Evaluation of cariprazine in the treatment of bipolar I and II depression: a randomized, double-blind, placebo-controlled, phase 2 trial

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This double-blind placebo-controlled, fixed/flexible-dose phase 2 trial assessed the efficacy, safety, and tolerability of cariprazine vs. placebo for depressive episodes associated with bipolar I or II disorder. Primary endpoint was change in Montgomery–Åsberg Depression Rating Scale (MADRS) total scores (baseline to week 8), and secondary endpoint was mean Clinical Global Impressions-Improvement score (week 8). Patients were randomized (*N*=233) 1:1:1 to placebo, 'low-dose' 0.25–0.5 mg/day or 'high-dose' 1.5–3.0 mg/day cariprazine. Adverse events, laboratory results, vital signs, extrapyramidal symptoms, and suicide risk were monitored. Neither cariprazine group significantly separated from placebo in primary (mixed-effect model repeated measures MADRS least-squares mean differences: low-dose=−0.7, *P*=0.7408; high-dose=0.0, *P*=0.9961) or secondary efficacy measures. No new safety signals with cariprazine were observed and common treatment-emergent adverse events (≥5% of cariprazine patients and twice the rate of placebo) included insomnia, akathisia, dry mouth, nausea, weight increased, diarrhea, restlessness, vomiting, musculoskeletal stiffness, migraine, and cough. Metabolic and weight changes were generally similar for cariprazine and placebo. Factors that may have affected the outcome of the trial were identified, which helped to inform the design and conduct of subsequent phase 2b/3 clinical trials of cariprazine in bipolar depression. *Int Clin Psychopharmacol* 35: 147–156

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Introduction

Acute and chronic major depressive episodes, subsyndromal depressive symptoms, and dysphoria with mixed features comprise the majority of time spent unwell for patients with bipolar I or bipolar II disorder (Kupka *et al.*, 2007). Episodes of depression are associated with increased rates of complications, including disability, morbidity, and suicide (Chen and Dilsaver, 1996; Bottlender *et al.*, 2000). Despite being a highly debilitating condition associated with significant psychiatric and medical comorbidities (Baldessarini *et al.*, 2010), depressive episodes associated with bipolar disorder are less understood than manic or hypomanic episodes and relatively few pharmacologic agents with proven treatment efficacy exist for their treatment (Post, 2012, 2016; Yatham *et al.*, 2018). Traditional antidepressants continue to be commonly used for the treatment of depressive episodes despite limited empirical evidence indicating their efficacy, and availability of evidence suggesting their use may induce a switch to hypomanic, manic, or mixed features episode when used long term or intensify disease severity by increasing mood cycle frequency (Pacchiarotti *et al.*, 2013; McGirr *et al.*, 2016).

Dopamine receptor modulators are efficacious as a class treatment of bipolar mania, but currently, only olanzapine-fluoxetine combination (SYMBYAX, 2009), quetiapine (Seroquel, 2013), cariprazine (Vraylar, 2019), and lurasidone (LATUDA, 2017) have obtained regulatory approval as first-line treatment options for acute bipolar depression. Unlike the other agents that show low or negligible affinity for D_3 receptors (Graff-Guerrero *et al.*, 2009; Mizrahi *et al.*, 2011), cariprazine exhibits preferential binding to D_3 receptors (Kiss *et al.*, 2010) and also has high affinity for serotonin 5-HT_{1A} receptors in preclinical models (Blier *et al.*, 1997). Presumably, through these interactions, cariprazine enhances cognition (Marder *et al.*, 2016), mood, and measures of reward, and reduces anhedonia in patients with schizophrenia (Gross and Drescher, 2012; Nakajima *et al.*, 2013; Papp *et al.*, 2014). Cariprazine is FDA-approved for the treatment of adults

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with schizophrenia as well as acute manic, acute mixed, or depressive episodes associated with bipolar I disorder and is under investigation for the treatment of major depressive disorder (MDD).

A clinical trial program systematically assessed the efficacy of cariprazine in the treatment of depressive episodes associated with bipolar disorder. To date, three phase 2b/3 trials (Durgam *et al.*, 2016; Earley et al., 2019a,b) reported on the efficacy of cariprazine in treatment of bipolar I depression. This is the first study to evaluate the efficacy, safety, and tolerability of flexible-dose ranges of cariprazine in the treatment of depressive episodes in patients with either bipolar I or II disorder.

Methods

This phase 2 study (protocol MD-52) was conducted from June 2009 to June 2010 in 26 centers in the USA (NCT00852202). The Institutional Review Board at each study center approved the study protocol and amendments. All patients were recruited and screened in compliance with the International Conference on Harmonization Good Clinical Practice Guideline and the Declaration of Helsinki and provided written consent after receiving a complete study description and prior to any study participation.

Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adult patients with bipolar I or II depression, which assessed two flexible dosages of cariprazine ('low-dose': 0.25–0.75 mg/day and 'high-dose': 1.5–3.0 mg/day) compared with placebo. The double-blind treatment period was 8 weeks, which was preceded by ≥1-week drug washout period and followed by a 2-week safety follow-up (no study medication). Eligible patients were randomized 1:1:1 to placebo, low-dose, or high-dose cariprazine using an interactive voice/web response system that assigned randomization and treatment allocation codes matching codes on the blinded medication packages. Patients, investigators, and study site personnel were blinded to allocation and treatment assignment; blinding was maintained throughout and until completion of the study.

All investigational products provided by the Sponsor were identical in appearance and packaging, with codes corresponding to treatment allocation; patients were instructed to take the investigational product once daily consistently in either the morning or evening. Patients in the low-dose cariprazine group received the 0.25 mg/day dose during weeks 1–4. Patients in the high-dose cariprazine group were titrated from 0.5 to 1.5 mg/day during the first week, and then continued 1.5 mg/day. After week 4, the dose was increased to the higher dose (0.75 mg/day for low-dose group or 3.0 mg/day for high-dose group) if the response determined to be inadequate [<40% improvement from baseline in Montgomery–Åsberg Depression Rating Scale (MADRS) total score] (Montgomery and Åsberg, 1979). After week 4, a dose decrease was allowed up to week 6, but no dose adjustments were allowed during the first four or final two weeks of the double-blind treatment period.

Patients

Adult outpatients (18–65 years of age) with a principal diagnosis of bipolar I or II disorder using the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (APA, 2000) criteria without psychotic features and with a current major depressive episode of ≥4 weeks and ≤12 months, <8 episodes of a mood disturbance (depression, mania, hypomania, or mixed state) in the previous 12 months, and having at least one verified manic, hypomanic, or mixed episode were included in the study. Enrollment criteria also included scores of ≥20 on the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) (Hamilton, 1960), ≥2 on Item 1 of the 24-item HAMD ($HAMD_{24}$) rating scale, and ≤12 on the Young Mania Rating Scale (YMRS) (Young *et al.*, 1978). A physical examination, clinical laboratory, and electrocardiogram (ECG) with no significant clinical results (as judged by investigators) were also required. Additional inclusion/exclusion criteria and permitted psychotropic medications are listed in Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/ICP/A74*.

Efficacy

Efficacy was assessed by the change from baseline to week 8 in MADRS total score (primary) and Clinical Global Impressions – Improvement (CGI-I) score (secondary). Additional efficacy parameters included changes from baseline to week 8 scores on the Clinical Global Impressions – Severity (CGI-S) (Guy, 1976), $HAMD_{24}$ and $HAMD_{17}$ scales, and rates of MADRS response (≥50% reduction from baseline in total score), MADRS remission (score ≤ 10), CGI-I response (score ≤ 2), and $HAMD_{17}$ remission (total score ≤ 7) at week 8.

Safety

Safety assessments included adverse event reporting (at every visit), clinical laboratory evaluations (at screening and end of study), and ECGs (at screening, weeks 1, 4 and 8). Safety assessments conducted at baseline and at each double-blind study visit included vital signs, mania (using YMRS) (Young *et al.*, 1978), and extrapyramidal symptoms (EPS) [Barnes Akathisia Rating Scale (BARS) (Barnes, 1989), the Abnormal Involuntary Movement Scale, and the Simpson–Angus Scale (SAS) (Simpson and Angus, 1970)]. Suicide risk was monitored at every visit using the Columbia-Suicide Severity Rating Scale (Posner *et al.*, 2011).

Data analyses

Efficacy analyses were performed on the intent-to-treat population (patients who took at least one dose of

investigational product and had at least one postbaseline MADRS assessment). MADRS total score changes from baseline to week 8 were analyzed by mixed-effects model for repeated measures (MMRMs) with treatment group, study center, visit, and treatment group-by-visit as covariates. Primary MADRS score comparison was between placebo and the average of the low- and high-dose cariprazine groups. If positive, a pairwise comparison between placebo and each cariprazine group was to be tested; this is a process for controlling for multiple comparisons. Two sensitivity analyses, using last-observation carried forward (LOCF) and observed cases approach, were performed on the primary efficacy parameter. An analysis-of-covariance model with treatment group and study center as factors and baseline MADRS total score as a covariate were used for both sensitivity analyses.

Analyses of the secondary outcome and additional continuous variables were each conducted using an MMRM method that was similar to the primary comparison, using the respective baseline scores as covariates. Analyses of categorical variables (response and remission rates) were done using a logistic regression model with treatment group and the corresponding baseline score as explanatory variables. All statistical analyses were performed using version 9.1.3 of Statistical Analysis Software (SAS Institute; Cary, North Carolina, USA).

Safety analyses were based on the safety population (randomized patients who took at least one dose of investigational product). For each safety parameter, the last assessment before the first dose of double-blind study medication was used as baseline; continuous variables were summarized by number of patients, mean, and SD, and categorical variables were summarized by number and percentage of patients.

Sample size

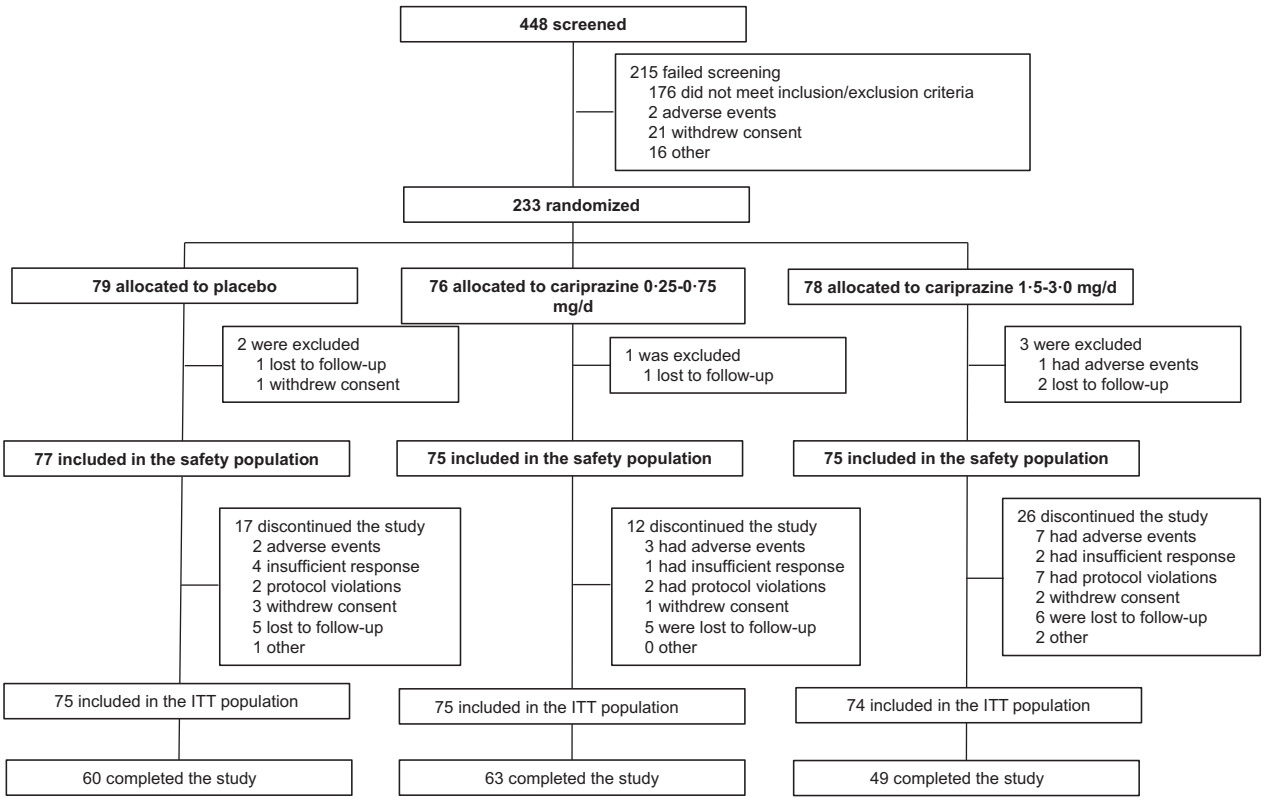
The sample size was determined by calculating that 75 patients per arm would provide 85% power to detect a treatment difference of 3.8 points in the primary efficacy parameter between the placebo group and the average of the two cariprazine treatment groups at the two-sided, 5% significance level, assuming a common SD of 8 for the primary efficacy parameter, a correlation coefficient of 0.5 for within-patient assessments, and a 30% patient drop-out rate.

Results

Patient disposition and demographics

Of 448 patients screened, 233 were randomized (Fig. 1). Of 227 patients in the safety population, 172 (75.8%) completed the study (placebo = 77.9%; low-dose cariprazine = 84.0%; high-dose cariprazine = 65.3%). 'Lost to

Fig. 1



CONSORT flow diagram for study patients.

Table 1 Patient characteristics at baseline in the safety population

	Cariprazine groups		
	Placebo group (*N*=77)	0.25–0.75 mg/day (*N*=75)	1.5–3.0 mg/day (*N*=75)
Demographic characteristics			
Age, years, mean (SD)	40.6 (10.7)	37.4 (10.7)	38.9 (11.2)
Female, *n* (%)	46 (59.7)	48 (64.0)	51 (68.0)
Race, *n* (%)			
Caucasian	54 (70.1)	56 (74.7)	62 (82.7)
Non-Caucasian	23 (29.9)	19 (25.3)	13 (17.3)
Bipolar disorder history			
Bipolar I, *n* (%); Bipolar II, *n* (%)	53 (68.8); 24 (31.2)	57 (76.0); 18 (24.0)	55 (73.3); 20 (26.7)
Number of depressive episodes, mean (SD)	17.4 (19.9)	14.8 (14.4)	16.1 (18.5)
Number of hypomanic, manic and mixed episodes, mean (SD)	16.6 (21.7)	10.7 (11.8)	16.2 (22.5)
Duration of bipolar disorder, years, mean (SD)	16.0 (10.3)	15.5 (9.7)	17.7 (10.5)
Duration of current depressive episode, months, mean (SD)	4.4 (3.1)	4.0 (3.0)	7.3 (26.0)
Baseline Rating Scale Scores, mean, SD			
MADRS	30.0 (5.0)	30.2 (5.0)	31.0 (4.6)
YMRS	6.1 (3.2)	6.1 (3.4)	6.0 (3.4)

MADRS, Montgomery–Åsberg Depression Rating Scale; *N*, number of patients in the Safety Population; *n*, number of patients in category; YMRS, Young Mania Rating Scale.

follow-up' was among the most common reasons for discontinuation in each treatment group, along with adverse events and protocol violations in the high-dose cariprazine group. Baseline demographics, clinical history, and baseline assessment scores were similar across treatment groups (Table 1). The majority of patients (72.7%) were diagnosed with bipolar I disorder. Mean baseline MADRS and YMRS scores of ~30.5 and ~6.1, respectively, suggested the patient population was moderately depressed on average, with low levels of mania (Snaith *et al.*, 1986; Berk *et al.*, 2008).

Efficacy

Primary efficacy parameter

MADRS scores were not significantly improved from baseline to week 8 compared with placebo for the average of the combined low- and high-dose cariprazine groups [least-squares mean difference (LSMD) = –0.3, 95% confidence interval (CI) = –3.8, 3.2; $P = 0.8522$]. Similarly, the improvement in MADRS total scores from baseline to week 8 was not appreciably different relative to placebo in low-dose cariprazine (LSMD = –0.7, 95% CI = –4.6, 3.3; $P = 0.7408$) or high-dose cariprazine groups (LSMD = 0.0, 95% CI = –4.1, 4.1, $P = 0.9961$) (Fig. 2).

Secondary and additional efficacy parameters

No significant difference between groups was observed in mean CGI-I scores at week 8, with a mean score of 2.1 points for all treatment groups. Additional efficacy parameters were also similar across treatment groups, with no significant differences between groups (Table 2).

Exploratory analysis of efficacy

To evaluate the influence of placebo response on the results, a band-pass filter analysis was conducted, which excluded patient data from study centers with >50% MADRS response rates in the placebo group. The band-pass filter analysis used MMRM with an unstructured covariance matrix using treatment group, pooled center, visit, and treatment group-by-visit interaction as factors, and baseline plus baseline-by-visit interaction as covariates. The data at week 6 were chosen for analysis as it has been suggested that treatment effect vs. placebo may be greater at 4–6 weeks than at week 8. In the band-pass analysis, significant differences vs. placebo were observed for both the low-dose cariprazine (LSMD = –5.0, 95% CI = –9.61, –0.48; $P < 0.05$) and high-dose cariprazine groups (LSMD = –5.2, 95% CI = –9.81, –0.52, $P < 0.05$) (Supplementary Fig. 1, Supplemental digital content 2, *http://links.lww.com/ICP/A75*).

Safety

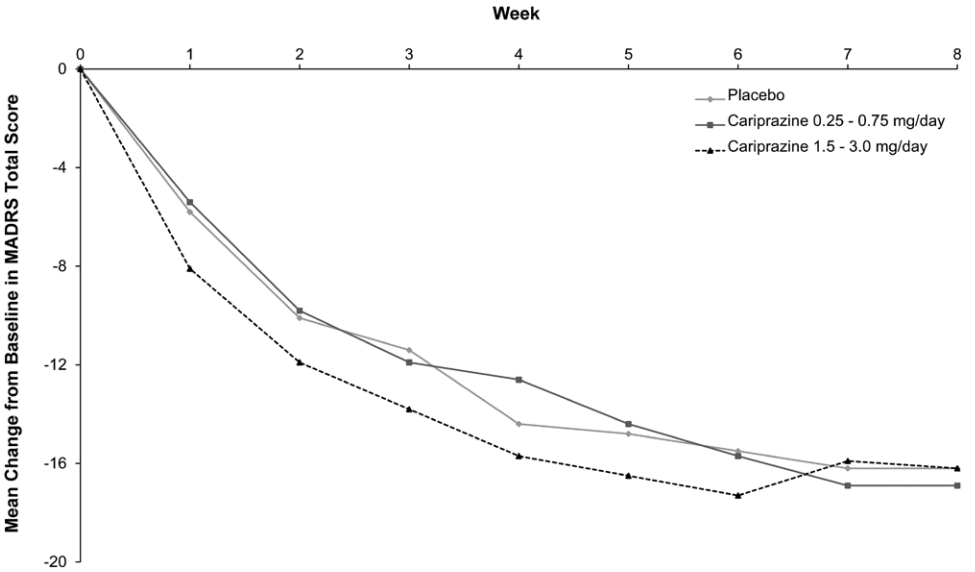
Extent of exposure

Median duration of treatment was similar across treatment groups (55–56 days) with a mean (SD) mg/day dose of 0.35 (0.12) and 1.52 (0.42) in the low-dose and high-dose cariprazine groups, respectively. Dose increases were administered in 38% of placebo, 45% of low-dose cariprazine, and 31% of high-dose cariprazine groups.

Adverse events

Overall treatment-emergent adverse events (TEAEs) were reported in similar percentages across all treatment groups (Table 3); however, adverse events leading to treatment discontinuation occurred more frequently in the high-dose group (9.3%) than in the placebo (2.6%) or low-dose cariprazine group (4.0%). Two patients each prematurely discontinued from the study due to suicidal ideation (high-dose cariprazine group), mania (low-dose cariprazine group), bipolar I disorder (high-dose cariprazine group), and depression (placebo and high-dose cariprazine groups). No premature discontinuations were due to EPS-associated TEAEs.

Fig. 2



Mean change from baseline in MADRS total score (MMRM, ITT population). ITT, intent to treat; MADRS, Montgomery–Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

Common TEAEs among both cariprazine groups occurring in ≥5% of patients and at least twice the rate of placebo included insomnia, akathisia, dry mouth, nausea, weight increased, diarrhea, restlessness, vomiting, musculoskeletal stiffness, migraine, and cough. Akathisia was reported in 17% of high-dose cariprazine, 3% of low-dose cariprazine, and 4% of placebo groups. TEAEs considered related to treatment occurred in 53, 55, and 69% of patients in the placebo, the low-, and high-dose cariprazine groups, respectively. Most adverse events were judged to be mild to moderate in intensity. Serious adverse events related to treatment occurred in six patients during the double-blind treatment period and were bipolar disorder and suicidal ideation (placebo), suicide attempt and spontaneous abortion (low-dose cariprazine), and bipolar I disorder and suicidal ideation (high-dose cariprazine). One death, a suicide in the placebo group, occurred 20 days after being lost to follow-up but was considered unrelated to treatment. Suicidal ideation (of the lowest severity classification) was reported by ~20% of patients in each cariprazine group and 12% of patients in the placebo group, and suicidal behavior was reported in one patient in the low-dose cariprazine group.

Treatment-emergent mania

Mean decrease in YMRS scores was similar across treatment groups with a score change of −2.1, −1.3, and −1.9 for placebo, low-dose cariprazine, and high-dose cariprazine, respectively. Treatment-emergent mania (postbaseline YMRS total score ≥ 16) was reported in 10, 8, and 15% of patients in the placebo, low-dose cariprazine, and high-dose cariprazine groups, respectively.

Clinical parameters

Changes in clinical laboratory values, vital signs, and ECGs were unremarkable, with a low incidence of potentially clinically significant values across treatment groups (Table 4). Changes in clinical laboratory values and vital sign parameters were similar across treatment groups (Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/ICP/A74*); however, changes in alanine aminotransferase and prolactin values were slightly higher in both cariprazine groups compared with placebo group. Mean (SD) kg weight changes were +0.30 (2.16), +0.62 (2.76), and +1.42 (2.93) in the placebo, low-dose cariprazine and high-dose cariprazine groups, respectively. Weight increases ≥7% of body weight occurred in 5% of the low-dose cariprazine and 7% of high-dose cariprazine groups.

Discussion

This exploratory phase 2 trial in patients with bipolar I or bipolar II depression failed to detect statistically significant differences between cariprazine and placebo on any prospectively defined efficacy outcomes. The results of this study are discordant with results from other trials evaluating dopamine receptor modulators, including quetiapine (Calabrese *et al.*, 2005; Thase *et al.*, 2006), lurasidone (Loebel *et al.*, 2014), and olanzapine (Tohen *et al.*, 2012), which all demonstrated efficacy for the treatment

Table 2 Secondary and additional efficacy outcomes at week 8 in the (ITT) population

		Cariprazine groups		
	Placebo group (n=75)	0.25–0.75 mg/day (n=75)	1.5–3.0 mg/day (n=74)	Cariprazine average – placebo[a]
Primary efficacy parameter: MADRS total score change at week 8, MMRM				
Baseline mean±SEM	29.9±0.6	30.2±0.6	30.9±0.5	–
Change mean±SEM	−16.6±1.5	−16.8±1.3	−16.1±1.6	–
LSMD vs. placebo (95% CI)	–	−0.7 (−4.6, 3.3)	0.0 (−4.1, 4.1)	−0.3 (−3.8, 3.2)
P value[b]	–	0.7408	0.9961	0.8522
Secondary efficacy parameter: CGI-I score at week 8, MMRM				
Mean±SEM	2.1±0.1	2.1±0.1	2.1±0.2	–
LSMD vs. placebo (95% CI)	–	−0.1 (−0.6, 0.3)	−0.2 (−0.6, 0.3)	–
P value[b]	–	0.5681	0.4539	–
Additional efficacy parameters				
CGI-S score change at week 8, MMRM				
Baseline, mean±SEM	4.3±0.1	4.4±0.1	4.4±0.1	–
Change at week 8, mean±SEM	−1.8±0.2	−1.7±0.2	−1.8±0.2	–
LSMD vs. placebo (95% CI)	–	0.0 (−0.4, 0.5)	−0.1 (−0.5, 0.4)	−0.0 (−0.4, 0.4)
P value[b]	–	0.9167	0.7138	0.8773
$HAMD_{24}$ total score change at week 8, MMRM				
Baseline, mean±SEM	29.4±0.5	30.2±0.5	30.0±0.5	–
Change at week 8, mean±SEM	−16.5±1.4	−17.0±1.2	−16.6±1.3	–
LSMD vs. placebo (95% CI)	–	−0.5 (−4.1, 3.0)	−0.2 (−3.8, 3.4)	−0.4 (−3.5, 2.7)
P value[b]	–	0.7642	0.9201	0.8178
$HAMD_{17}$ total score change at week 8, MMRM				
Baseline, mean±SEM	23.3±0.3	23.8±0.4	23.8±0.3	–
Change at week 8, mean±SEM	−13.0±1.1	−13.0±0.9	−12.7±1.1	–
LSMD vs. placebo (95% CI)	–	−0.2 (−2.9, 2.5)	0.2 (−2.6, 3.0)	0.0 (−2.4, 2.4)
P value	–	0.8936	0.8891	0.9962
MADRS response (≥50% reduction from baseline at week 8), LOCF				
Responders, $n/N1$ (%)[c]	37/75 (49.3)	42/75 (56.0)	40/74 (54.1)	–
Odds ratio vs. placebo (95% CI)	–	1.32 (0.69, 2.51)	1.25 (0.65, 2.38)	–
P value[c]	–	0.4026	0.5066	–
MADRS remission (MADRS total score ≤10 at week 8), LOCF				
Remitters, $n/N1$ (%)[c]	29/75 (38.7)	36/75 (48.0)	32/74 (43.2)	–
Odds ratio vs. placebo (95% CI)	–	1.50 (0.78, 2.88)	1.29 (0.66, 2.51)	–
P value[c]	–	0.2298	0.4512	
CGI-I response (CGI-I score ≤2 at week 8), LOCF				
Responders, $n/N1$ (%)[c]	41/57 (54.7)	48/75 (64.0)	42/74 (56.8)	–
Odds ratio vs. placebo (95% CI)	–	1.53 (0.79, 2.96)	1.12 (0.58, 2.14)	–
P value[c]	–	0.2076	0.7422	–
$HAMD_{17}$ remission ($HAMD_{17}$ total score ≤7 at week 8), LOCF				
Responders, $n/N1$ (%)[d]	28/75 (37.3)	30/75 (40.0)	28/74 (37.8)	–
Odds ratio vs. placebo (95% CI)	–	1.16 (0.60, 2.24)	1.06 (0.54, 2.06)	–
P value[c]	–	0.6681	0.8710	–

CGI-I, Clinical Global Impressions – Improvement; CGI-S, Clinical Global Impression-Severity; CI, confidence interval; HAMD, Hamilton Depression Rating Scale, ITT, Intent-to-treat; LOCF, last observation carried forward; LSMD, least squares mean difference; MADRS, Montgomery–Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

[a]P values are based upon a comparison of the average effect of cariprazine 0.25–0.75 mg/day and cariprazine 1.5–3.0 mg/day with that of placebo.

[b]P values are from an MMRM model with treatment group, pooled study center, visit, and treatment group-by-visit interaction as factors, and baseline value and baseline-by-visit interaction as the covariates.

[c]P values were based on a logistic regression model with treatment group and corresponding baseline scores as explanatory variables.

[d]n, number of patients in category; $N1$, number of patients available for analysis at a specific time point in the ITT population.

of bipolar depression. Learnings from the present trial, as discussed below, were used to design three subsequent phase 2b/3 randomized controlled trials of cariprazine for the treatment of bipolar I depression, which successfully demonstrated improvement in depressive symptoms with both 1.5 and 3.0 mg/day cariprazine vs. placebo (Durgam *et al.*, 2016; Earley et al., 2019a,b).

In the present trial, a high rate of placebo response was a major confounding factor. Although all four trials had comparable mean baseline MADRS scores (30.0–31.3), the average change from baseline in MADRS total score for placebo patients in the present trial was approximately −16 at week 6 (Fig. 2), while it was much smaller for placebo groups in subsequent positive studies (−11.1 to −12.9) (Durgam *et al.*, 2016; Earley et al., 2019a,b).

The exploratory post-hoc band-pass analysis supports greater efficacy at week 6 and indicates that a high placebo response at some clinical sites may have impaired the ability to detect treatment differences in the total population. Flexible dosing may also have reduced the ability to see differences at later time points. Given the option to increase to a higher dose (including the placebo group, because all patients and investigators were blinded), patients on placebo who did not respond initially may have been given a higher 'dose' later. This could increase the chances of a placebo effect, whereby they report a perceived improvement in symptoms despite only receiving placebo. Even with fixed-dosing, patients who receive placebo may tend to report progressive symptom improvement over time. Evidence of this

Table 3 Summary of adverse events in the safety population

Adverse event summary	Placebo group (*N*=77)	Cariprazine groups	
		0.25–0.75 mg/day (*N*=75)	1.5–3.0 mg/day (*N*=75)
Deaths, *n*	1[a]	0	0
Patients with any TEAEs, *n* (%)	61 (79.2)	59 (78.7)	60 (80.0)
Serious adverse events, *n* (%)	2 (2.6)	2 (2.7)	2 (2.7)
AEs leading to discontinuation, *n* (%)	2 (2.6)	3 (4.0)	7 (9.3)
Common adverse events (≥5% in any treatment group in the double-blind treatment period), *n* (%)			
Insomnia	7 (9)	13 (17)	15 (20)
Akathisia	3 (4)	2 (3)	13 (17)
Headache	10 (13)	11 (15)	12 (16)
Dry mouth	4 (5)	6 (8)	10 (13)
Nausea	3 (4)	9 (12)	9 (12)
Upper respiratory tract infection	8 (10)	8 (11)	8 (11)
Nasopharyngitis	5 (7)	6 (8)	7 (9)
Fatigue	5 (7)	6 (8)	6 (8)
Weight increased	1 (1)	1 (1)	6 (8)
Diarrhea	5 (7)	10 (13)	5 (7)
Anxiety	5 (7)	2 (3)	5 (7)
Restlessness	2 (3)	2 (3)	5 (7)
Vomiting	1 (1)	1 (1)	5 (7)
Musculoskeletal stiffness	0	0	4 (5)
Constipation	4 (5)	5 (7)	3 (4)
Migraine	1 (1)	5 (7)	0
Cough	1 (1)	4 (5)	0

N, number of patients in the safety population; *n*, number of patients with treatment-emergent adverse events; TEAE, treatment-emergent adverse events.
[a]One patient died within 30 days of the last dose of study medication. This patient was entered into the study twice (at different study sites). She first received cariprazine 1.5–3.0 mg/day for 57 days and completed the study. During the last week of participation at the first study site, the patient entered the study again at different sites and received double-blind placebo for 14 days and was lost to follow-up; it was learned that the patient committed suicide 20 days after the last dose of study medication. The death was not considered related to treatment.

Table 4 Potentially clinically significant postbaseline laboratory values in the safety population during the double-blind treatment period

Parameter, Unit		PCS criteria (Unit)	Placebo (*N*=77), *n*/*N*1 (%)[a]	Cariprazine groups	
				0.25–0.75 mg/day (*N*=75), *n*/*N*1 (%)[a]	1.5–3.0 mg/day (*N*=75), *n*/*N*1 (%)[a]
Cholesterol	LDL	≥1.2×ULN (mmol/L)	5/55 (9.1)	3/50 (6.0)	1/53 (1.9)
	Total	>1.3×ULN (mmol/L)	6/64 (9.4)	3/59 (5.1)	1/60 (1.7)
CPK		>1.5×ULN (U/L)	5/65 (7.7)	1/58 (1.7)	1/58 (1.7)
Glucose, fasting		<0.8×LLN (mmol/L)	0/58	0/56	1/55 (1.8)
		>1.2×ULN (mmol/L)	0/58	2/56 (3.6)	0/55
Triglycerides		>1.2×ULN (mmol/L)	1/58 (1.7)	2/52 (3.8)	6/61 (9.8)
Albumin		>1.1×ULN (g/L)	0/70	1/64 (1.6)	0/65
Blood urea nitrogen		>1.2×ULN (mmol/L)	1/70 (1.4)	0/64	0/65
Uric acid (urate)		>1.1×ULN (μmol/L)	2/70 (2.9)	0/63	0/63

No patients had PCS albumin, alkaline phosphatase, ALT, AST, calcium, chloride, total bilirubin, HDL, creatinine, potassium, protein, sodium, eosinophil, hemoglobin, neutrophil, or platelet values.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; LDL, low density lipoprotein; LLN, lower limit of normal; *N*, number of patients in the safety population; PCS, potentially clinically significant; ULN, upper limit of normal.
[a]Percentages are calculated as (*n*/*N*1)×100 (*n*=number of patients who had a non-PCS baseline value and at least one PCS postbaseline value; *N*1=number of patients with a non-PCS value and at least one postbaseline assessment).

was seen in a subsequent fixed-dose trial where symptom improvement began to plateau around 4–6 weeks in the active treatment groups but continued to decline in the placebo group (Durgam *et al.*, 2016).

In retrospect, the study probably did not have sufficient power to detect efficacy given the smaller sample size; the anticipated difference of 3.8 points was overly optimistic, and a more realistic estimate would have been lower. In the subsequent studies of cariprazine in bipolar depression, the average difference was ~2.7 points for the 1.5 and 3 mg groups combined (Saraf *et al.*, 2019). Moreover, the current study included an ineffective low-dose (0.25–0.75 mg) group, which further reduced the expected treatment effect and power. Additionally, approximately one-quarter of the patients in the study population had a bipolar II disorder diagnosis, which may have increased variability and impaired the ability to detect a treatment effect. Nevertheless, this study provided useful information that was used to improve the design and success of subsequent studies of cariprazine. While the primary efficacy analysis did not observe an effect for low-dose cariprazine (0.25–0.75 mg), it did show that high-dose cariprazine (1.5–3.0 mg) had a signal. Subsequent studies used 1.5 or 3.0 mg fixed-doses

were restricted to bipolar I disorder, and were powered with twice as many patients randomized to double-blind treatment.

A high proportion of failures in clinical trials of treatments for depressive symptoms in patients with acute bipolar depression and MDD have presumably resulted from higher than expected rates of placebo response and is recognized as a major impediment to the clinical development of new medications (Khan *et al*., 2003; Yatham *et al*., 2016). Various analyses have shown that antidepressant monotherapy trials with placebo response rates higher than 30% have a low probability of demonstrating statistically significant efficacy for active compounds over placebo (Khan *et al*., 2003; Iovieno and Papakostas, 2012). A post-hoc band-pass filter analysis of the data from this study suggested that both low- and high-dose cariprazine were effective in treating depression if all the data from centers that had >50% placebo response were excluded, confirming that higher placebo response was a major contributor to the failure of this study to detect a significant treatment effect. Strategies for addressing high placebo response rates and improving the ability to detect meaningful differences between active compounds and placebo in clinical trials include reducing the number of trial sites, keeping the number of capsules the same even with the dose increase, reducing the duration of the double-blind phase, and developing novel study designs and analyses (Khan *et al*., 2004).

Learnings in the present study, which were applied to subsequent phase 2b/3 trials in the program, included employing a more gradual titration methodology, to potentially lower rates of akathisia and discontinuations due to adverse events, assessment of higher doses of cariprazine, and inclusion of only patients with bipolar type I disorder. In this study, aggressive dose escalation may have had a negative impact on efficacy and tolerability outcomes, particularly in the high-dose cariprazine patients who experienced high levels of discontinuation due to adverse events. Rates of discontinuations in the high-dose cariprazine group were higher than comparable dose groups in other cariprazine bipolar depression trials (Durgam *et al*., 2016; Earley et al., 2019a,b). Also, increasing attrition over time may partly explain why the initial numerical separation between high-dose cariprazine and placebo was not maintained. This trend was also observed in two failed aripiprazole bipolar depression studies (Thase *et al*., 2008), which also had an aggressive titration methodology, high rates of attrition (~41–47%), and initial separation from placebo (from baseline to week 6) that was not maintained at trial endpoint (week 8) (Thase *et al*., 2008; Post, 2016).

Additionally, the phase 3 trials in the cariprazine program reported rates of akathisia of less than 10% (Earley et al., 2019a,b), compared to 17% in this study. High akathisia rates may have negatively affected efficacy outcomes, as its symptoms may be experienced by the patient and interpreted by the clinician as a worsening of the underlying depression. The titration methodology was modified in the phase 3 trials to only allow dose escalations to the highest dose (3.0 mg/day) after two weeks of treatment at 1.5 mg/day. Furthermore, the present study may have selected a cariprazine dose too low to effectively treat depressive symptoms, partially explaining the lack of significant improvement in the low-dose (0.25–0.75 mg/day) group. The mean daily dose of cariprazine for the group was only 0.35 mg/day, and significant improvement in depressive symptoms has not been previously reported with daily dose less than 1.5 mg/day (Durgam *et al*., 2016). This learning was applied to the phase 3 program by assessing a minimum cariprazine dose of 1.5 mg/day (Earley et al., 2019a,b).

Cariprazine was generally well tolerated in this study, and TEAEs occurred with similar frequency across treatment groups. As would be expected for a dopamine receptor modulator, the incidence of akathisia (both as a reported adverse event and as measured by the BARS) was highest among patients treated with high-dose cariprazine (1.5–3.0 mg/day) and the rates may be partially explained by the titration methodology used, as previously discussed. Other than akathisia, the incidence of EPS events was low and comparable to placebo in both cariprazine dose groups. The incidence of somnolence and sedation, which were significantly higher for dopamine receptor modulators vs. placebo analyzed in a meta-analysis (De Fruyt *et al*., 2012), were low among all treatment groups in this study. Mean weight gain was highest in the high-dose cariprazine patients, but no treatment groups exceeded 1.5 kg. Weight gain exceeding 7% of body weight was more frequently reported among patients in the high-dose cariprazine group than other groups, with an overall incidence of approximately 7%. Metabolic parameter shifts into abnormal ranges were minimal and not considered to be clinically relevant. The reasonable benefit–risk ratio of cariprazine in regards to weight gain and metabolic findings is important because patients with bipolar disorder and those treated with dopamine receptor modulators often experience an increased risk of cardiovascular disease, metabolic disorders, diabetes, and clinical obesity (Correll *et al*., 2008), and because incidences of these complications can lead to decreased medication adherence (Kemp, 2014).

Limitations

Limitations of this study included the lack of an active comparator to establish assay sensitivity and exclusion of patients with significant medical and psychiatric conditions, including suicidality, which is prevalent in this population (APA, 2002; Valtonen *et al*., 2006), limiting the generalizability of these findings. Although more aligned

with clinical practice, the fixed-flexible dose design prevented assessment of specific cariprazine doses.

Conclusion

Although cariprazine did not significantly separate from placebo in this bipolar depression trial, factors that may have affected the outcome of the trial were identified. These factors helped to inform the design and conduct of subsequent phase 2b/3 clinical trials, which found significant improvements in depressive symptoms in patients with bipolar I disorder and a current depressive episode. Efforts to understand the causes of placebo response and minimize its occurrence in bipolar depression treatment trials will improve research efforts and support the development of the new treatments that are needed for bipolar depression. Both cariprazine doses did not affect metabolic parameters and weight changes to a clinically significant degree and had favorable tolerability profiles.

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Data reported in this manuscript are available within the article (and/or) its supplementary materials. Allergan will share de-identified patient-level data and/or study-level data, including protocols and clinical study reports, for Phase 2-4 trials completed after 2008 that are registered on ClinicalTrials.gov or EudraCT. The indication studied in the trial must have regulatory approval in the United States and/or the European Union and the primary manuscript from the trial must be published prior to data sharing. To request access to the data, the researcher must sign a data use agreement. All shared data are to be used for noncommercial purposes only. More information can be found on http://www.allerganclinicaltrials.com/.

Conflicts of interest

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