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Research paper

# The safety and tolerability of cariprazine in patients with manic or mixed episodes associated with bipolar I disorder: A 16-week open-label study

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ABSTRACT

*Background:* We evaluated the safety/tolerability of longer-term open-label treatment with cariprazine in patients who had responded to cariprazine for acute bipolar mania.

*Methods:* In this multinational, multicenter study, open-label, flexible-dose, cariprazine 3–12 mg/d was administered for up to 16 weeks to patients (18–65 years) with bipolar mania. Safety evaluations included adverse events (AEs), laboratory values, vital signs, and extrapyramidal symptom (EPS) scales. Symptom change was evaluated by Young Mania Rating Scale (YMRS) total score change from baseline using the last observation carried forward approach.

*Results:* Of the 402 patients taking cariprazine, 33% completed the trial; the most frequent reasons for discontinuation were withdrawal of consent (20%), AEs (16%), and protocol violation (14%). Most common AEs leading to discontinuation were akathisia (4.7%) and depression (1.5%). Mean treatment duration was 57.7 days; mean cariprazine dose was 6.2 mg/d. The incidence of serious AEs was 7.5% (most common: mania [2.2%], depression [1.2%]); 83.3% had treatment-emergent AEs, including akathisia (32.6%), headache (16.7%), constipation (10.7%), and nausea (10.4%). Mean body weight increased < 1 kg; 9.3% had ≥7% weight gain; 5.7% had sedation; 3% had somnolence. Mean changes in laboratory values, vital signs, ECGs, and ophthalmology parameters were not clinically significant. Mean YMRS total score decreased by −15.2 at week 16.

*Limitations:* Uncontrolled, open-label design.

*Conclusions:* Open-label cariprazine 3–12 (mean 6.2) mg/d for up to 16 weeks was generally well tolerated, with low (< 10%) rates of sedation and ≥7% weight gain. Although akathisia occurred in 33%, it yielded discontinuation in < 5%.

## 1. Introduction

Bipolar I disorder is a complex psychiatric disorder with a highly variable course. The distinguishing diagnostic feature is the occurrence of at least one manic or mixed episode, which commonly entails psychosis and/or psychiatric hospitalization. In addition to abnormally elevated mood, patients with bipolar I disorder also commonly experience frequent depressive episodes, cognitive impairment, functional impairment, sleep disturbance, psychotic symptoms, anxiety, substance use, and medical disorders (Judd et al., 2002; Osby et al., 2001; Sachs et al., 2011). While classically considered to be episodic and remitting, bipolar disorder is currently conceptualized as a disease with a more chronic presentation in which residual symptoms, emotional lability, and greater risk for psychiatric and medical comorbidities occur between acute mood episodes (Leboyer and Kupfer, 2010).

Long-term treatment is usually required to manage bipolar disorder (Yatham et al., 2013); initial treatment produces symptomatic recovery and stabilization of the acute mood episode, while maintenance treatment is necessary for recurrence prevention, reduction of subthreshold symptoms, and enhanced functioning (Geddes and Miklowitz, 2013).

*Abbreviations:* AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CGI-S, Clinical Global Impressions-Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; EPS, extrapyramidal symptoms; ITT, intent-to-treat; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; OC, observed cases; SCID, Structured Clinical Interview; SAS, Simpson-Angus Scale; YMRS, Young Mania Rating Scale

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Atypical antipsychotic monotherapy is among the recommended first-line treatment options for bipolar mania (Yatham et al., 2013). Although atypical antipsychotics are categorized as a drug class, they differ in pharmacology, safety, tolerability, and efficacy (Liauw and McIntyre, 2010). Despite decreased risks of extrapyramidal symptoms (EPS) and tardive dyskinesia compared with first-generation antipsychotics, second-generation antipsychotics are commonly associated with other problematic adverse effects including clinically significant weight gain, sedation and somnolence (particularly with older agents), and akathisia (particularly with newer agents) (Cha and McIntyre, 2012). The efficacy of pharmacotherapy depends on patient treatment adherence. As such, a medication's safety and tolerability profile is important since treatment adherence is positively associated with higher medication satisfaction and negatively associated with side effects, negative attitudes toward medications, changes in appearance, and interference with life goals (Yatham et al., 2013).

Cariprazine, a dopamine $D_3$ and $D_2$ receptor partial agonist that preferentially binds to $D_3$ receptors (Kiss et al., 2010), is FDA-approved for the treatment of adult patients with schizophrenia (1.5–6 mg/d) or manic or mixed episodes associated with bipolar I disorder (3–6 mg/d). The short-term efficacy and safety/tolerability of cariprazine in adult patients with acute manic or mixed episodes associated with bipolar I disorder was demonstrated in three 3-week, phase 2 or phase 3 double-blind, placebo-controlled studies (Calabrese et al., 2015; Durgam et al., 2015; Sachs et al., 2015). Flexible-dose cariprazine 3–12 mg/d was used in 2 studies, and a fixed/flexible dose scheme (3–6 mg/d or 6–12 mg/d) was used in the third. In each trial, improvement from baseline to week 3 in Young Mania Rating Scale (YMRS) total score (Young et al., 1978) (primary efficacy measure) and Clinical Global Impressions-Severity (CGI-S) (Guy, 1976a) (secondary efficacy measure) was significantly greater for cariprazine versus placebo, and cariprazine was safe and generally well tolerated; akathisia was a more common adverse event than sedation/somnolence or weight gain.

This longer-term, open-label study was conducted to further characterize the safety and tolerability of cariprazine in patients with bipolar mania. The target population was patients previously diagnosed with bipolar I disorder who were currently untreated or not adequately responding to or tolerating their current treatment as judged by the investigator and symptom rating scale criteria at study entry (YMRS $\geq$18; Montgomery-Åsberg Depression Rating Scale [MADRS] $<$ 18) (Montgomery and Asberg, 1979).

## 2. Methods

This study was conducted from February 2010 to February 2012 in 39 centers in the United States, Germany, Hungary, Poland, and Spain in full compliance with guidelines for good clinical practice and the Declaration of Helsinki; all participants provided written informed consent. Since this was an open-label study, there was no blinding to treatment, and no control group was included.

### 2.1. Study design

This 20-week multicenter, phase 3, open-label, flexible-dose study of cariprazine 3–12 mg/d (NCT01059539) was conducted in patients with manic or mixed episodes associated with bipolar I disorder. The study consisted of a 4- to 7-day wash-out period, followed by 16 weeks of open-label treatment and a 3-week safety follow-up period. All patients received 1.5 mg of cariprazine on day 0 and 3 mg on days 1 and 2; starting on day 3, dosage could be increased in 3-mg increments if response was inadequate and there were no tolerability issues. Patients could receive a maximum dose of 6 mg on days 3 and 4; on days 5 and 6, the maximum dose was 9 mg. On day 7 and after, the maximum dose was 12 mg. In the case of a dose-limiting adverse event (AE), the dose could be decreased to the previous level at any time during the study.

All patients were hospitalized during screening and for the first 2–3 weeks of open-label treatment. By the end of week 3, all patients were discharged and followed-up as outpatients, or discontinued from the study in cases of clinical instability. Patients who were discontinued entered the 3-week safety follow-up period during which they were cross-titrated and stabilized on an appropriate medication as deemed necessary by the investigator. Patients with insufficient therapeutic response could be discontinued from the study at any time; insufficient response was defined as a YMRS or MADRS total score increase $\geq$30% from baseline to the end of week 2 or thereafter, or inadequate response based on investigator judgment, tolerability issues, or worsening of symptoms.

### 2.2. Patients

Patients with documented inadequate response or intolerance to their current treatment or patients not currently receiving any treatment were eligible to participate in this longer-term study. Male or female adults, aged 18–65 years (inclusive) had to meet *Diagnostic and Statistical Manual for Mental Disorders* (DSM-IV-TR) criteria (APA, 2000) for bipolar I disorder, confirmed by the Structured Clinical Interview (SCID) (First et al., 2007). Patients were required to have had a manic or mixed episode (with or without psychotic symptoms) that required treatment within 12 months of the study. To be included, clinical criteria required that patients currently had a YMRS total score $\geq$18 and a MADRS score $<$ 18. This YMRS score is consistent with requiring that patients have substantive current mood elevation symptoms; although patients with DSM-IV-TR mixed episodes were permitted, a MADRS score $<$ 18 taken together with a YMRS score $\geq$18 is consistent with patients having more severe mood elevation than depression.

Patients were excluded from the study if they had a principal axis I diagnosis other than bipolar I, severe personality disorder, rapid cycling (defined as $>$ 4 major depressive, manic, mixed, or hypomanic episodes in the prior 12 months), cognitive or psychotic disorders, alcohol or substance dependence/abuse (prior 3 months), or pregnancy. Patients experiencing their first manic episode were not eligible to participate. Suicide risk, defined as suicide attempt in the past year, score $\geq$5 on item 10 of the MADRS, and/or significant risk determined by investigator judgment or Columbia-Suicide Severity Rating Scale (C-SSRS) assessment (Posner et al., 2011), was exclusionary. Additionally, any concurrent medical condition that might interfere with the conduct of the study, confound the interpretation of study results, or endanger patient well-being was exclusionary. Psychotropic medications other than cariprazine were not allowed except for lorazepam for agitation (after day 8, maximum = 2 mg/d); eszopiclone (maximum = 3 mg/d), zolpidem (maximum = 10 mg/d), zolpidem extended release (maximum = 12.5 mg/d), chloral hydrate (maximum = 2000 mg/d acutely with approval), or zaleplon (maximum = 20 mg/d) for insomnia; or diphenhydramine (50 mg/d), benztropine (up to 4 mg/day [or 2 mg/day if given parenterally]), or propranolol (heart rate and blood pressure dependent dosing) for EPS.

### 2.3. Safety and efficacy evaluations

Safety assessments included AE reports, clinical laboratory parameters, vital signs, electrocardiograms (ECGs), ophthalmologic exams, and C-SSRS assessment. AE reports and findings from EPS/movement disorder rating scales were used to assess treatment-emergent EPS; EPS/movement disorder scales comprised the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976b), the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989), and the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970). Efficacy assessments were collected, but in view of the open, uncontrolled design, they were not categorized as primary or secondary; outcomes included change from baseline in MADRS and YMRS total score, and YMRS response ($\geq$50% reduction from baseline) and remission (YMRS $\leq$12) rates.

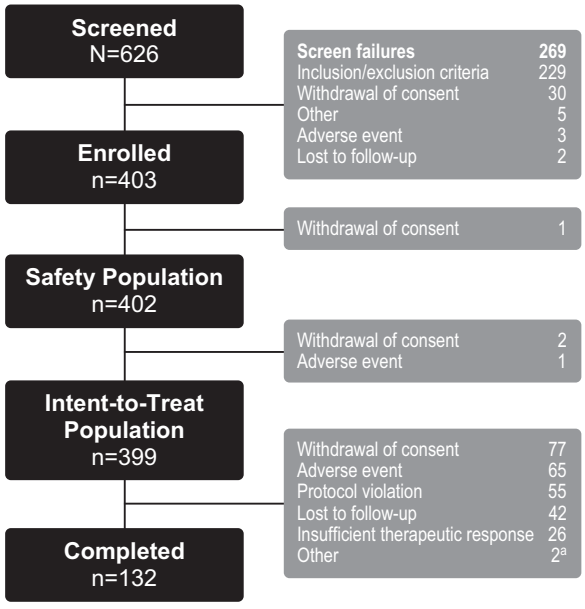



**Fig. 1.** Patient Disposition.

### 2.4. Statistical analyses

The open-label treatment period was defined as the first day open-label cariprazine was received to the last scheduled assessment at week 16 (or early termination). Safety and efficacy baselines were the last value for each parameter recorded before the first dose of cariprazine. Safety parameters were summarized by descriptive statistics in the safety population (all patients who received ≥1 dose of cariprazine). Efficacy analyses were based on the intent-to-treat (ITT) population (all patients in the safety population who had ≥1 postbaseline YMRS assessment) and summarized by descriptive statistics using the last observation carried forward (LOCF) approach. Descriptive statistics were additionally summarized for all efficacy variables without imputation of missing values using the observed cases [OC] approach. No inferential statistical analyses were performed.

## 3. Results

Of the 402 patients in the safety population, 32.8% completed the study; the most frequent reasons for discontinuation were withdrawal of consent (19.7%), AEs (16.4%), and protocol violation (13.7%) (Fig. 1).

Demographic and clinical characteristics are presented in Table 1. The mean age of participants was approximately 41 years and there were more men (57%) than women (43%). Over 95% of patients were white or black/African American. Mean body weight was 86.5 kg; mean BMI was 29.2 kg/m$^2$, which is in the overweight range 25.0–30.0). The mean duration of bipolar I disorder was 13.5 years and the mean duration of the current manic episode before study entry was > 21 days for slightly more than half of the patients.

### 3.1. Safety

#### 3.1.1. Extent of exposure

The mean (SD) duration of open-label treatment was 57.7 (43.6) days (median [range] = 42.0 [1, 127] days); the mean (SD) daily dose of cariprazine was 6.2 (2.6) mg/d (median [range] = 5.9 [1.5, 11.7] mg/d). The final daily dose of cariprazine (the last total daily dose taken by the patient) was 1.5 mg for 1% of patients, 3 mg/d for 27.1%, 6 mg/d for 30.3%, 9 mg/d for 24.4%, and 12 mg/d for 17.2%. The modal daily dose (the most frequent dose taken per patient during open-label treatment) was 1.5 mg/d for 1.0% of patients, 3 mg/d for 29.1%, 6 mg/d for 28.1%, 9 mg/d for 25.9%, and 12 mg/d for 15.9%.

**Table 1**
Patient demographic and clinical characteristics.

| | | Cariprazine (n = 402) |
|---|---|---|
| **Patient demographic characteristics (Safety population)** | | |
| Age, mean (SD), y | | 41.4 (10.5) |
| Male, n (%) | | 230 (57.2) |
| Weight, mean (SD), kg | | 86.5 (17.8) |
| BMI, mean (SD), kg/m$^2$ | | 29.2 (5.3) |
| Race, n (%) | | |
| White | | 206 (51.2) |
| Black/African American | | 182 (45.3) |
| Other | | 14 (3.5) |
| **Psychiatric history** | | |
| Duration of bipolar I disorder, mean (SD), y | | 13.5 (9.2) |
| Age at onset, mean (SD), y | | 27.9 (11.3) |
| Duration of current episode, n (%) | | |
| ≤7 days | | 19 (4.7) |
| > 7 to ≤14 days | | 102 (25.4) |
| > 14 to ≤21 days | | 67 (16.7) |
| > 21 days | | 214 (53.2) |
| **Rating scale scores at baseline (ITT population)** | | |
| YMRS total score | Mean (SD) | 26.1 (5.0) |
| | Median (min, max) | 25.0 (18, 51) |
| MADRS total score | Mean (SD) | 9.9 (3.5) |
| | Median (min, max) | 10.0 (1, 17) |

BMI, body mass index; ITT, intent-to-treat, MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; YMRS, Young Mania Rating Scale.

#### 3.1.2. Adverse events

A summary of AEs is presented in Table 2; no deaths occurred during this study. The most common AEs leading to study discontinuation were akathisia (19 [4.7%] patients) and depression (6

**Table 2**
Adverse events (safety population).

| | Cariprazine (n = 402) n (%) |
|---|---|
| **Open-label period** | |
| Patients with ≥1 AE leading to discontinuation | 66 (16.4) |
| Patients with ≥1 SAE | 30 (7.5) |
| Patients with ≥1 TEAE | 335 (83.3) |
| **Safety follow-up period** | |
| Patients with ≥1 SAE | 4 (1.0) |
| Patients with ≥1 TEAE | 34 (8.5) |
| Patients with ≥1 newly emergent TEAE[a] | 30 (7.5) |
| **Most common TEAEs (≥5% of patients) during open-label treatment** | |
| Akathisia | 131 (32.6) |
| Headache | 67 (16.7) |
| Constipation | 43 (10.7) |
| Nausea | 42 (10.4) |
| Dyspepsia | 38 (9.5) |
| Toothache | 35 (8.7) |
| Back pain | 32 (8.0) |
| Tremor | 31 (7.7) |
| Insomnia | 28 (7.0) |
| Extrapyramidal disorder | 27 (6.7) |
| Restlessness | 26 (6.5) |
| Vomiting | 24 (6.0) |
| Sedation | 23 (5.7) |
| Weight increased | 23 (5.7) |
| Diarrhea | 20 (5.0) |

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a] TEAE that occurred during the safety follow-up period that was not present before or increased in severity during the safety follow-up period.

[1.5%] patients); treatment-emergent AEs (TEAEs) reported in ≥10% of patients were akathisia, headache, constipation, and nausea. The vast majority (98.0%) of TEAEs were considered mild or moderate in severity; of the TEAEs that were considered severe, the most common were akathisia, extrapyramidal disorder, and anxiety (3 patients each). TEAEs were considered related to treatment in 65.2% of patients; all or nearly all TEAEs of akathisia, tremor, extrapyramidal disorder, restlessness, and sedation were considered related to cariprazine. Sedation and somnolence were reported in 23 (5.7%) and 12 (3.0%) patients, respectively. Serious AEs (SAEs) resulted in discontinuation for 17 (4.2%) patients during open-label treatment; SAEs that occurred in more than 1 patient each were worsening of mania (9 patients; 3 related to treatment), depression (5 patients; 4 related), akathisia (3 patients; 3 related), and suicidality (4 patients; 0 related). No newly emergent AE was reported by more than 2 patients during safety follow-up; diarrhea, headache, anxiety, mania, psychotic disorder, and suicidal ideation were reported in 2 patients each.

### 3.1.3. Extrapyramidal symptoms

EPS were assessed by rating scale and AE reports. Based on EPS rating scales, treatment-emergent parkinsonism (SAS total score ≤3 at baseline and > 3 postbaseline) and akathisia (BARS total score ≤2 at baseline and > 2 postbaseline) were observed in 35 (8.7%) patients and 148 (36.8%) patients, respectively.

Although 151 (37.6%) patients had TEAEs of akathisia/restlessness, only 19 (4.7%) patients discontinued cariprazine due to akathisia. EPS-related TEAEs other than akathisia/restlessness occurred in 91 (22.6%) patients, although only 8 (2.0%) patients discontinued cariprazine due to EPS other than akathisia/restlessness. The most commonly reported EPS-related TEAEs were akathisia (32.6%), tremor (7.7%), extrapyramidal disorder (6.7%), and restlessness (6.5%), whereas no other EPS-related TEAE occurred in > 2% of patients. Of new cases of akathisia/restlessness, 142 (94%) were reported during the first 4 weeks of treatment; only 9 new cases were reported from weeks 5–16. Most TEAEs of akathisia/restlessness (98%) were considered mild or moderate in severity and related to treatment. SAEs of akathisia were reported for 3 patients (all discontinued from the study); 1 of the 3 patients had an additional SAE of tremor. During open-label treatment, a minority of patients (129 [32.1%]) used anti-EPS medication to manage EPS (most commonly used: anti-parkinsonian drugs = 64 [15.9%], beta blockers [eg, propranolol] for akathisia = 74 [18.4%]).

### 3.1.4. Laboratory and metabolic parameters

During open-label treatment, mean changes from baseline to the end of open-label treatment in liver function parameters were generally small and not clinically significant, with the exception of alanine aminotransferase (ALT) (Table 3). Three patients discontinued from the study due to nonserious mild/moderate increases in transaminase levels; potentially clinically significant values were seen in 11 (2.8%) patients for ALT (≥3× upper limit of normal [ULN]), 5 (1.3%) patients for aspartate aminotransferase (AST) (≥3× ULN), and 2 (0.5%) patients for bilirubin (> 1.5× ULN). No patient met the criteria for Hy's law. From baseline to the end of the open-label period, mean prolactin values decreased from 13.9 ng/mL to 10.1 ng/mL.

Mean changes from baseline to the end of the open-label treatment for most metabolic parameters were not clinically significant (Table 3). Mean (SD) change from baseline in insulin levels was an exception (33.7 [143.5] pmol/L); a high level of variability in individual insulin values was noted at baseline and at the end of the study, which should be considered when interpreting these findings.

Treatment-emergent shifts in metabolic parameters from normal/borderline baseline values to high values at the end of the study were evaluated. Shifts from a normal/borderline baseline value to a high value at end of treatment occurred in 15/351 (4.3%) patients for total cholesterol (< 240 mg/dL to ≥240 mg/dL), in 12/337 (3.6%) patients for LDL cholesterol (< 160 mg/dL to ≥160 mg/dL), and in 34/317 (10.7%) patients for triglycerides (< 200 mg/dL to ≥200 mg/dL). For HDL cholesterol, shifts from a normal baseline value (≥40 mg/dL) to a low postbaseline value (< 40 mg/dL) occurred in 24/343 (7.0%) patients. For fasting serum glucose, shifts from a normal/impaired baseline value (< 126 mg/dL) to a high postbaseline value (≥126 mg/dL) occurred in 19/361 (5.3%) patients.

Changes in most other clinical laboratory parameters were generally not clinically meaningful. Change from baseline in mean creatine phosphokinase (CPK) was an exception, with an increase from 164.7 U/L at baseline to 212.6 U/L at the end of treatment noted. During open-label treatment, 97 (28.2%) patients had potentially clinically significant CPK values at least once; no CPK-related TEAEs were considered serious or led to study discontinuation. CPK > 1000 U/L was reported in 17 (4.9%) patients. Of patients with CPK > 1000 U/L, 2 had CPK > 5000 U/L, and 1 patient had a high CPK value (4676 U/L) in association with an increased urine myoglobin value.

**Table 3**
Mean change from baseline to endpoint in clinical laboratory values and safety parameters (safety population).

| | Cariprazine (N = 402) Mean (SD) |
|---|---|
| **Clinical laboratory parameters** | |
| Alanine aminotransferase, U/L | 4.2 (20.0) |
| Aspartate aminotransferase, U/L | 1.6 (11.6) |
| Alkaline phosphatase, U/L | −1.2 (17.8) |
| Bilirubin, total, mg/dL | 0.0 (0.2) |
| Total cholesterol, mg/dL | −5.0 (32.8) |
| Fasting low-density lipoprotein (LDL) cholesterol, mg/dL | −2.8 (27.4) |
| High-density lipoprotein (HDL) cholesterol, mg/dL | −2.1 (10.7) |
| Fasting triglycerides, mg/dL | 4.8 (73.0) |
| Fasting glucose, mg/dL | 5.5 (17.1) |
| Insulin, pmol/L | 33.7 (143.5) |
| Creatine phosphokinase, U/L | 47.9 (330.4) |
| Prolactin, ng/mL | −3.8 (17.8) |
| **Vital signs** | |
| Systolic blood pressure, supine, mm Hg | 1.4 (10.9) |
| Diastolic blood pressure, supine, mm Hg | 1.8 (8.6) |
| Pulse, supine, bpm | −0.9 (12.2) |
| Body weight, kg | 0.9 (3.5) |
| Waist circumference, cm | 1.0 (4.9) |
| **Electrocardiogram parameters** | |
| Ventricular heart rate, bpm | 2.3 (13.2) |
| QRS interval, msec | −0.8 (6.6) |
| PR interval, msec | −0.7 (14.9) |
| QT interval, msec | −5.4 (27.8) |
| QTcB interval, msec | 0.3 (21.8) |
| QTcF interval, msec | −1.7 (17.4) |

Endpoint is defined as the last assessment in the open-label treatment period.
QTcB, QT interval corrected for heart rate using the Bazett formula; QTcF, QT interval corrected for heart rate using the Fredericia formula.

### 3.1.5. Vital signs and cardiac safety

Mean changes from baseline to endpoint for vital signs are presented in Table 3. Potentially clinically significant changes in vital signs occurred in 11 patients during open-label treatment; each of these 11 patients had a single potentially clinically significant blood pressure or pulse rate parameter. Changes in ECG parameters during open-label treatment were not clinically significant; no patient had a postbaseline QTcB or QTcF > 500 msec. The most common vital sign-related TEAEs were hypertension (4.2%) and blood pressure increase (2.0%); all other vital sign TEAEs occurred in < 2% of patients. Orthostatic hypotension (≥20 mm Hg reduction in systolic or ≥10 mm Hg reduction in diastolic blood pressure changing from a supine to standing position) was reported in 13.7% of patients. Body weight increase ≥7% was reported in 9.3% of patients; body weight decrease ≥7% was reported in 3.5% of patients.

#### 3.1.6. Ophthalmologic evaluations

There were no clinically significant mean changes observed in ophthalmologic parameters (data not shown); the only eye disorder-related TEAEs reported in > 1% of patients were blurred vision (2.5%) and dry eye (2.2%). Less than 1% of patients experienced increased intraocular pressure, and no SAE related to an eye disorder was reported. One patient discontinued due to a small, early cataract in the periphery of the right eye; the cataract was assessed as mild and non-serious and, in the ophthalmologist's opinion, it was present at baseline and missed on examination due to its peripheral location.

#### 3.1.7. Suicidal ideation/behavior

During open-label treatment, C-SSRS-assessed suicidal ideation was reported in 35 patients (8.8%); most of these patients (22 of the 35) were in the least severe category ("wish to be dead") indicating no active ideation or intent. C-SSRS-assessed suicidal behavior (actual attempt) was recorded for 3 (0.8%) patients.

AEs of suicidal ideation were reported in 4 (1.0%) patients during open-label treatment and in 2 patients during the safety follow-up period. During open-label treatment, AEs of suicidal behavior were reported for the same 3 patients who had C-SSRS-assessed suicidal behavior. The events were recorded as SAEs for 2 of the patients with suicidal ideation; 1 of these patients discontinued from the study. For 2 of the 3 patients with suicidal behavior AEs, the event was recorded as an SAE and resulted in study discontinuation. All 4 patients with suicide-related SAEs had previously attempted suicide; no suicide-related AE was considered related to cariprazine.

### 3.2. Efficacy

At baseline, the mean YMRS total score was 26.1, indicating a moderately to severely ill patient population (Young et al., 1978); the mean baseline MADRS total score was 9.9. Using the LOCF approach, mean (SD) change from baseline to week 16 was −15.2 (9.2) for YMRS total score (Fig. 2A) and −1.6 (7.5) for MADRS total score (Fig. 2B). Using the OC approach, mean (SD) change from baseline to week 16 was −20.7 (6.0) for YMRS total score and −4.3 (7.0) for MADRS total score. Most of the decrease in YMRS total score occurred by week 3 (LOCF = −13.6 [8.5]; OC = −15.3 [7.8]); most of the decrease in MADRS total score that occurred by week 3 (LOCF = −2.9 [5.1]; OC = −3.5 [4.9]) was sustained through week 16.

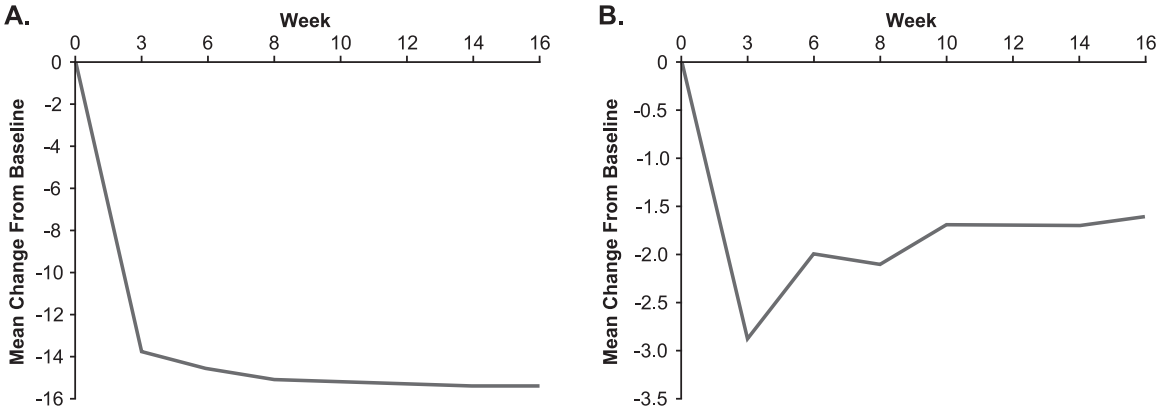
YMRS response was achieved by 64.2% of patients by week 16, although most patients (57.6%) had met the criteria by week 3 (LOCF analysis). Similarly, 57.4% and 60.9% of patients met remission criteria (total YMRS score ≤12) at weeks 3 and 6, respectively; 63.4% of patients were remitters at week 16 (LOCF analysis).

## 4. Discussion

Cariprazine 3–12 mg/d was generally well tolerated in the treatment of adult patients with manic or mixed episodes associated with bipolar I disorder in this 16-week open-label safety study. Mean changes in laboratory, metabolic, cardiac parameters, and vital signs were generally not clinically meaningful. Of interest, the mean baseline BMI (29.2 kg/m$^2$) indicated that the patient population was overweight and changes in variables that could affect cardiovascular risk should be interpreted within this context. The most common AE was akathisia (32.6%); although it was considered related to treatment in most cases, the majority of events were mild or moderate and resulted in discontinuation in only 4.7% of patients. The modal daily dose for 57.2% of patients was within the FDA-approved dose range for cariprazine in bipolar I disorder (3–6 mg/d). No new safety or tolerability issues were uncovered with longer-term use of cariprazine in patients with manic or mixed episodes associated with bipolar I disorder in this study.

The range of allowed doses for cariprazine was higher in this study (3–12 mg/d) than in the previous long-term, open-label studies of cariprazine in patients with schizophrenia (1.5–4.5 and 3–9 mg/d) (Cutler et al., 2014; Durgam et al., 2017). However, safety findings for cariprazine in this 16-week bipolar study were generally consistent with the findings observed in the 48-week open-label studies of cariprazine in schizophrenia (Cutler et al., 2014; Durgam et al., 2017). In these long-term schizophrenia studies, approximately 82% of patients had at least 1 TEAE, which was similar to the incidence of TEAEs reported in this longer-term bipolar mania study (83.3%). In both indications, akathisia was the most commonly reported TEAE in the open-label studies (bipolar mania = 32.6%; schizophrenia = 14.0–15.7%); however, ≤1% of patients with schizophrenia and 4.7% of patients with bipolar disorder discontinued cariprazine due to akathisia. These results are consistent with the literature, which generally reports a lower rate of akathisia in schizophrenia trials compared with bipolar mania trials; this may be related to differences in doses, and underlying characteristics and symptoms of bipolar mania and schizophrenia (Gao et al., 2008; Kane et al., 2009). The most commonly reported SAEs in the longer-term open-label studies in cariprazine were associated with worsening of the relevant underlying psychiatric condition. Specifically, worsening of bipolar disorder was reported as an SAE in 2.7% of patients in this long-term study, and worsening of schizophrenia was a reported SAE in 4.3% of patients in each of the long-term schizophrenia studies. There were no SAEs of akathisia, restlessness, or EPS-related AEs in the long-term schizophrenia studies, but there were 4 EPS-related SAEs in this longer-term bipolar study. Changes in metabolic, clinical laboratory, and ECG parameters were generally not clinically significant

The safety profiles of atypical antipsychotics differ across agents,




ITT population=399.
ITT, intent-to-treat; MADRS, Montgomery-Åsberg Depression Rating Scale; LOCF, last observation carried forward; YMRS, Young Mania Rating Scale.

**Fig. 2.** Mean change from baseline to week 16 in (A) YMRS and (B) MADRS total scores (LOCF, ITT population).

but they are commonly associated with clinically significant AEs including weight gain and associated metabolic complications, sedation and somnolence, and akathisia (Cha and McIntyre, 2012). In this open-label bipolar mania study, the only TEAEs other than akathisia that were reported in at least 10% of patients were headache, constipation, and nausea. The incidences of sedation (5.7%) and somnolence (3.0%) were relatively low, which is consistent with diminished cognitive responsivity or subjective sleepiness not being common with cariprazine. TEAEs led to the discontinuation of 16.4% of patients during open-label treatment; akathisia (4.7%) and depression (1.5%) were the most common AEs leading to discontinuation. Of note, patients included in this study had documented history of inadequate response or intolerance to their current treatment, or they were not currently receiving any treatment, which may suggest a particular sensitivity to pharmacologic treatment in this patient population.

The occurrence of akathisia was common in this longer-term, open-label cariprazine study in bipolar mania. No other EPS-related TEAE was reported in ≥10% of patients, and only 2.0% of patients discontinued from the study as a result of other EPS-related TEAEs, suggesting that akathisia was the predominant EPS-related issue associated with cariprazine. Most new cases of akathisia/restlessness were reported during the first 2–4 weeks of treatment; the number of new cases decreased dramatically thereafter. SAEs of akathisia were reported in only 3 patients; 1 additional SAE of tremor was reported in a patient with a concurrent SAE of akathisia. Per study protocol, medication to manage symptoms of akathisia/restlessness was allowed during open-label treatment. The use of medication generally appeared to correlate with the severity of the akathisia/restlessness AE (mild = 64/97 [66.0%]; moderate = 41/51 [80.4%]; severe = 2/3 [66.7%]). Medication use and the relatively low rate of discontinuation (4.7%) suggest that patients with akathisia and their providers were able to manage akathisia, and patients could continue treatment with cariprazine. Additional studies are needed to assess the prevalence, baseline risk factors, time course, dose-response relationship, and management of treatment-emergent akathisia related to cariprazine.

Risk factors for cardiovascular morbidity/mortality, including cardiovascular disease, hypertension, hyperlipidemia, obesity, diabetes, and sedentary lifestyle, are among the most common medical conditions that occur in patients with bipolar disorder (Goldstein et al., 2009; Kilbourne et al., 2004). Given these risk factors, the generally small mean changes and clinically insignificant effects of cariprazine on metabolic and cardiovascular parameters that were observed in this study are especially important. Since obesity is a cardiovascular and metabolic risk factor, it is of note that the mean BMI at baseline was in the overweight category. Increases in mean body weight were less than 1 kg during open-label treatment. Weight increase of ≥7% from baseline was seen in 9.3% of patients, which may be related to the longer duration of treatment. Shifts from normal baseline values to abnormal values at the end of open-label treatment occurred in < 11% of patients for relevant metabolic parameters. Mean changes in diastolic and systolic blood pressure and ECG parameters were small; no patient had QTcB or QTcF intervals > 500 ms.

More comprehensive safety assessment for cariprazine also entails consideration of the three 3-week double-blind, placebo-controlled pivotal studies in the treatment of adults with manic and mixed episodes associated with bipolar I disorder (Calabrese et al., 2015; Durgam et al., 2015; Sachs et al., 2015). Of note, safety findings from this longer-term open-label study and the acute double-blind studies were consistent; no new safety or tolerability concerns were observed in open-label treatment. In all studies, cariprazine was generally well tolerated in patients with manic or mixed episodes associated with bipolar I disorder. Rates of TEAEs were similar in the open-label (83.3%) and double-blind studies (75.1–85.6%) and although the rate of AE-related discontinuations was slightly higher during open-label treatment (16.4%) than during double-blind treatment (9.0–14.8%), this could be related to the longer open-label study duration. Most TEAEs in all studies were considered mild or moderate in severity.

Akathisia, the most common TEAE in both longer- and short-term treatment, occurred at a higher overall incidence in the longer-term open study (32.6%) than in the acute double-blind studies (17.4–22.2%), although most new cases in the longer-term study occurred in the first 4 weeks of treatment. Mean changes in metabolic parameters in this longer-term open-label study were consistent with changes in the 3-week short-term studies; there was no prolactin elevation in any study. The risk of orthostatic hypotension did not appear to be affected by the length of cariprazine treatment (longer-term study = 13.7%; short-term treatment = 8.8–17.5%). The incidence of ≥7% weight gain was higher in open-label treatment (9.3%) than in the acute treatment (1.2–2.5%), which again may be related to the difference in study duration.

Due to the flexible-dose design of this longer-term open-label study, it was not possible to assess the potential for dose-response relationships for TEAEs. However, in acute study RGH-MD-33 where a fixed/flexible dose design was used, there was a lower incidence of akathisia for cariprazine 3–6 mg/d versus 6–12 mg/d (17.4% vs 21.9%); a similar pattern was seen for ≥7% weight gain (1.2% vs 2.4% in low- vs high-dose groups). This suggests that some important adverse effects may occur with lower incidence when cariprazine is administered in the FDA-recommended dose range for acute manic/mixed episodes associated with bipolar I disorder (3–6 mg/d) than at higher doses.

Although this open-label study was designed to evaluate the safety and tolerability of cariprazine, efficacy outcomes were collected. Most of the decrease in YMRS and MADRS total scores occurred during the first 3 weeks of the study and was generally maintained through the end of the study, suggesting that symptom improvement persisted during open-label treatment with cariprazine. Additionally, more than 60% of patients met YMRS responder and remitter criteria at 16 weeks.

### 4.1. Limitations

The primary limitation of this study was the open-label design and lack of a control group for comparison. Understanding of rates of AEs or laboratory abnormalities observed with cariprazine treatment was also limited due to the lack of a placebo control. The flexible-dose design permitted dosing outside the FDA-approved dose range; while dose adjustment based on response and tolerability closely mirrors dosing in clinical practice, it may limit the ability to assess dose-response relationships for safety parameters. The lack of a control group particularly limited the ability to draw long-term efficacy conclusions in this population; change in depressive symptoms should be interpreted with caution since patients with moderate or severe depression were excluded from the study. The study's inclusion and exclusion criteria may limit the generalizability of findings. Although patients with significant suicide risk were ineligible to participate in the study due to ethical considerations, it is possible that excluding patients with score ≥5 on item 10 of the MADRS may have correspondingly omitted patients with mixed episodes, further limiting generalizability. Additionally, 16 weeks of open-label treatment may not be adequate to assess long-term safety; other antipsychotics have been evaluated for periods of 6–12 months to assess long-term safety and tolerability in bipolar mania (Ketter et al., 2016a, 2016b).

## 5. Conclusion

Cariprazine was safe and generally well tolerated in longer-term treatment of adult patients with acute manic or mixed episodes associated with bipolar I disorder. Low rates of sedation and somnolence, as well as low propensity for weight gain and a favorable metabolic profile are important longer-term findings, since these effects can be treatment-limiting for patients taking atypical antipsychotics. Although a high rate of akathisia was observed (32.6%), the akathisia discontinuation rate was only 4.7%. Our results were consistent with

safety findings from earlier acute phase 2 and phase 3 double-blind studies of cariprazine in patients with bipolar disorder and from long-term studies of cariprazine in schizophrenia.

## Conflicts of interest/Author disclosures

Terence A. Ketter has had financial interests/arrangements or affiliations with organizations that could be perceived as real or apparent conflicts of interest. Dr. Ketter has received Grant/Research Support (through Stanford University) from the Agency for Healthcare Research and Quality, AstraZeneca Pharmaceuticals LP, Cephalon Inc. (now Teva Pharmaceuticals), Merck & Co., Inc., Pfizer, Inc., and Sunovion Pharmaceuticals; has served as a Consultant/Advisory Board Member for Acadia Pharmaceuticals, Allergan Pharmaceuticals, Depomed, Genentech, Janssen Pharmaceuticals, Merck & Co., Inc., Myriad Genetic Laboratoriess, Inc., ProPhase, Sunovion Pharmaceuticals, and Teva Pharmaceuticals; has received Lecture Honoraria (not Speaker's Bureau payments) from Abbott Laboratories, Inc., GlaxoSmithKline, Pfizer, Inc., and Sunovion Pharmaceuticals; and has received Royalties from American Psychiatric Publishing, Inc. In addition, Dr. Ketter's spouse is an employee of and stockholder in Janssen Pharmaceuticals.

Gary S. Sachs is a full-time employee of Bracket. He has had financial interests/arrangements or affiliations with organizations that could be perceived as real or apparent conflicts of interest. Dr. Sachs has served as a Consultant/Advisory Board Member for Allergan Pharmaceuticals, Janssen Pharmaceuticals, Intra-Cellular Therapies, Lundbeck, Merck & Co., Inc., Otsuka, Sunovion Pharmaceuticals, and Supernus Pharmaceuticals.

Suresh Durgam, Kaifeng Lu, and Anju Starace acknowledge a potential conflict of interest as employees of Allergan. István Laszlovszky and György Németh acknowledge a potential conflict of interest as employees of Gedeon Richter Plc.

## Contributors

Suresh Durgam and Anju Starace were involved in the design and conduct of the study as well as the interpretation of data. Kaifeng Lu contributed to the statistical design of the study and the interpretation of data. István Laszlovszky and György Németh were involved in the design of the study and interpretation of data. Terence A. Ketter and Gary S. Sachs contributed as clinical experts for data interpretation. All authors participated in the development of the manuscript and approved the final version for submission.

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## Trial registration

ClinicalTrials.gov identifier: NCT01059539

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## References

APA, 2000. Diagnostic and Statistical Manual of Mental Disorders, Fourth ed., Text Revision ed. American Psychiatric Association, Washington DC.

Barnes, T.R., 1989. A rating scale for drug-induced akathisia. Br. J. Psychiatry 154, 672–676.

Calabrese, J.R., Keck Jr., P.E., Starace, A., Lu, K., Ruth, A., Laszlovszky, I., Nemeth, G., Durgam, S., 2015. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. J. Clin. Psychiatry 76, 284–292.

Cha, D.S., McIntyre, R.S., 2012. Treatment-emergent adverse events associated with atypical antipsychotics. Expert Opin. Pharmacother. 13, 1587–1598.

Cutler, A.J., Wang, Y., Migliore, R., Lu, K., Laszlovszky, I., Nagy, K., Durgam, S., 2014. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia. Poster presented at In: Proceedings of the 4th Biennial Schizophrenia International Research Conference; April 5–9, 2014; Florence, Italy.

Durgam, S., Greenberg, W.M., Li, D., Lu, K., Laszlovszky, I., Németh, G., Migliore, R., Volk, S., 2017. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week, single-arm, open-label extension study. Psychopharmacology 234, 199–209.

Durgam, S., Starace, A., Li, D., Migliore, R., Ruth, A., Németh, G., Laszlovszky, I., 2015. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. Bipolar Disord. 17, 63–75.

First, M.B., Williams, J.B.W., Spitzer, R.L., Gibbon, M., 2007. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinical Trials Version (SCID-CT). Biometrics Research. New York State Psychiatric Institute, New York.

Gao, K., Kemp, D.E., Ganocy, S.J., Gajwani, P., Xia, G., Calabrese, J.R., 2008. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. J. Clin. Psychopharmacol. 28, 203–209.

Geddes, J.R., Miklowitz, D.J., 2013. Treatment of bipolar disorder. Lancet 381, 1672–1682.

Goldstein, B.I., Fagiolini, A., Houck, P., Kupfer, D.J., 2009. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. Bipolar Disord. 11, 657–662.

Guy, W., 1976a. The Clinician Global Severity and Impression Scales. ECDEU Assessment Manual for Psychopharmacology. National Institute of Mental Health, Rockville, MD, pp. 218–222 DHEW Publication No. 76–338.

Guy, W., 1976b. The Abnormal Movement Scale. ECDEU Assessment Manual for Psychopharmacology. National Institute of Mental Health, Rockville, MD, pp. 218–222 DHEW Publication No. 76–338.

Judd, L.L., Akiskal, H.S., Schettler, P.J., Endicott, J., Maser, J., Solomon, D.A., Leon, A.C., Rice, J.A., Keller, M.B., 2002. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch. Gen. Psychiatry 59, 530–537.

Kane, J.M., Fleischhacker, W.W., Hansen, L., Perlis, R., Pikalov 3rd, A., Assuncao-Talbott, S., 2009. Akathisia: an updated review focusing on second-generation antipsychotics. J. Clin. Psychiatry 70, 627–643.

Ketter, T.A., Amchin, J., Frye, M.A., Gross, N., 2016a. Long-term safety and efficacy of armodafinil in bipolar depression: a 6-month open-label extension study. J. Affect. Disord. 197, 51–57.

Ketter, T.A., Sarma, K., Silva, R., Kroger, H., Cucchiaro, J., Loebel, A., 2016b. Lurasidone in the long-term treatment of patients with bipolar disorder: a 24-week open-label extension study. Depress Anxiety 33, 424–434.

Kilbourne, A.M., Cornelius, J.R., Han, X., Pincus, H.A., Shad, M., Salloum, I., Conigliaro, J., Haas, G.L., 2004. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disord. 6, 368–373.

Kiss, B., Horváth, A., Némethy, Z., Schmidt, E., Laszlovszky, I., Bugovics, G., Fazekas, K., Hornok, K., Orosz, S., Gyertyán, I., Ágai-Csongor, E., Domány, G., Tihanyi, K., Adham, N., Szombathelyi, Z., 2010. Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. J. Pharmacol. Exp. Ther. 333, 328–340.

Leboyer, M., Kupfer, D.J., 2010. Bipolar disorder: new perspectives in health care and prevention. J. Clin. Psychiatry 71, 1689–1695.

Liauw, S.S., McIntyre, R.S., 2010. Atypical antipsychotic tolerability and switching strategies in bipolar disorder. Expert Opin. Pharmacother. 11, 2827–2837.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Osby, U., Brandt, L., Correia, N., Ekbom, A., Sparen, P., 2001. Excess mortality in bipolar and unipolar disorder in Sweden. Arch. Gen. Psychiatry 58, 844–850.

Posner, K., Brown, G.K., Stanley, B., Brent, D.A., Yershova, K.V., Oquendo, M.A., Currier, G.W., Melvin, G.A., Greenhill, L., Shen, S., Mann, J.J., 2011. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am. J. Psychiatry 168, 1266–1277.

Sachs, G.S., Dupuy, J.M., Wittmann, C.W., 2011. The pharmacologic treatment of bipolar disorder. J. Clin. Psychiatry 72, 704–715.

Sachs, G.S., Greenberg, W.M., Starace, A., Lu, K., Ruth, A., Laszlovszky, I., Németh, G., Durgam, S., 2015. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, Phase III trial. J. Affect. Disord. 174, 296–302.

Simpson, G.M., Angus, J.W., 1970. A rating scale for extrapyramidal side effects. Acta Psychiatr. Scand. Suppl. 212, 11–19.

Yatham, L.N., Kennedy, S.H., Parikh, S.V., Schaffer, A., Beaulieu, S., Alda, M., O'Donovan, C., Macqueen, G., McIntyre, R.S., Sharma, V., Ravindran, A., Young, L.T., Milev, R., Bond, D.J., Frey, B.N., Goldstein, B.I., Lafer, B., Birmaher, B., Ha, K., Nolen, W.A., Berk, M., 2013. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 15, 1–44.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435.