: number needed to treat=7) (37).

An exploratory analysis of the 8-week completer population investigated why MADRS total score reductions were greater in the cariprazine 1.5-mg/day group than in the 3.0-mg/day group. Similar and significant reductions in MADRS score were observed in both dosage groups compared with the placebo group for study completers, but the completion rate was considerably higher in the 1.5-mg/day group (80%) than in the 3.0-mg/day group (64%). Adverse events and withdrawal of consent were the most common reasons for discontinuation in the 3.0-mg/day group. Similar reduction in MADRS scores among completers but lower discontinuation rates in the 1.5-mg/day compared with the 3.0-mg/day group suggests similar efficacy with either dosage but better tolerability with 1.5 mg/day. A slower titration schedule might have lowered the dropout rate in the cariprazine 3.0-mg/day group, but this was not specifically evaluated. These findings may explain the better overall effectiveness of cariprazine at 1.5 mg/day; however, the analysis was post hoc and did not control for multiple comparisons, which limits the conclusions that can be drawn.

Although atypical antipsychotics comprise a single drug class, marked pharmacodynamic differences exist among them, which may account for inconsistent effects in bipolar depression (41). Efficacy compared with placebo in bipolar depression has been demonstrated for quetiapine (32, 33, 35, 36), olanzapine (38, 39), and lurasidone (37); of note, both quetiapine and olanzapine are associated with weight gain and metabolic abnormalities. Interestingly, other atypical antipsychotics, such as ziprasidone and aripiprazole, have not been found to be superior to placebo in treating bipolar depression, but they have less propensity to cause weight gain and metabolic problems (42, 43).

Cariprazine was generally well tolerated over the course of treatment. Discontinuations due to adverse events were similar for placebo and cariprazine at 3.0 mg/day, and lower for cariprazine at 0.75 and 1.5 mg/day. Similar to other atypical antipsychotics, the incidence of akathisia was higher with cariprazine than placebo; akathisia was lower with cariprazine at 0.75 and 1.5 mg/day than at 3.0 mg/day. Excluding akathisia/restlessness, the incidence of extrapyramidal symptom-related adverse events was low across groups. Rates of somnolence, sedation, and weight gain, which were found in a meta-analysis to be significantly greater with atypical antipsychotics compared with placebo (40), were generally low and descriptively similar for placebo and cariprazine. Additionally, rates of treatment-emergent mania were low and similar for cariprazine and placebo; antidepressants, which are widely used in bipolar disorder despite a weak efficacy and safety evidence base (44), have variable risks of inducing manic or hypomanic states (1).

Since both bipolar disorder and atypical antipsychotics are associated with somatic disorders, including diabetes, hypertension, metabolic syndrome, and cardiovascular disease (45), small mean changes in metabolic parameters, body weight, and waist circumference for cariprazine patients in this study are important. Although higher fasting glucose and triglyceride levels were seen with cariprazine at 3.0 mg/day, this was not the case at 1.5 mg/day, which appears to be the most favorable dosage in this study in terms of efficacy and safety outcomes.

Interpretation of these results is limited by the lack of an active comparator and short treatment duration. Since only patients with bipolar I disorder without serious psychiatric comorbidities were enrolled, the generalizability of findings to patients with psychiatric comorbidities or bipolar II disorder is unclear. The study was not powered to detect a potential dose response, so it is unknown whether there is a relationship between cariprazine dosage and therapeutic effect. Some analyses were post hoc, with no adjustments made for multiple comparisons; results should be interpreted accordingly. Strengths of the study included the fixed-dosage design, evaluation of three dosages of cariprazine, prospective remission analyses, and statistical adjustment for multiple comparisons.

In conclusion, cariprazine at 1.5 mg/day showed statistically significant improvement on MADRS score and CGI-S change from baseline compared with placebo. Cariprazine was generally well tolerated. Of the cariprazine dosages studied, 1.5 mg/day demonstrated the most robust efficacy and good safety, suggesting that it may be an effective dosage for the treatment of bipolar I depression. Given the limited number of positive studies for atypical antipsychotics in bipolar I depression, future studies are warranted to extend these phase II findings.

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