**ORIGINAL ARTICLE**

# Efficacy and safety of cariprazine in bipolar I depression: A double-blind, placebo-controlled phase 3 study

Willie R. Earley[1] | Maria V. Burgess[1] | Barbara Khan[1] | Ludmyla Rekeda[2] | Trisha Suppes[3] | Mauricio Tohen[4] (ID) | Joseph R. Calabrese[5]

[1]Department of Clinical Development, Allergan plc, Madison, NJ, USA

[2]Department of Biostatistics, Allergan plc, Madison, NJ, USA

[3]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine and V.A. Palo Alto Health Care System, Palo Alto, CA, USA

[4]Department of Psychiatry and Behavioral Sciences, University of New Mexico, Albuquerque, NM, USA

[5]Department of Psychiatry, Case Western Reserve School of Medicine, Cleveland, OH, USA

**Correspondence**
Willie R. Earley, Clinical Development-CNS Allergan, 5 Giralda Farms, Madison, NJ 07940, USA.
Email: willie.earley@allergan.com

## Abstract

**Objective:** To assess the efficacy, safety, and tolerability of cariprazine in the treatment of the depressed phase of bipolar I disorder in adults (NCT02670538).

**Methods:** In this phase 3 double-blind placebo-controlled study, adult patients with bipolar I disorder according to the *Diagnostic and Statistical Manual — 5th Edition* criteria and a current depressive episode were randomized to placebo (n = 167), cariprazine 1.5 mg/day (n = 168) or cariprazine 3.0 mg/day (n = 158). Efficacy parameters were changes in the Montgomery-Åsberg Depression Rating Scale (MADRS) total scores (primary) and Clinical Global Impressions — Severity (CGI-S) scores (secondary) from baseline to Week 6 compared to placebo. A mixed-model for repeated measures was used to estimate the least-squares mean differences (LSMD); *P*-values were adjusted for multiplicity. Adverse events (AEs), laboratory results, vital signs, and suicide risk were monitored.

**Results:** Cariprazine 1.5 mg/day significantly reduced depressive symptoms on the primary (MADRS LSMD = −2.5; adjusted *P* = .0417) and secondary (CGI-S LSMD = −0.3; adjusted *P* = .0417) efficacy parameters vs placebo; differences were not statistically significant for cariprazine 3.0 mg/day. Common treatment-emergent AEs (≥5% in either cariprazine group and at least twice the incidence of placebo) were akathisia, restlessness, nausea, and fatigue. Mean metabolic parameter changes were low and generally comparable among groups; mean weight increases were ≤0.5 kg for all groups.

**Conclusions:** Cariprazine 1.5 mg/day significantly reduced depressive symptoms in adults with bipolar I depression compared to placebo, but differences were not significant for cariprazine 3.0 mg/day. The safety and tolerability profiles were similar to previous studies of cariprazine.

**KEYWORDS**
atypical antipsychotic, bipolar depression, bipolar I disorder, cariprazine, randomized controlled trial

# 1 | INTRODUCTION

In symptomatic patients with bipolar I disorder, depressive episodes are present three times more often than manic episodes,[1-4] occur earlier in the disease course, and are the predominant mood state late in the course of illness.[2] Depressive episodes in bipolar I disorder are associated with increased rates of disability, morbidity, and suicide.[5,6] Depressive episodes are also less responsive to standard pharmacological treatments for bipolar I disorder compared with mania.[7] Although the traditional antidepressants are frequently utilized for the treatment of bipolar I depression, clinical trials have demonstrated limited efficacy[8] and indicate their potential to cause the induction of hypomanic, manic, or mixed feature episodes when used for long-term treatment.[9,10] Currently, FDA-approved treatments for the acute treatment of bipolar I depression include atypical antipsychotics, used as monotherapy, adjunctive, or in combination with an antidepressant.[11-13]

Cariprazine is FDA-approved for the treatment of adults with schizophrenia as well as acute manic, acute mixed, or depressive episodes associated with bipolar I disorder[14] and is under investigation for the treatment of major depressive disorder.[15,16] Cariprazine is a dopamine $D_3$-preferring $D_3/D_2$ and serotonin 5-$HT_{1A}$ receptor partial agonist[17,18] with antidepressant and pro-cognitive-like effects reported in preclinical models,[19,20] partially mediated by the $D_3$ receptor.[20] In animal models and patients with schizophrenia, cariprazine positively affects cognition,[21] mood, measures of reward, and/or reduced levels of anhedonia[19] presumably through its high affinity and occupancy of the $D_2$ and $D_3$ receptors, which are found in areas of the brain associated with these functions.

The hypothesis that cariprazine may be an effective treatment for depressive episodes associated with bipolar I disorder (bipolar I depression) in adults has been supported by two previous (phase 2b and 3) randomized placebo-controlled clinical trials.[22,23] In each trial, cariprazine 1.5 mg/day was significantly more effective than placebo in reducing depressive symptoms, as measured by change in MADRS total score from baseline to Week 6. Cariprazine 3.0 mg/day significantly reduced depressive symptoms in the phase 3 trial, while in the phase 2 trial a clinically significant reduction in symptoms occurred, but once adjustments were made for multiple comparisons, statistical significance was not maintained.[22] The first phase 2 trial (NCT00852202) in the program did not demonstrate statistical significance for either of the flexible-dose ranges (0.25-0.75, 1.5-3.0 mg/day), but did provide useful information for the future exploration of cariprazine in the treatment of bipolar depression. For example, the exploratory study enrolled patients with either bipolar I and II depression, while each of the subsequent trials only enrolled patients with bipolar I depression. The present study was designed to further evaluate the efficacy, safety, and tolerability of cariprazine 1.5 and 3.0 mg/day in the treatment of bipolar I depression.

# 2 | METHODS

This study was conducted at 89 study centers in the United States, Bulgaria, Croatia, Romania, Serbia, Slovakia, and Ukraine from March 2016 to January 2018. The final study protocol was approved by institutional review boards for US sites or ethics committees and government agencies for other sites. Patients were screened and recruited in compliance with the International Conference on Harmonization Good Clinical Practice Guideline and the Declaration of Helsinki and provided written informed consent after receiving a complete description of the study.

## 2.1 | Study design

A multinational, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose (cariprazine 1.5 or 3.0 mg/day) study was conducted in adult patients with bipolar I depression (NCT02670538). The double-blind period was 6 weeks in duration, which was preceded by a 1- to 2-week screening/washout period and followed by a 1-week safety follow-up (no study medication). Patients were randomized 1:1:1 to placebo, cariprazine 1.5 mg/day, or cariprazine 3.0 mg/day using an interactive voice/web response system (Premier Research) by assignment of computer-generated numbers. The system also monitored enrollment and allocated investigational product using a code matching the assigned medication. Blinding of all patients and study staff was maintained throughout the study. All oral capsules (study drug and placebo) were provided in blister packs and were identical in appearance. Patients were instructed to take them at approximately the same time each day (morning or evening, at the discretion of the investigator). All patients randomized to study medication began with cariprazine 1.5 mg/day; the cariprazine 1.5 mg/day group remained at that dose throughout the study, and the 3.0 mg/day group took 1.5 mg/day for the first 2 weeks of the double-blind period and increased to 3.0 mg/day for the following 4 weeks. In the event of tolerability issues at the assigned dose, drugs holidays for a maximum of 3 days were permitted, but patients were discontinued if a holiday of ≥4 days was needed.

## 2.2 | Patients

Adult (18-65 years) patients with bipolar I disorder using the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[24] criteria without psychotic features and a current major depressive episode ≥4 weeks and <12 months confirmed by the Mini-International Neuropsychiatric Interview (MINI) were included in the study. Patients were required to have a 17-item Hamilton Depression Rating Scale (HAMD-17)[25] total score ≥20 and item-1 score ≥2, Clinical Global Impressions - Severity (CGI-S) score ≥4,[26] and Young Mania Rating Scale (YMRS)[27] score ≤12.

For study inclusion, physical examination, clinical laboratory, and ECG results were normal or not judged to be clinically significant by investigators. Pregnancy in women with childbearing

potential was excluded with negative serum β-human chorionic gonadotropin testing. Patients with 4 or more mood episodes in the prior 12 months or any current psychiatric diagnoses, including personality disorders of significant severity to interfere with the study (as judged by the principal investigator), besides bipolar I disorder, or specific phobias, were excluded from the study. Patients were not permitted to have an alcohol or substance use disorder within the previous 6 months; suicide risk (based on Columbia-Suicide Severity Rating Scale [C-SSRS][28] assessment, suicide attempt in the last year, HAMD-17 item-3 score ≥3, or MADRS item-10 score ≥4) or risk of injury to self or others (based on investigator's judgment); nonresponse in the current depressive episode to ≥2 antidepressant trials of adequate dose; or treatment failure (in current depressive episode) of quetiapine, lurasidone, or olanzapine and fluoxetine combination. Patients with concurrent medical conditions were excluded if they were judged to have the potential to interfere with study participation, confound interpretation of results, or endanger the patient's well-being. The only psychotropic drugs permitted for use during the study were eszopiclone, zolpidem, zopiclone, chloral hydrate, or zaleplon (for insomnia), lorazepam or equivalent benzodiazepine (maximum daily dosage 2.0 mg if the dose had been stable for 1 month prior to screening), rescue doses of lorazepam or equivalent benzodiazepine (for agitation/restlessness/hostility; maximum daily dose 2.0 mg for a maximum of 3 consecutive days), rescue doses of diphenhydramine or benztropine (for extrapyramidal symptoms [EPS]), or propranolol (for akathisia that emerged or worsened during the study).

## 2.3 | Efficacy

Efficacy was assessed by the change from baseline to Week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS)[29] total score (primary) and CGI-S score (secondary) compared to placebo. Additional efficacy parameters included changes in HAMD-17 total score, Hamilton Anxiety Rating Scale (HAM-A) total score,[30] and Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR$_{16}$)[31] score. MADRS and CGI-S assessments were administered at each study visit, which included screening, baseline/randomization, Weeks 1, 2, 4, and 6 (double-blind treatment period) and the remaining efficacy assessments were administered at screening, baseline/randomization, and at least one post-baseline visit.

## 2.4 | Safety

Physical examination, ECG, and clinical laboratory monitoring were conducted at screening and at Week 6. Adverse events (AEs) were monitored at each visit after screening. Vital signs, except height, which was recorded at Visit 1, were recorded at every visit. YMRS assessments were administered at screening, baseline, and Weeks 4 and 6. EPS scales (eg the Barnes Akathisia Rating Scale [BARS],[32] the Abnormal Involuntary Movement Scale [AIMS],[26] and the Simpson-Angus Scale [SAS])[33] were administered at baseline and

each double-blind study visit. Suicide risk, using the C-SSRS, was monitored at every visit.

## 2.5 | Data analyses

Efficacy analyses were based on the intent-to-treat (ITT) population (patients who had taken at least one dose of study medication and had a baseline and ≥1 post-baseline MADRS assessment). MADRS total score changes from baseline to Week 6 were analyzed by a mixed-effects model for repeated measures (MMRM) with treatment group, pooled study center, visit, and treatment group–by-visit interaction as fixed effects, and the baseline MADRS score and baseline MADRS score-by-visit interaction as covariates. Study centers with <2 patients in at least 1 treatment group (ITT population) were pooled to form pseudo-centers so each treatment group had at least 2 patients per treatment group. An unstructured covariance matrix was used to model the covariance of within-patient scores, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom. The analysis was performed based on all postbaseline scores using only the observed cases without imputation of missing values.

Sensitivity analyses were performed using a pattern-mixture model based on non-future dependent missing value restrictions[34] to assess the robustness of primary MMRM results.

Analysis of change from baseline in CGI-S score, HAM-A total score, QIDS-SR$_{16}$ total score, and HAMD-17 total score was performed using a similar MMRM to that used for the primary analysis. The same parameters were analyzed by-visit using analysis of covariance (ANCOVA) with last observation carried forward (LOCF) imputation with treatment group and pooled study center as factors and the baseline value as the covariate.

Response and remission rates were reported by treatment group and visit with a logistic regression model used to model the probability of an event (response or remission) as a function of a treatment group and corresponding baseline score with an LOCF approach for imputation. All statistical analyses were performed using SAS, version 9.3 (SAS Institute).

Safety analyses were based on the safety population (randomized patients who took ≥1 dose of investigational product).

## 2.6 | Sample size

To determine sample size, it was calculated that 160 patients per arm provided approximately 82% statistical power to show statistically significantly higher effect in each dose of cariprazine vs placebo and 90% power to show the efficacy of least 1 of the doses was statistically significantly improved compared to placebo for the primary endpoint. These calculations assumed an effect size of 0.36 (treatment group difference relative to standard deviation [SD]). All statistical powers were calculated adjusting for multiple comparisons using matched parallel gatekeeping procedure[35] with the family-wise type I error rate being controlled at a 0.05 level. Statistical hypothesis tests for all efficacy measures were performed at a significance threshold of 0.05 (2-sided).

Safety parameters included AEs, clinical laboratory parameters, vital sign measurements, ECG parameters, YMRS scores, C-SSRS scores, and EPS scales (AIMS, BARS, and SAS) scores. For each safety parameter, the last nonmissing safety assessment before the first dose of double-blind investigational product was used as the baseline.

# 3 | RESULTS

## 3.1 | Patient disposition and demographics

A total of 493 patients were randomized to double-blind treatment, of 866 screened (Figure 1). Approximately 81% of patients completed the study; rates of completion were similar between all groups. The most common reasons for premature discontinuations (combined population) were lost to follow-up, AEs, and withdrawal of consent. AEs led to premature discontinuations in approximately 3%-7% of patients in each group. Patient demographics and psychiatric history (Table 1) were generally comparable among groups. The baseline MADRS, CGI-S, and HAMD-17 scores at baseline were comparable among treatment groups and each in the moderate range of the respective scales (Table 2).

## 3.2 | Efficacy

### 3.2.1 | Primary

The reduction from baseline to Week 6 in MADRS total score (depressive symptom improvement) was statistically significant for cariprazine 1.5 mg/day treatment compared to placebo (Table 2). Cariprazine 3.0 mg/day reduced MADRS total score vs placebo at the primary endpoint, but the difference (LSMD = −1.8) did not reach significance ($P = .1051$). Significant improvements vs placebo were observed at Week 2 for cariprazine 3.0 mg/day and for Week 4 1.5 mg/day (Figure 2A). The effect sizes at Week 6 for cariprazine 1.5 and 3.0 mg/day vs placebo were 0.28 and 0.20 respectively.

### 3.2.2 | Secondary

CGI-S scores for cariprazine 1.5 mg/day treated patients were significantly improved from baseline to Week 6 vs placebo (Table 2; Figure 2B); the difference was not significant for cariprazine 3.0 mg/day.

### 3.2.3 | Additional

Improvements in HAMD-17 total and QIDS-SR$_{16}$ scores from baseline to Week 6 were not significant for cariprazine 1.5 and 3.0 mg/day compared to placebo. Cariprazine 1.5 mg/day significantly improved HAM-A scores from baseline to Week 6 compared to placebo, but the difference vs placebo did not reach significance for cariprazine 3.0 mg/day ($P = .3527$). At Week 6, the percentage of patients who met the criterion for MADRS response was not significant vs placebo; cariprazine 1.5 mg/day: 40.7% and placebo: 35.6% ($P = .3383$). Similarly, at Week 6, the percentages of patients that met the criteria for remission were 25.9% and 19.6% for cariprazine 1.5 mg/day and placebo respectively ($P = .1648$). Despite the lack of significance in the analysis of HAMD-17 mean change from baseline, a significantly greater percentage of cariprazine 1.5 mg/day patients met the criteria for HAMD-17 remission (30.6% vs 16.4%; $P = .0051$) (Figure 3). For cariprazine 3.0 mg/day vs placebo, no response or remission rates were significantly different vs placebo; Week 6 MADRS response: 42.5% vs 35.6% ($P = .2088$), MADRS remission: 26.1% vs 19.6% ($P = .1625$), and HAMD-17 remission: 22.7% vs 16.4% ($P = .1797$).

## 3.3 | Safety

### 3.3.1 | Extent of exposure

Mean treatment durations were similar across treatment groups; placebo, cariprazine 1.5, and 3.0 mg/day were 39.1, 37.5, and 37.6 days.



**FIGURE 1** CONSORT flow diagram for study patients. AE, adverse event; Incl/Excl criteria, patient did not meet inclusion/exclusion criteria; LOE, lack of efficacy; LTF, lost to follow-up; NC, noncompliance with study drug; PV, protocol violation; WOC, withdrawal of consent
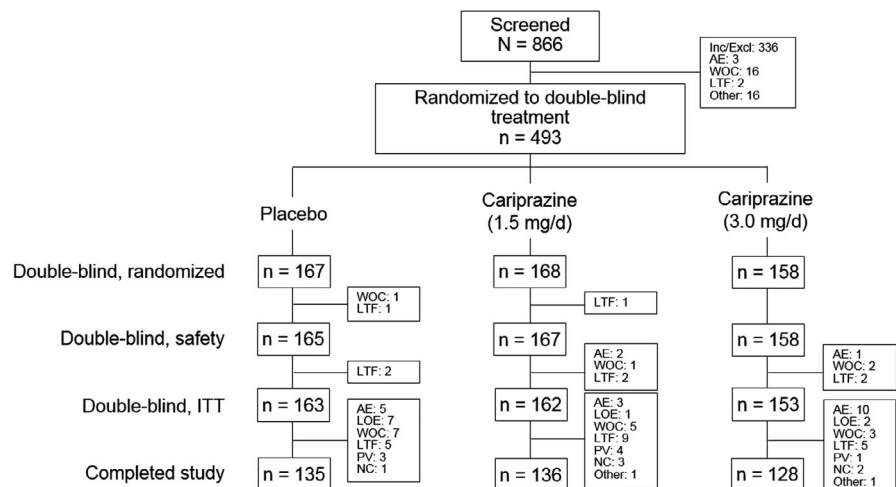
**TABLE 1** Patient baseline characteristics by treatment group (Safety population)

| | Placebo (n = 165) | | Cariprazine 1.5 mg/d (n = 167) | | 3.0 mg/d (n = 158) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Female | 97 | 58.8 | 107 | 64.1 | 103 | 65.2 |
| Race | | | | | | |
| White | 120 | 72.7 | 120 | 71.9 | 117 | 74.1 |
| Black or African American | 45 | 27.3 | 41 | 24.6 | 39 | 24.7 |
| Asian | 0 | | 3 | 1.8 | 2 | 1.3 |
| Multiple[a] | 0 | | 3 | 1.8 | 0 | |
| | Mean | SD | Mean | SD | Mean | SD |
| Age, years | 44.6 | 11.5 | 42.2 | 12.0 | 43.9 | 11.8 |
| Weight, kg | 84.97 | 20.28 | 85.90 | 21.45 | 83.47 | 20.56 |
| BMI, kg/m$^2$ | 29.72 | 7.41 | 29.80 | 7.31 | 29.42 | 7.42 |
| **Psychiatric history** | n | % | n | % | n | % |
| Bipolar I disorder, current or most recent episode depressed (DSM-5 code) | | | | | | |
| Mild | 0 | | 3 | 1.8 | 1 | 0.6 |
| Moderate | 130 | 78.8 | 118 | 70.7 | 117 | 74.1 |
| Severe | 33 | 20.0 | 46 | 27.5 | 39 | 24.7 |
| Attempted suicide in the past year | 0 | | 0 | | 0 | |
| | Mean | SD | Mean | SD | Mean | SD |
| Duration of current episode of bipolar I disorder, months[b] | 3.7 | 2.8 | 3.6 | 2.5 | 3.5 | 2.5 |
| Number of lifetime depressive episodes | 7.2 | 8.2 | 6.8 | 7.2 | 6.7 | 9.3 |
| Number of lifetime manic/mixed episodes | 4.5 | 4.2 | 3.8 | 3.3 | 3.9 | 5.0 |
| Number of mood episodes (manic, mixed, hypomanic depressive) in the past year | 1.5 | 0.6 | 1.6 | 0.7 | 1.5 | 0.7 |

Abbreviations: BMI, body mass index; n, number of patients within a specific category.

[a]Patients who reported ≥ 2 races, including patients who reported White and ≥ 1 other race.

[b]Duration of current episode of bipolar I disorder (months) = the number of months between the date of informed consent and the date of onset of current episode of bipolar I disorder.

### 3.3.2 | Adverse events

Summary of AEs are presented in Table 3. Common treatment-emergent AEs (TEAE; ≥5% in either cariprazine treatment group and twice the rate of placebo) were akathisia, restlessness, nausea, and fatigue. AEs leading to discontinuation occurred in 3% of placebo and cariprazine 1.5 mg/day patients and 7% of cariprazine 3.0 mg/day patients. The only AE leading to discontinuation that occurred in ≥2% of patients in any group was akathisia. Most TEAEs were rated mild or moderately severe by the investigator; the incidence of severe TEAEs were lower in the cariprazine 1.5 and 3.0 mg/day groups (2.3% and 2.1%, respectively) relative to placebo (4.6%). Serious AEs occurred in 5 placebo, 1 cariprazine 1.5 mg/day, and no 3.0 mg/day patients, and included bipolar disorder, depression, lumbar vertebral fracture, mania, noncardiac chest pain, and substance abuse. No deaths occurred in any treatment period.

The overall incidence of EPS-related TEAEs increased in a dose-related manner across the treatment groups (6.1%, 10.8%, and 19.0% of patients in placebo, cariprazine 1.5, and 3.0 mg/day groups) and most were mild or moderate in intensity. Akathisia and restlessness were the most common TEAEs, and akathisia followed a dose-dependent pattern of incidence (3.1%, 5.5%, and 11.0% for placebo, cariprazine 1.5, and 3.0 mg/day). Treatment-emergent restlessness rates were placebo: 3%, cariprazine 1.5 mg: 2.4%, and 3.0 mg/day: 7% of patients. No suicidal behavior was reported in the double-blind treatment or safety follow-up periods.

### 3.3.3 | Treatment-emergent mania

Rates of treatment-emergent mania (postbaseline YMRS total score ≥16) did not occur in any cariprazine 3.0 mg/day-treated patients and were low and comparable in the placebo and 1.5 mg/day groups (1.3% and 1.2%).

**TABLE 2**  Efficacy parameters, response, and remission at week 6 (ITT population, MMRM)

| | | | Baseline | | Week 6 | | | | | |
| | | | | | Change from baseline | | Difference vs placebo | | | |
| | Group | N | Mean | SD | LS Mean | SE | LSMD | 95% CI[a] | P-value[a] | Adjusted P-value[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Primary efficacy parameter: MADRS** | | | | | | | | | | |
| MMRM | Placebo | 163 | 31.3 | 4.1 | −12.4 | 0.75 | — | — | — | — |
| | CAR 1.5 mg/d | 162 | 31.5 | 4.3 | −14.8 | 0.76 | −2.5 | −4.6, −0.4 | .0208 | .0417 |
| | CAR 3.0 mg/d | 153 | 31.4 | 4.7 | −14.1 | 0.78 | −1.8 | −3.9, 0.4 | .1051 | .1051 |
| **Secondary efficacy parameter: CGI-S** | | | | | | | | | | |
| MMRM | Placebo | 163 | 4.5 | 0.5 | −1.2 | 0.09 | — | — | — | — |
| | CAR 1.5 mg/d | 162 | 4.5 | 0.6 | −1.5 | 0.09 | −0.3 | −0.6, −0.1 | .0174 | .0417 |
| | CAR 3.0 mg/d | 153 | 4.5 | 0.6 | −1.4 | 0.09 | −0.2 | −0.4, 0.1 | .1370 | .1370 |
| **Additional efficacy parameters** | | | | | | | | | | |
| **HAMD-17** | | | | | | | | | | |
| ANCOVA (LOCF[c]) | Placebo | 163 | 24.7 | 3.0 | −10.6 | 0.59 | — | — | — | — |
| | CAR 1.5 mg/d | 162 | 24.7 | 3.5 | −12.2 | 0.60 | −1.6 | −3.2, 0.1 | .0590 | — |
| | CAR 3.0 mg/d | 153 | 24.5 | 3.1 | −11.1 | 0.60 | −0.5 | −2.1, 1.2 | .5599 | — |
| **HAM-A** | | | | | | | | | | |
| MMRM | Placebo | 163 | 18.7 | 5.6 | −7.1 | 0.51 | — | — | — | — |
| | CAR 1.5 mg/d | 162 | 18.9 | 6.2 | −8.6 | 0.51 | −1.5 | −2.9, −0.1 | .0393 | — |
| | CAR 3.0 mg/d | 153 | 18.7 | 6.0 | −7.8 | 0.53 | −0.7 | −2.1, 0.8 | .3527 | — |
| **QIDS-SR$_{16}$** | | | | | | | | | | |
| MMRM | Placebo | 163 | 15.3 | 3.5 | −6.0 | 0.42 | — | — | — | — |
| | CAR 1.5 mg/d | 162 | 15.6 | 3.7 | −7.0 | 0.42 | −1.1 | −2.2, 0.1 | .0752 | — |
| | CAR 3.0 mg/d | 153 | 15.6 | 3.8 | −7.0 | 0.43 | −1.1 | −2.2, 0.1 | .0787 | — |

| | Group | N | n | n/N (%) | OR | 95% CI | P-value[c] |
|---|---|---|---|---|---|---|---|
| **Odds ratio vs placebo (LOCF)** | | | | | | | |
| MADRS response (≥50% score reduction from baseline) | Placebo | 163 | 58 | 35.6 | — | — | — |
| | CAR 1.5 mg/d | 162 | 66 | 40.7 | 1.2 | 0.8, 1.9 | .3383 |
| | CAR 3.0 mg/d | 153 | 65 | 42.5 | 1.3 | 0.8, 2.1 | .2088 |
| MADRS remitters (total score ≤10) | Placebo | 163 | 32 | 19.6 | — | — | — |
| | CAR 1.5 mg/d | 162 | 42 | 25.9 | 1.5 | 0.9, 2.5 | .1648 |
| | CAR 3.0 mg/d | 153 | 40 | 26.1 | 1.5 | 0.9, 2.5 | .1625 |
| HAMD-17 remitters[d] (total score ≤7) | Placebo | 146 | 24 | 16.4 | — | — | — |
| | CAR 1.5 mg/d | 144 | 44 | 30.6 | 2.2 | 1.3, 3.9 | .0051 |
| | CAR 3.0 mg/d | 141 | 32 | 22.7 | 1.5 | 0.8, 2.7 | .1797 |

Abbreviations: ANCOVA, analysis of covariance; CGI-S, Clinical Global Impressions – Severity; CI, confidence interval; HAM-A, Hamilton Rating Scale for Anxiety; HAMD-17, 17-item Hamilton Depression Rating Scale; LOCF, last-observation carried forward; LS, least squares; LSMD, least-squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed model repeated measures; OR, odds ratio; QIDS-SR$_{16}$, Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report); SD, standard deviation; SE, standard error.

[a]P-value and 95% confidence interval for the difference using contrast t test.

[b]Adjusted P-values: adjustment was performed using matched parallel gatekeeping procedure to control the overall Type I error rate for multiple comparisons of 2 active doses vs placebo at Week 6 for the primary and secondary efficacy parameters.

[c]The P-value for a between-treatment comparison at each visit is based on a logistic regression model which included treatment group and corresponding baseline total score value. The P-value is from a Z-test. LOCF was used for imputation.

[d]N represents number of patients with postbaseline HAMD-17 values.

**(A)** MADRS total score
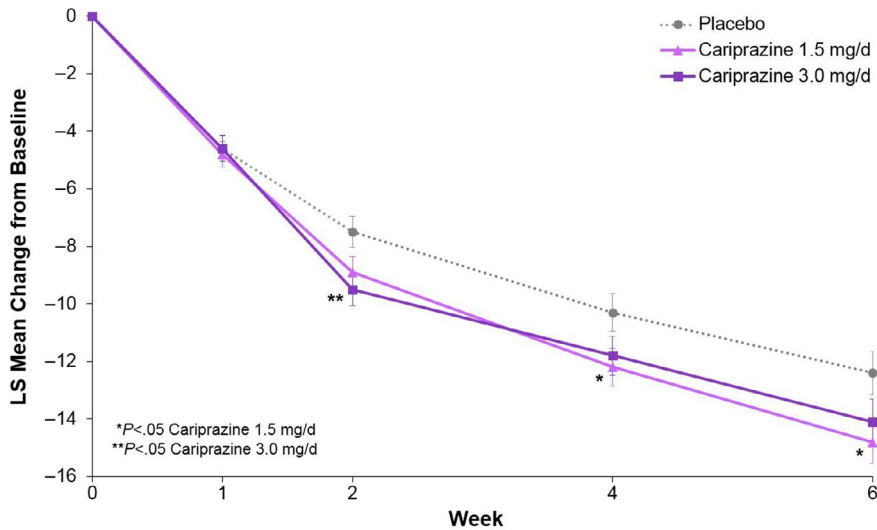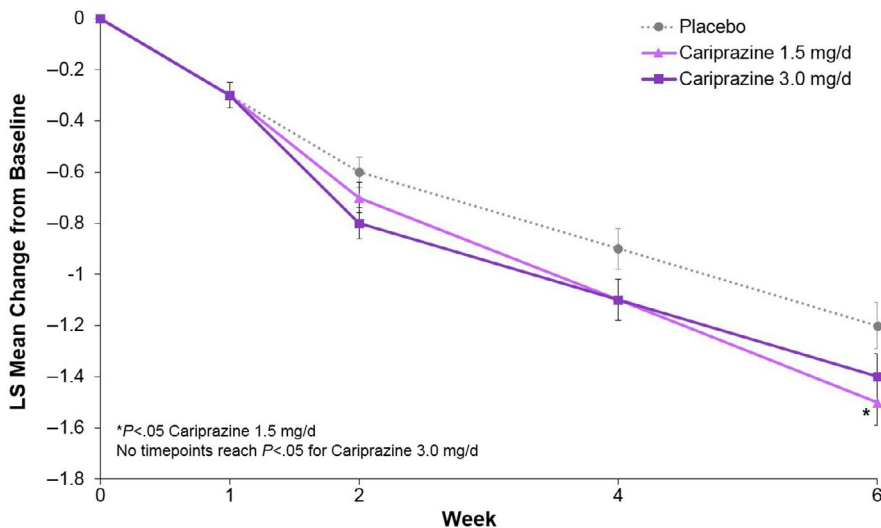


**(B)** CGI-S score



**FIGURE 2** Mean change from baseline to Week 6 by visit in a) MADRS total score; b) CGI-S score (LSM ± SE; ITT population, MMRM). Estimates derived from an MMRM with fixed factors (treatment group, pooled study center, and visit), baseline (a covariate), and interactions (treatment group by visit, baseline by visit). ITT population consists of randomized patients who had received ≥1 dose of double-blind treatment and ≥1 postbaseline MADRS total score assessment. CGI-S, Clinical Global Impressions -Severity; ITT, intent-to-treat; LS, least squares; LSM, least squares mean; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures; SE, standard error [Colour figure can be viewed at wileyonlinelibrary.com]

### 3.3.4 | Clinical parameters

The incidence of patients with treatment-emergent potentially clinically significant (PCS) values for metabolic parameters were generally low, similar across treatment groups, and did not follow a dose-response relationship (Table 4). Rates of metabolic parameter shifts were low and generally comparable to placebo except for triglycerides. Mean change in fasting serum glucose levels from baseline to Week 6 were 1.992 (SD = 14.317), 2.984 (13.592), and 3.983 (13.751) mg/dL for placebo, cariprazine 1.5 and 3.0 mg/day (Table 5).

Mean (SD) weight changes from baseline were placebo: −0.2 (2.0) kg, cariprazine 1.5 mg/day: +0.5 (2.4) kg, and 3.0 mg/day: +0.0 (2.2) kg. Weight increases ≥7% body weight occurred in no placebo, four 1.5 mg/day cariprazine, and three 3.0 mg/day patients. No patient in any group met the criteria for potential drug-induced liver injury (Hy's Law).

## 4 | DISCUSSION

In this phase 3 study, cariprazine 1.5 mg/day significantly reduced depressive symptoms in patients with bipolar I depression at the primary endpoint (Week 6). Significant reduction from baseline in MADRS total score was also observed at Week 4. The cariprazine 1.5 mg/day results presented herein are consistent with data from the two prior phase 2b/3 trials,[22,23] which demonstrated significant reductions in depressive symptoms across multiple measures at this dose in similarly designed studies. Mean CGI-S scores, which quantifies the severity of overall illness, were also significantly lower compared to placebo with cariprazine 1.5 mg/day treatment from baseline to Week 6. No significant between-group differences were found for the additional efficacy measures of HAMD-17 and QIDS-SR$_{16}$.

Cariprazine 3.0 mg/day was not significantly superior to placebo in the primary or secondary efficacy parameters at Week 6.

**FIGURE 3** MADRS response, MADRS remission, and HAMD-17 remission at Week 6 (ITT population, LOCF). The P-value for a between-treatment comparison at each visit is based on a logistic regression model, which included treatment group and the baseline MADRS[a] and HAMD-17[b] total score value. The P-value is from a Z-test. LOCF was used for imputation. HAMD-17, 17-item Hamilton Depression Rating Scale; ITT, intent-to-treat; LOCF, last observation carried forward; MADRS, Montgomery-Asberg Depression Rating Scale [Colour figure can be viewed at wileyonlinelibrary. com]
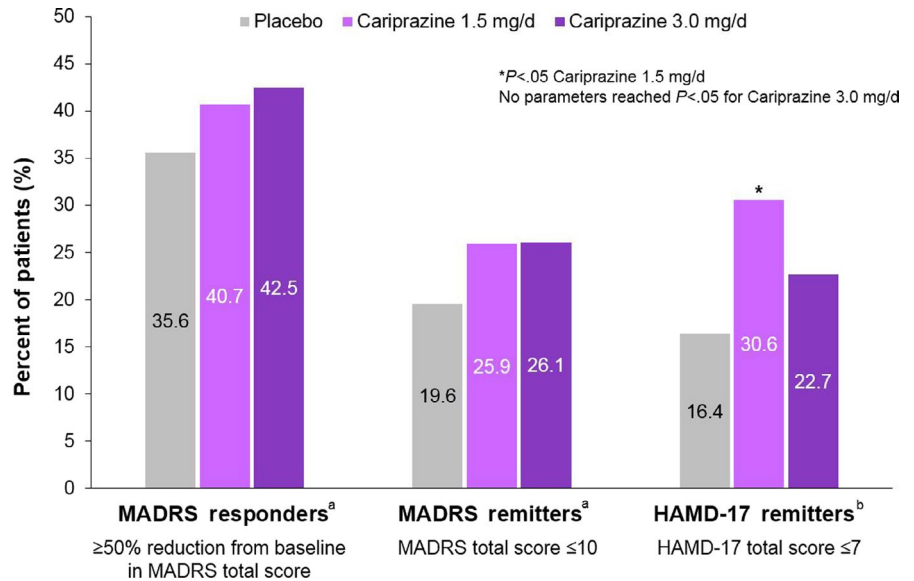


**TABLE 3** Summary of adverse events (safety population, double-blind phase)

| | Placebo (N = 165) | | Cariprazine | | | |
| | | | 1.5 mg (N = 167) | | 3.0 mg (N = 158) | |
| | N | % | N | % | N | % |
|---|---|---|---|---|---|---|
| **Overall adverse event summary** | | | | | | |
| Patients with any treatment-emergent adverse event (TEAE)[a] | 75 | 45.5 | 82 | 49.1 | 78 | 49.4 |
| Patients with serious adverse event[b] | 5 | 3.0 | 1 | 0.6 | 0 | |
| Deaths[b] | 0 | | 0 | | 0 | |
| Patients with adverse events leading to discontinuation | 5 | 3.0 | 5 | 3.0 | 11 | 7.0 |
| **Common TEAEs (≥5% in either cariprazine group and twice the rate of placebo)[c]** | | | | | | |
| Akathisia | 3 | 1.8 | 9 | 5.4 | 15 | 9.5 |
| Restlessness | 5 | 3.0 | 4 | 2.4 | 11 | 7.0 |
| Nausea | 5 | 3.0 | 13 | 7.8 | 8 | 5.1 |
| Fatigue | 2 | 1.2 | 9 | 5.4 | 5 | 3.2 |

*Note:* Adverse events coded to MedDRA preferred term.
[a]Includes events that began or worsened on or after the treatment start date within the double-blind treatment period +30 d after study drug last dose; for patients who did not participate in the safety follow-up period, events that began or worsened within 30 d after the last dose of double-blind investigational product are also included.
[b]Includes any deaths and serious adverse events that occurred during double-blind treatment period; for patients who did not participate in the safety follow-up period, events within 30 d after the last dose of double-blind investigational product are also included.
[c]Patients are counted only once within each preferred term.

The findings for the 3.0 mg/day dose results are contrasted with the previous phase 3 trial[23] that reported cariprazine 3.0 mg/day significantly reduced MADRS total scores compared to placebo. The magnitude of change (MADRS: −14.1 points and CGI-S −1.4 points) is generally comparable to previous cariprazine trials and those observed in trials of other atypical antipsychotics that are approved for the treatment of bipolar I depression.[3,22,36-43] The lack of statistical significance for the cariprazine 3.0 mg/day dose

in the present study is possibly due to chance (Type II error) and intra-study variability, as the 3.0 mg/day dose was effective in an identically designed study.[23]

Rates of MADRS response at Week 6 were 41% and 43% for cariprazine 1.5 and 3.0 mg/day, respectively, vs placebo (36%). The lack of significance in MADRS response may be attributed to the high placebo response rate at Week 6 in this trial, which commonly occurs in drug trials of bipolar I depression.[43-46] A similar trend

**TABLE 4** Patients with treatment-emergent significant changes in lipids and glucose (safety population, double-blind phase)

| Clinical laboratory parameter Criterion | Baseline (mg/dL) | Postbaseline (mg/dL) | Placebo (N = 165) n/N1 (%) | Cariprazine 1.5 mg (N = 167) n/N1 (%) | Cariprazine 3.0 mg (N = 158) n/N1 (%) |
|---|---|---|---|---|---|
| Cholesterol, total | | | | | |
| Normal to high | <200 | ≥240 | 2/83 (2.4) | 2/88 (2.3) | 1/84 (1.2) |
| Borderline to high | ≥200 and <240 | ≥240 | 6/39 (15.4) | 5/41 (12.2) | 3/39 (7.7) |
| Normal/borderline to high | <240 | ≥240 | 8/122 (6.6) | 7/129 (5.4) | 4/123 (3.3) |
| Normal to borderline/high | <200 | ≥200 | 16/83 (19.3) | 10/88 (11.4) | 14/84 (16.7) |
| Combined LDL direct and calculated, fasting | | | | | |
| Normal to high | <100 | ≥160 | 1/38 (2.6) | 0 | 0 |
| Borderline to high | ≥100 and <160 | ≥160 | 7/72 (9.7) | 4/70 (5.7) | 4/58 (6.9) |
| Normal/borderline to high | <160 | ≥160 | 8/110 (7.3) | 4/110 (3.6) | 4/105 (3.8) |
| Normal to borderline/high | <100 | ≥100 | 12/38 (31.6) | 6/40 (15.0) | 13/47 (27.7) |
| Cholesterol HDL | | | | | |
| Normal to low | ≥40 | <40 | 11/125 (8.8) | 14/137 (10.2) | 8/128 (6.3) |
| Triglycerides, fasting | | | | | |
| Normal to high | <150 | ≥200 | 3/82 (3.7) | 4/89 (4.5) | 5/88 (5.7) |
| Normal to very high | <150 | ≥500 | 0 | 0 | 0 |
| Borderline to high | ≥150 and <200 | ≥200 | 7/28 (25.0) | 7/17 (41.2) | 14/109 (12.8) |
| Borderline to very high | ≥150 and <200 | ≥500 | 0 | 0 | 0 |
| Normal/borderline to high | <200 | ≥200 | 10/110 (9.1) | 11/106 (10.4) | 14/109 (12.8) |
| Normal/borderline to very high | <200 | ≥500 | 0 | 0 | 0 |
| Normal to borderline/high/ very high | <150 | ≥150 | 8/82 (9.8) | 10/89 (11.2) | 11/88 (12.5) |
| Treatment-emergent triglycerides | | | | | |
| Treatment-emergent very high, fasting | <500 | ≥500 | 0 | 0 | 0 |
| Treatment-emergent very high, non-fasting and random | <500 | ≥500 | 0 | 0 | 0 |
| Treatment-emergent >1000 mg/ dL (all cases) | <1000 | ≥1000 | 0 | 0 | 0 |
| Change in cholesterol | | | | | |
| Change in fasting or non-fasting total cholesterol ≥40 mg/dL | Any value | Increase ≥40 | 13/150 (8.7) | 8/153 (5.2) | 9/145 (6.2) |
| Change in fasting LDL cholesterol ≥30 mg/dL | Any value | Increase ≥30 | 12/129 (9.3) | 11/126 (9.3) | 7/120 (5.8) |
| Change in fasting or non-fasting HDL cholesterol ≥20 mg/dL | Any value | Decrease ≥20 | 4/150 (2.7) | 1/153 (0.7) | 3/145 (2.1) |
| Change in fasting triglycerides ≥50 mg/dL | Any value | Increase ≥50 | 17/131 (13.0) | 20/136 (15.9) | 17/120 (14.2) |

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number of patients who met the criterion; N, total number of patients in the safety population; N1, number of patients with baseline meeting the baseline criteria and with at least one nonmissing postbaseline value during the double-blind treatment period.

was observed with MADRS remission rates: 26%, 26%, and 20% for 1.5, 3.0 mg/day, and placebo respectively. Rates of HAMD-17 remission were significantly improved with cariprazine 1.5 mg/day (31%), but not with 3.0 mg/day (23%) compared to placebo (16%). The planned effect size in the current trial was assumed = 0.36, based on the initial positive Phase 3 trial of cariprazine for treatment of bipolar I depression,[22] which reported actual effect sizes of 0.20, 0.43, and 0.26 for cariprazine 0.75 mg/day vs placebo, cariprazine 1.5 mg/day vs placebo, and cariprazine 3.0 mg/day vs placebo respectively. The actual effect size for cariprazine 1.5 mg/

**TABLE 5** Changes from baseline and incidence of other safety parameters (safety population, double-blind phase)

| | | | | Cariprazine | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo (N = 165) | | | 1.5 mg/d (N = 167) | | | 3.0 mg/d (N = 158) | | |
| Parameter | N | Mean | SD | N | Mean | SD | N | Mean | SD |
| Liver function | | | | | | | | | |
| Alanine aminotransferase, U/L | 149 | 1.3 | 9.6 | 152 | 1.2 | 9.0 | 145 | 0.5 | 8.9 |
| Aspartate aminotransferase, U/L | 149 | 1.6 | 15.3 | 152 | −0.1 | 6.7 | 145 | 0.2 | 5.8 |
| Total bilirubin, mg/dL | 149 | −0.006 | 0.167 | 152 | −0.018 | 0.146 | 145 | 0.001 | 0.156 |
| Metabolic parameters | | | | | | | | | |
| HDL cholesterol, mg/dL | 149 | −0.430 | 10.308 | 152 | −0.704 | 8.980 | 145 | 0.634 | 10.815 |
| LDL cholesterol, mg/dL[a] | 149 | 0.577 | 28.950 | 152 | −9.711 | 25.033 | 145 | −7.317 | 24.899 |
| Total cholesterol, mg/dL | 149 | −1.040 | 31.607 | 152 | −9.237 | 28.991 | 145 | −5.428 | 29.546 |
| Fasting triglycerides, mg/dL | 129 | −4.806 | 51.763 | 124 | 8.702 | 53.013 | 120 | 0.842 | 56.659 |
| Fasting glucose, mg/dL | 128 | 1.992 | 14.317 | 123 | 2.984 | 13.592 | 118 | 3.983 | 13.751 |
| Chemistry parameters | | | | | | | | | |
| Creatinine, mg/dL | 149 | 0.02 | 0.19 | 152 | 0.06 | 0.84 | 145 | 0.02 | 0.11 |
| Vital signs | | | | | | | | | |
| Systolic blood pressure, mm Hg[b] | 163 | 0.3 | 9.5 | 165 | −0.3 | 10.0 | 155 | 0.7 | 9.0 |
| Diastolic blood pressure, mm Hg[b] | 163 | 0.6 | 7.4 | 165 | 0.1 | 7.3 | 155 | 0.1 | 8.0 |
| Pulse rate, bpm[b] | 163 | −0.1 | 10.2 | 165 | −0.6 | 9.2 | 155 | −0.3 | 8.9 |
| Body weight, kg | 163 | −0.2 | 2.0 | 165 | 0.5 | 2.4 | 155 | 0.0 | 2.2 |
| Waist circumference, cm | 154 | −0.3 | 2.8 | 157 | 0.2 | 3.3 | 148 | 0.0 | 3.5 |
| **Other safety outcomes** | n/N1[c] | | % | n/N1[c] | | % | n/N1[c] | | % |
| Treatment-emergent parkinsonism (SAS rating)[d] | 1/163 | | 0.6 | 3/165 | | 1.8 | 4/155 | | 2.6 |
| Treatment-emergent akathisia (BARS rating)[e] | 5/163 | | 3.1 | 9/165 | | 5.5 | 17/155 | | 11.0 |
| Treatment-emergent mania (YMRS rating)[f] | 2/158 | | 1.3 | 2/162 | | 1.2 | 0 | | |

Abbreviations: BARS, Barnes Akathisia Rating Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SAS, Simpson-Angus Scale; YMRS, Young Mania Rating Scale.

[a]LDL direct and LDL calculated are combined.
[b]Value recorded in supine position.
[c]n/N1 = number of patients who met criteria during double-blind treatment/total number of patients with ≥1 postbaseline assessment of interest.
[d]SAS ≤3 at baseline and >3 postbaseline.
[e]BARS ≤2 at baseline and >2 postbaseline.
[f]YMRS total score ≥16 or greater at any visit.

day was 0.28 in both the previous and current trials (both positive), but the effect size of 0.20 for cariprazine 3.0 mg/day in the current study was lower than the effect size of 0.34 in the previous positive trial.[16] Although the Cohen's 'd' effect size of 0.28 is in the range generally considered small to medium, the treatment group difference in MADRS was −2.5 points and a between-group MADRS difference of more than 1.6 to 1.9 is considered clinically significant in studies of MDD.[47]

Pharmacological agents currently approved by the FDA for treatment of acute bipolar I depression include quetiapine,[11] olanzapine/fluoxetine combination,[13] lurasidone,[12] and cariprazine,[14] but notably not all atypical antipsychotics have demonstrated efficacy in

treatment of bipolar I depression compared with placebo (eg, aripiprazole[48] and ziprasidone).[45] The differential efficacy of approved agents and cariprazine with aripiprazole and ziprasidone may be explained by distinct mechanisms of action for different class members. Interestingly, studies have reported weight gain and metabolic abnormalities associated with quetiapine and olanzapine, but cariprazine, like lurasidone,[37] demonstrated a low propensity for these complications in the current and previous studies.[22,23] Cariprazine-treated patients in this study had a mean weight increase of 0.5 kg or less from baseline, and less than 2% of patients experienced a weight gain ≥7% of their body weight. Metabolic parameters and shifts into abnormal range were small and not judged to be clinically relevant. Mean

fasting serum glucose level changes from baseline were increased with cariprazine treatment compared to placebo, but due to the large overlapping standard deviations are not believed to be clinically significant. The overall metabolic results are particularly significant in this patient population because bipolar I disorder and treatment with atypical antipsychotics both increase the risk of comorbid physical conditions including being clinically overweight/obese, diabetes, metabolic disorders, and cardiovascular disease.[49] Of note, obesity has been shown to be associated with decreases in cognitive ability[50] and medication adherence may be negatively affected in patients who experience metabolic disruptions or weight gain.[51]

Overall rates of treatment-emergent AEs were comparable in each treatment group. Rates of discontinuation due to AEs were similar among placebo and cariprazine 1.5 mg/day but were slightly higher for cariprazine 3.0 mg/day. Overall completion rates were comparable among groups and exceeded 80% for treatment, higher than reported in other studies of atypical antipsychotic efficacy in treatment of bipolar I depression studies (completion rates: 48%-80%),[3,22,36-42] which may in part be attributed to the gradual dose titration methodology used as well as tolerability of the study medication. Akathisia rates in cariprazine groups were higher than placebo and increased with increasing dose (1.8%, 5.4%, and 9.5% for placebo, cariprazine 1.5, and 3.0 mg/day, respectively); this dose-dependent relationship is similar to that observed in lurasidone bipolar depression trials (2.4%, 7.9%, and 10.8% for placebo, lurasidone 20-60, and 80-120 mg/day respectively).[37] This is consistent with the observation that among the atypical agents used for treatment of bipolar depression, cariprazine and lurasidone are the class members most likely to cause EPS.[52] Rates of treatment-emergent mania were low and similar to placebo in cariprazine treated groups, which indicates that cariprazine is not associated with destabilization of mood or manic switch in patients with bipolar I disorder and a current depressive episode. Cariprazine is approved by the FDA for treatment of manic and mixed episodes, without inducing depression,[53] and the present study shows that it is efficacious in treating symptoms of bipolar I depression without inducing mania, indicating that cariprazine may be uniquely suited to treat both poles of the disorder.

Interpretation of these results is limited by the relatively short treatment duration and lack of active comparator. The fixed-dose design prevents the assessment of the efficacy and tolerability of cariprazine at additional doses. The exclusion of patients with most psychiatric comorbidities, including suicidality, prevents the generalizability to these patients.

In conclusion, cariprazine 1.5 mg/day showed statistically significant improvement on MADRS total score (primary measure) and CGI-S score (secondary measure) changes from baseline compared to placebo, but differences were not significant for cariprazine 3.0 mg/day. A previous identically designed study showed significant reduction of depressive symptoms in patients with bipolar I disorder at both the 1.5 and 3.0 mg/day doses. Given the prior results, cariprazine at both doses are recommended for treatment of patients with bipolar I depression, and selection of the appropriate dose requires the discretion of the healthcare professional and implementation of

titration for the higher dose. No new safety signals were observed at the 1.5 and 3.0 mg/day doses and low rates of weight gain were reported.

## CONFLICT OF INTEREST

Drs Earley, Burgess, Rekeda, and Ms Khan are full-time employees of Allergan. Dr Earley owns stock in Allergan and AstraZeneca. Drs Burgess, Rekeda, and Ms Khan own stock in Allergan. Dr Suppes in the past 36 months has reported grants from National Institute of Mental Health, Sunovion Pharmaceuticals, Elan Pharma International Limited, VA Cooperative Studies Program, Pathway Genomics, Stanley Medical Research Institute, National Institute of Health, Palo Alto Health Sciences, and National Institute on Drug Abuse; consulting fees from Sunovion and Allergan, Inc; honoraria from Medscape Education, Global Medical Education, and CMEology; and royalties from Jones and Bartlett, UpToDate, and Hogrefe Publishing. Dr Tohen has been a consultant or received honoraria from AstraZeneca, Abbott, Bristol-Meyers Squibb, Eli Lily, GlaxoSmithKline, Johnson & Johnson, Alkermes, Otsuka, Roche, Lundbeck, Elan, Merck, Pamlab, Alexza, Forest, Sunovion, and Wyeth. Dr Calabrese has received funding from the Department of Defense, the Health Resources Services Administration, and NIMH; research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, the Cleveland Foundation, Eli Lilly, GlaxoSmithKline, Janssen, NARSAD, Repligen, the Stanley Medical Research Institute, Takeda, and Wyeth; served on advisory boards for Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo, EPI Q, Forest Laboratories, the France Foundation, Gedeon Richter, GlaxoSmithKline, Janssen, Johnson & Johnson, Lundbeck, Merck, Neurosearch, Ortho-McNeil, Otsuka, Pfizer, Repligen, Schering-Plough, Servier, Solvay, Supernus, Synosia, Takeda, and Wyeth; and provided CME lectures supported by AstraZeneca, Bristol-Myers Squibb, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, Merck, Sanofi-Aventis, Schering-Plough, Pfizer, Solvay, and Wyeth.

## DATA AVAILABILITY STATEMENT

Data reported in this manuscript are available within the article. Additional data from the NCT02670551 study can be requested at http://www.allerganclinicaltrials.com/PatientDataRequest.htm.

## ORCID

*Mauricio Tohen* [ID] https://orcid.org/0000-0001-8049-4351

## REFERENCES

1. Judd LL, Akiskal HS, Schettler PJ, et al. Psychosocial disability in the course of bipolar i and ii disorders a prospective, comparative, longitudinal study. *Arch Gen Psychiatry.* 2005;62:1322-1330.

2. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry.* 2002;59:530-537.

3. Calabrese JR, Huffman RF, White RL, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord.* 2008;10:323-333.

4. Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord.* 2007;9:531-535.

5. Bottlender R, Jäger M, Strauss A, Moller HJ. Suicidality in bipolar compared to unipolar depressed inpatients. *Eur Arch Psychiatry Clin Neurosci.* 2000;250:257-261.

6. Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorder relative to subjects with other axis I disorders. *Biol Psychiatry.* 1996;39:896-899.

7. Calabrese JR, Shelton MD, Rapport DJ, Kimmel SE, Elhaj O. Long-term treatment of bipolar disorder with lamotrigine. *J Clin Psych.* 2002;63(Suppl 10):18-22.

8. Thase ME, Sachs GS. Bipolar depression: Pharmacotherapy and related therapeutic strategies. *Biol Psychiatry.* 2000;48:558-572.

9. Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L. Antidepressant-induced manic and cyclic acceleration: A controversy revisited. *Am J Psychiatry.* 1995;152:1130-1138.

10. McGirr A, Vöhringer PA, Ghaemi SN, Lam RW, Yatham LN. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. *The Lancet Psychiatry.* 2016;3(12):1138-1146.

11. Seroquel XR. *(quetiapine fumarate extended-release) [package insert].* Wilmington, DE: AstraZeneca Pharmaceuticals LP. 2013.

12. *Latuda (lurasidone HCL) tablets [package insert].* Marlborough, MA: Sunovion Pharmaceuticals Inc.; 2017.

13. *Zyprexa (olanzapine) [package insert].* Indianapolis, IN: Eli Lilly and Company. 2009.

14. *VRAYLAR (cariprazine) [package insert].* Irvine, CA: Allergan plc; 2019.

15. Fava M, Durgam S, Earley W, et al. Efficacy of adjunctive low-dose cariprazine in major depressive disorder: a randomized, double-blind, placebo-controlled trial. *Int Clin Psychopharmacol.* 2018;33(6):312-321.

16. Durgam S, Earley W, Guo H, et al. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. *J Clin Psychiatry.* 2016;77(3):371-378.

17. Silfstein M, Abi-Dargham A, D'Souza DC, et al. Cariprazine demonstrates high dopamine D3 and D2 receptor occupancy in patients with schizophrenia: a clinical PET study with [11C]-(+)-PHNO. *Neuropsychopharmacology.* 2013;38(S2):S520.

18. Kiss B, Horti F, Bobok A. In vitro and in vivo comparison of [(3)H](+)-PHNO and [(3)H]raclopride binding to rat striatum and lobes 9 and 10 of the cerebellum: a method to distinguish dopamine D(3) from D(2) receptor sites. *Synapse.* 2011;65(6):467-478.

19. Papp M, Gruca P, Lasoń-Tyburkiewicz M, Adham N, Kiss B, Gyertyán I. Attenuation of anhedonia by cariprazine in the chronic mild stress model of depression. *Behav Pharmacol.* 2014;25:567-574.

20. Duman RS, Duric V, Banasr M, Adham N, Kiss B, Gyertyan I. Cariprazine exhibits dopamine D3 receptor-dependent antidepressant-like activity in the chronic unpredictable stress model

of anhedonia. 51st Annual Meeting of the American College of Neuropsychopharmacology; December 2–6, 2012; Hollywood, Florida. 2012.

21. Marder S, Laszlovszky I, Szalai E, et al. Efficacy of cariprazine on predominant negative symptoms of patients with schizophrenia: post hoc analysis of PANSS data, Marder factors, and cognition. *Eur Neuropsychopharmacol.* 2016;26:S550.

22. Durgam S, Earley W, Lipschitz A, et al. An 8-Week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. *Am J Psychiatry.* 2016;173(3):271-281.

23. Earley W, Burgess MV, Rekeda L, et al. Cariprazine treatment of bipolar depression: A randomized, double blind, placebo-controlled phase 3 study. *Am J Psychiatry.* 2019;176(6):439-448.

24. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 5th edn. Arlington, VA: American Psychiatric Publishing; 2013.

25. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56-62.

26. Guy W. *ECDEU assessment manual for psychopharmacology. US Dept Health, Education, and Welfare Publication (ADM).* Rockville, MD: National Institute of Mental Health; 1976:218-222.

27. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity, and sensitivity. *Br J Psychiatry.* 1978;133:429-435.

28. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry.* 2011;168(12):1266-1277.

29. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134(4):382-389.

30. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol.* 1959;32:50-55.

31. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry.* 2003;54(5):573-583.

32. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry.* 1989;154(5):672-676.

33. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl.* 1970;212(45):11-19.

34. Kenward MG, Molenberghs G, Thijs H. Pattern-mixture models with proper time dependence. *Biometrika.* 2003;90:53-71.

35. Chen X, Luo X, Capizzi T. The application of enhanced parallel gatekeeping strategies. *Stat Med.* 2005;24:1385-1397.

36. Calabrese JR, Keck PE, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry.* 2005;162:1351-1360.

37. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry.* 2014;171:160-168.

38. McElroy SL, Weisler RH, Chang W, et al. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry.* 2010;71:163-174.

39. Suppes T, Datto C, Minkwitz M, Nordenhem A, Walker C, Darko D. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. *J Affect Disord.* 2010;121(1–2):106-115.

40. Thase ME, Macfadden W, Weisler RH, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol.* 2006;26(6):600-609.

41. Tohen M, McDonnell DP, Case M, et al. Randomised, double-blind, placebo-controlled study of olanzapine in patients with bipolar I depression. *Br J Psychiatry.* 2012;201(5):376-382.

42. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;50:1079-1088.

43. Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry*. 2010;71:150-162.

44. Yatham LN, Vieta E, Goodwin GM, et al. Agomelatine or placebo as adjunctive therapy to a mood stabiliser in bipolar I depression: randomised double-blind placebo-controlled trial. *Br J Psychiatry*. 2016;208(1):78-86.

45. Lombardo I, Sachs G, Kolluri S, Kremer C, Yang R. Two 6-week, randomized, double-blind, placebo-controlled studies of ziprasidone in outpatients with bipolar I depression: did baseline characteristics impact trial outcome? *J Clin Psychopharmacol*. 2012;32(4):470-478.

46. Sachs GS, Ice KS, Chappell PB, et al. Efficacy and safety of adjunctive oral ziprasidone for acute treatment of depression in patients with bipolar I disorder: A randomized, double-blind, placebo-controlled trial. *J Clin Psych*. 2011;72(10):1413-1422.

47. Masson SC, Tejani AM. Minimum clinically important differences identified for commonly used depression rating scales. *J Clin Epidemiol*. 2013;66(7):805-807.

48. Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. *J Clin Psychopharmacol*. 2008;28:13-20.

49. Correll CU, Frederickson AM, Kane JM, Manu P. Equally increased risk for metabolic syndrome in patients with bipolar disorder and schizophrenia treated with second-generation antipsychotics. *Bipolar Disord*. 2008;10:788-797.

50. Depp CA, Strassnig M, Mausbach BT, et al. Association of obesity and treated hypertension and diabetes with cognitive ability in bipolar disorder and schizophrenia. *Bipolar Disord*. 2014;16(4):422-431.

51. Kemp DE. Managing the side effects associated with commonly used treatments for bipolar depression. *J Affect Disord*. 2014;169:S34-S44.

52. Orsolini L, Tomasetti C, Valchera A, et al. An update of safety of clinically used atypical antipsychotics. *Expert Opin Drug Saf*. 2016;15(10):1329-1347.

53. Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, Phase III trial. *J Affect Disord*. 2015;174:296-302.