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# Long-Term Remission With Cariprazine Treatment in Patients With Schizophrenia:

## A Post Hoc Analysis of a Randomized, Double-Blind, Placebo-Controlled, Relapse Prevention Trial

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### ABSTRACT

**Background:** Long-term remission is an important treatment goal in schizophrenia. Cariprazine, a dopamine D<sub>3</sub>/D<sub>2</sub> receptor and serotonin 5-HT<sub>1A</sub> receptor partial agonist, is approved in the United States and Europe to treat adults with schizophrenia.

**Methods:** Post hoc analyses of data from a long-term cariprazine relapse prevention study (NCT01412060; September 27, 2011–September 3, 2014) investigated the efficacy of cariprazine for maintaining remission in clinically stable patients with DSM-IV-TR–defined schizophrenia. Patients were stabilized with open-label cariprazine (20 weeks), then randomized 1:1 to cariprazine (3, 6, or 9 mg/d) or placebo for double-blind treatment (up to 72 weeks). Symptomatic remission was defined as scores  $\leq 3$  on 8 items from the General, Positive, and Negative Symptoms subscales of the Positive and Negative Syndrome Scale (PANSS). Sustained remission included meeting remission criteria at the current and all prior double-blind visits or for  $\geq 6$  consecutive months.

**Results:** At randomization, 169/200 patients (84.5%) met symptomatic remission criteria. During double-blind treatment, time to loss of sustained remission was significantly longer ( $P = .0020$ ) for cariprazine versus placebo (hazard ratio = 0.51); 60.5% of cariprazine-treated and 34.9% of placebo-treated patients sustained remission through the final visit (odds ratio [OR] = 2.85;  $P = .0012$ ; number needed to treat [NNT] = 4). Almost twice as many cariprazine-treated (39.6%) as placebo-treated (21.2%) patients met symptomatic remission criteria at all visits  $\geq 6$  consecutive months immediately before/including the final double-blind visit (OR = 2.44;  $P = .0057$ ; NNT = 6). More cariprazine-treated (41.6%) than placebo-treated (27.3%) patients sustained remission for any  $\geq 6$  consecutive month period (OR = 1.90,  $P = .0379$ ; NNT = 7).

**Conclusions:** Cariprazine was associated with significantly longer sustained remission, higher remission rates, and increased likelihood of sustaining remission for  $\geq 6$  consecutive months versus placebo.

**Trial Registration:** ClinicalTrials.gov identifier: NCT01412060

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Schizophrenia, a chronic and complex neuropsychiatric syndrome, is characterized by multiple episodes of relapse over the course of the illness.<sup>1</sup> Frequently associated with treatment nonadherence,<sup>2</sup> relapse promotes disease progression through slower and less complete recovery, difficulty regaining the previous level of function, increased rates of hospitalization, and the potential for treatment resistance.<sup>2,3</sup> Using a long-term treatment strategy to prevent relapse may allow a patient to achieve remission, with the goal of functional recovery.<sup>2</sup> Sustained remission, or the long-term alleviation of symptoms to levels that do not significantly influence behavior,<sup>4</sup> is associated with improved outcomes, including social functioning.<sup>5,6</sup> Given the importance of maintaining remission in people with schizophrenia, there is a need for treatments that have long-term efficacy and tolerability to minimize the risks of treatment nonadherence and relapse.

The Remission in Schizophrenia Working Group (RSWG) developed a consensus definition and operational criteria for symptomatic remission based on 3 dimensions of schizophrenia psychopathology: psychoticism, disorganization, and negative symptoms.<sup>4</sup> The criteria to define remission consist of a symptomatic component and a time component. The symptomatic component requires that patients have scores corresponding to a severity level of mild or better ( $\leq 3$ ) on 8 individual items of the Positive and Negative Syndrome Scale (PANSS)<sup>7</sup> chosen to map the 3 dimensions of psychopathology and the 5 criteria for schizophrenia specified in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)<sup>8</sup> (ie, delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, blunted affect, social withdrawal, and lack of spontaneity). The time component requires that symptomatic criteria be met for  $\geq 6$  consecutive months. Meeting both the symptomatic and time

- Schizophrenia is a chronic illness that requires effective long-term treatment to improve patient well-being and functional recovery.
- Sustained remission is a critical concept of treatment response that emphasizes symptom stability over prolonged periods of time for patients with schizophrenia.
- These post hoc analyses suggest that cariprazine may be an effective treatment for sustaining stable, prolonged remission in patients with schizophrenia who have previously tolerated and responded to cariprazine.

criteria is referred to as sustained remission. Importantly, this definition of remission uses an absolute threshold of symptom severity, not degree of improvement from a baseline score, suggesting that it can be used throughout the course of the disease and may permit between-trial comparisons of different antipsychotics and their efficacy in promoting remission.<sup>5</sup>

Cariprazine is a potent, orally active, dopamine D<sub>3</sub>-preferring D<sub>3</sub>/D<sub>2</sub> receptor partial agonist and serotonin 5-HT<sub>1A</sub> receptor partial agonist approved for the treatment of adults with schizophrenia (United States and Europe) and acute manic or mixed episodes associated with bipolar I disorder (United States). Cariprazine has 2 active metabolites, desmethyl cariprazine and didesmethyl cariprazine. The combined half-life for all 3 active moieties is 1 week,<sup>9</sup> which is relatively longer than that of other oral atypical antipsychotics.<sup>10,11</sup> This longer half-life may be associated with sustained blood cariprazine levels and some continued effect after antipsychotic treatment interruption or discontinuation, which may have the potential to lessen relapse events in cases of intermittent or partial treatment noncompliance and increase the likelihood of sustained remission. Cariprazine has demonstrated efficacy in several short-term, placebo- and active-controlled trials in patients with acute schizophrenia.<sup>12–14</sup> In a long-term, double-blind, placebo-controlled trial to assess the effectiveness of cariprazine in relapse prevention,<sup>15</sup> time to relapse, the primary efficacy endpoint, was significantly longer for cariprazine versus placebo ( $P = .001$ ). The hazard of relapse for cariprazine-treated patients was less than half that of placebo-treated patients (hazard ratio; HR [95% CI] = 0.45 [0.28 to 0.73]). During double-blind treatment, 24.8% of cariprazine- and 47.5% of placebo-treated patients met relapse criteria, with a number needed to treat (NNT) of 5. To investigate the ability of cariprazine to sustain remission in stable patients with schizophrenia, we conducted post hoc analyses of data from this relapse prevention study applying the RSWG remission criteria.<sup>4</sup>

## METHODS

### Study Design

Post hoc analyses were performed using data from the long-term (up to 92 weeks), multinational, randomized,

double-blind, placebo-controlled relapse prevention study of cariprazine in patients with schizophrenia (NCT01412060, September 27, 2011–September 3, 2014). Detailed methods and results, including a CONSORT diagram and safety outcomes, have been previously published.<sup>15</sup> Briefly, patients were initially stabilized with flexible-dose cariprazine (3–9 mg/d) during a 20-week, open-label phase. Patients who met stabilization criteria (PANSS total score  $\leq 60$ ;  $\geq 20\%$  decrease in PANSS total score from baseline; Clinical Global Impressions-Severity of Illness [CGI-S]<sup>16</sup> score  $\leq 4$ ; score  $\leq 4$  on 7 PANSS items [delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, hostility, uncooperativeness, and poor impulse control]) were randomized 1:1 to fixed-dose cariprazine (3, 6, or 9 mg/d [same dose as in the stabilization phase]) or placebo for up to 72 weeks of double-blind treatment. The study was administratively terminated for all active patients when the last randomized patient completed 26 weeks of treatment. This study was approved by an institutional review board (US study centers) or independent ethics committee (non-US study centers) and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

### Patients

The relapse prevention study included male and female inpatients aged 18–60 years, with a *DSM-IV-TR*<sup>8</sup> diagnosis of schizophrenia for a minimum of 1 year and a current psychotic episode of  $< 4$  weeks' duration. Clinical inclusion criteria included a PANSS total score  $\geq 70$  and  $\leq 120$  and a score  $\geq 4$  (moderately severe) on  $\geq 2$  of the following PANSS items: delusions, hallucinatory behavior, conceptual disorganization, and suspiciousness/persecution. Patients were excluded if they were experiencing their first psychotic episode or if they were diagnosed with another psychiatric disorder (eg, psychotic disorders, bipolar I or II disorder, substance abuse/dependence within 3 months of study); medical conditions (eg, clinically significant cardiovascular disease, seizure disorder, hypo- or hyperthyroidism) that could interfere with the conduct of the study were also exclusionary.

### Post Hoc Analyses

Post hoc analyses were based on data from the double-blind intent-to-treat (ITT) population (patients who took  $\geq 1$  dose of study medication and had a baseline and  $\geq 1$  double-blind postbaseline PANSS total score or CGI-S assessment). Symptomatic remission based on RSWG criteria was defined as a score  $\leq 3$  (mild) on 8 PANSS items: mannerisms and posturing (G5), unusual thought content (G9), blunted affect (N1), social withdrawal (N4), lack of spontaneity (N6), delusions (P1), conceptual disorganization (P2), and hallucinatory behavior (P3).<sup>4</sup>

### Outcomes

The efficacy of cariprazine was assessed using 4 definitions of sustained remission that were based on recommended

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**Table 1. Baseline Demographic and Disease Characteristics (Double-Blind ITT Population)**

Characteristic	Total	Placebo (n=99)	Cariprazine 3–9 mg/d (n=101)
Age, mean (SD), y	38.4 (10.5)	37.7 (10.1)	39.2 (10.9)
Men, n (%)	132 (66.0)	70 (70.7)	62 (61.4)
Race, n (%)			
White	83 (41.5)	38 (38.4)	45 (44.6)
Black/African American	61 (30.5)	30 (30.3)	31 (30.7)
Other	56 (28.0)	31 (31.3)	25 (24.8)
Duration of schizophrenia, mean (SD), y	11.2 (10.0)	10.5 (9.5)	11.9 (10.4)
PANSS total score at DB baseline, mean (SD)	50.9 (6.7)	50.5 (6.1)	51.3 (7.2)
CGI-S total score at DB baseline, mean (SD)	2.7 (0.6)	2.6 (0.6)	2.8 (0.6)
Met symptomatic remission criteria at DB baseline, n (%)	169 (84.5)	83 (83.8)	86 (85.1)

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness, DB = double-blind, ITT = intent-to-treat, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation.

RSWG symptomatic and time criteria: (1) meeting symptomatic remission criteria at the visit in question and all previous double-blind visits, (2) meeting symptomatic remission criteria for 6 consecutive months starting at double-blind baseline, (3) meeting symptomatic remission criteria at each visit for 6 consecutive months prior to a patient's last visit in remission during the double-blind period, and (4) meeting symptomatic remission criteria for 6 consecutive months preceding a patient's final study visit.

Time to loss of sustained remission, duration of sustained remission, and percentage of patients achieving remission criteria were compared between placebo and pooled cariprazine (3–9 mg/d) treatment groups.

### Statistical Analyses

Patients who completed open-label treatment and met stabilization criteria were randomized to double-blind treatment; randomization was considered the double-blind baseline. For randomized patients, time to loss of sustained remission (equivalent to duration of sustained remission) was defined as no longer meeting symptomatic criteria for remission, or as having discontinued due to relapse, using a last-observation-carried-forward (LOCF) approach. Time to loss of sustained remission was estimated using Kaplan-Meier analysis; *P* values were based on the log-rank test. The HR and 95% CI were based on the Cox proportional hazards regression model, with treatment group as an explanatory variable. The percentage of patients meeting 6-month remission criteria as well as the corresponding odds ratios (ORs) and 95% CIs were calculated using an observed cases approach for each definition of sustained remission; *P* values were based on the Fisher exact test. The NNT was calculated by dividing 1 by the risk difference and rounding up to the next integer. Treatment compliance (measured by site investigators) was defined as the number of capsules actually taken by a patient during a period divided by the number of capsules prescribed for the

same period multiplied by 100; results were presented by descriptive statistics.

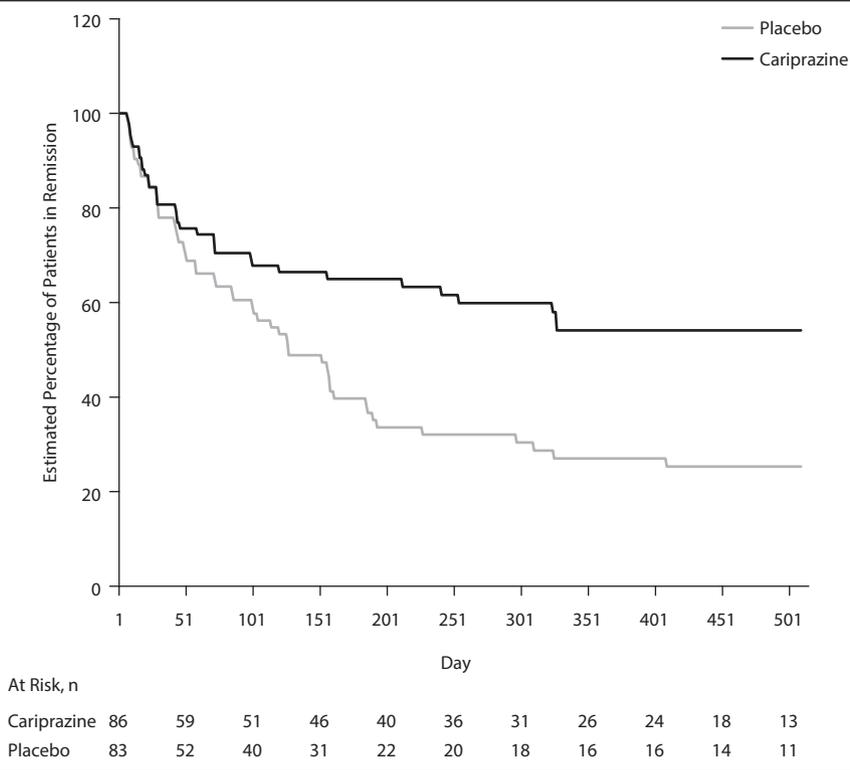
### RESULTS

Open-label treatment was completed by 264 of 765 patients (34.5%); the most common reason for premature discontinuation was withdrawal of consent (~20%). The double-blind ITT population comprised 200 stable patients (cariprazine = 101, placebo = 99); of cariprazine-treated patients, 14 were taking 3 mg/d, 37 were taking 6 mg/d, and 50 were taking 9 mg/d. Significantly more placebo than cariprazine patients prematurely discontinued double-blind treatment for reasons other than relapse; the most common reason for discontinuation in both treatment groups was administrative termination per the study protocol. Baseline demographics and disease characteristics were generally similar between the randomized treatment groups (Table 1). At double-blind baseline, high and similar numbers of patients in both treatment groups (84%–85%) met symptomatic remission criteria (Table 1). Overall mean treatment compliance based on pill counts was high in both treatment groups (placebo = 99.3%; cariprazine = 98.5%).

During double-blind treatment, time to loss of sustained remission was significantly longer (*P* = .0020) in the cariprazine group than in the placebo group (HR [95% CI] = 0.51 [0.33 to 0.79]) (Figure 1); 60.5% of cariprazine- and 34.9% of placebo-treated patients sustained remission through the final visit (OR [95% CI] = 2.85 [1.52 to 5.32]; *P* = .0012; NNT = 4). This corresponds to a significantly longer time to loss of sustained remission with cariprazine than with placebo. The 25th percentile (95% CI) for time to loss of sustained remission, which signifies that 25% of patients lost sustained remission at or before that time, was 43 (22 to 71) days for placebo- and 58 (22 to 155) days for cariprazine-treated patients. For the 50th percentile, time to loss of sustained remission was 126 (85 to 184) days with placebo, and it could not be estimated for cariprazine because fewer than half of the patients lost sustained remission in this group (Table 2). Although there were too few patients to estimate the time to loss of sustained remission in the cariprazine group for the 50th percentile, based on the estimated lower limit of the 95% confidence interval, it would be greater than 240 days, more than double the time for the placebo group. Separation of the placebo- and cariprazine-treatment group curves was first evident at approximately 7 weeks after the start of double-blind treatment, and it was maintained until the end of the study.

Of patients in the double-blind ITT population, more cariprazine-treated (46.5%) than placebo-treated (29.3%) patients met sustained remission criteria 6 months after the double-blind baseline; the difference between the treatment groups was statistically significant in favor of cariprazine (OR [95% CI] = 2.1 [1.17 to 3.76]; *P* = .0136; NNT = 6) (Figure 2). Similarly, significantly more cariprazine-treated (41.6%) than placebo-treated (27.3%) patients had sustained remission at all visits for at least 6 consecutive months prior

**Figure 1. Kaplan-Meier Estimate of Time to Loss of Sustained Remission During the Double-Blind Phase<sup>a</sup>**



<sup>a</sup>Remission probability with placebo or cariprazine treatment in the intent-to-treat population. Loss of remission is defined as patients who no longer met remission criteria or who discontinued due to relapse.

**Table 2. Survival Analysis Summary of Time to Loss of Sustained Remission During the Double-Blind Treatment Period (LOCF)<sup>a</sup>**

	Placebo (n=99)	Cariprazine 3–9 mg/d (n=101)
Patients meeting remission criteria at randomization, n (%)	83 (83.8)	86 (85.1)
Patients with sustained remission, n (%)	29 (34.9)	52 (60.5)
Duration of sustained remission, days (95% CI) <sup>a,b</sup>		
75th Percentile	... (189 to ...)	... (... to ...)
50th Percentile (median)	126 (85 to 184)	... (240 to ...)
25th Percentile	43 (22 to 71)	58 (22 to 155)
P value <sup>c</sup>	.0020	
Hazard ratio (95% CI)	0.51 (0.33 to 0.79)	

<sup>a</sup>For patients meeting remission criteria at randomization, the duration of sustained remission (equivalent to time to loss of remission) was defined as the number of days during double-blind treatment before the first assessment at which remission criteria were no longer met or a patient discontinued due to relapse.

<sup>b</sup>Estimated from Kaplan-Meier model.

<sup>c</sup>Based on the log rank test.

Abbreviation: LOCF = last observation carried forward.

Symbol: ... = value cannot be estimated from the data available.

to their last study visit in remission (OR [95% CI] = 1.90 [1.05 to 3.44]; *P* = .0379; NNT = 7). Almost twice as many cariprazine-treated (39.6%) as placebo-treated (21.2%) patients met symptomatic remission criteria at all visits for ≥ 6 consecutive months prior to the patient’s final visit in the double-blind period (OR [95% CI] = 2.44 [1.30 to 4.55]; *P* = .0057; NNT = 6).

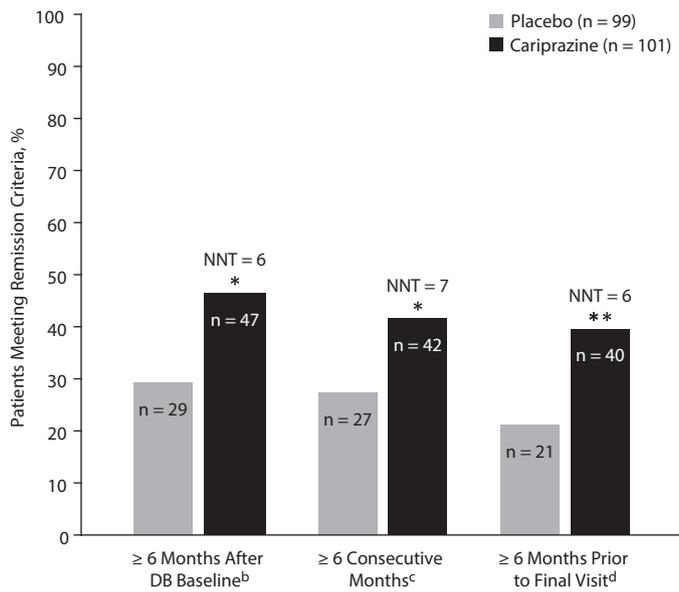
**DISCUSSION**

In this post hoc analysis of data from a long-term, placebo-controlled, relapse prevention study, cariprazine was associated with a statistically significant and clinically meaningful longer time to loss of sustained remission than placebo. Significantly more cariprazine- than placebo-treated patients met sustained remission criteria using multiple time component criteria, with medium-to-large effect sizes (NNT = 6 to 7) that were clinically meaningful. These findings suggest that cariprazine was effective in maintaining remission in stable patients with schizophrenia.

Achieving sustained remission is an important step toward well-being and recovery for patients with schizophrenia. The lifetime nature of schizophrenia necessitates ongoing pharmacologic treatment to prevent relapse in most patients<sup>2</sup>; as such, identifying treatments

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**Figure 2. Six-Month Sustained Remission Rates During the Double-Blind Phase<sup>a</sup>**



<sup>a</sup>The number of patients meeting symptomatic remission criteria and various time component criteria with cariprazine and placebo.

<sup>b</sup>Patients met remission criteria at DB baseline and all consecutive visits for ≥ 183 days.

<sup>c</sup>Patients met symptomatic remission criteria at all consecutive visits for ≥ 183 days prior to and including their last study visit in remission.

<sup>d</sup>Patients met symptomatic remission criteria at their final study visit and at all consecutive visits for ≥ 183 days prior to that visit.

Abbreviations: DB = double-blind, NNT = number needed to treat.

\* $P < .05$ .

\*\* $P < .01$ .

that can produce symptom stability over a long period of time is an important component of comprehensive clinical management. Patients who are able to maintain stability for long durations may be less likely to lose remission status or relapse, even when they are partially or intermittently nonadherent to their medication. Treatment nonadherence is frequently associated with failure to maintain remission in patients with schizophrenia,<sup>5</sup> and approximately 50%–75% of patients with schizophrenia are only partially adherent.<sup>17</sup> The results of our post hoc analyses suggest that cariprazine has the ability to sustain remission for at least 6 months, a timeframe that was selected by the RSWG based on the long-term course of schizophrenia and the characteristics intrinsic to its psychopathology (eg, delusions, hallucinations, disorganization, negative symptoms).<sup>4</sup>

In this post hoc analysis, 29/99 (29.3%) and 47/101 (46.5%) of placebo- and cariprazine-treated patients, respectively, met sustained remission criteria at 6 months after the double-blind baseline using RSWG remission criteria. These results need to be interpreted in the context of other studies that also used RSWG remission criteria. For example, a post hoc analysis evaluated sustained remission using data from a long-term, randomized, placebo-controlled relapse prevention study of quetiapine extended-release in patients with schizophrenia.<sup>18</sup> After an open-label stabilization period, almost all placebo-treated (94/102 [92.2%]) and quetiapine-treated (86/93 [92.5%]) patients were in symptomatic remission at randomization; after 6 months,

Long-Term Remission With Cariprazine in Schizophrenia 6/102 placebo-treated patients (5.9%) and 15/93 quetiapine-treated patients (16.1%) met sustained remission criteria (NNT = 10). Quetiapine compared with placebo significantly increased time to loss of sustained remission and duration of remission, with an HR of 0.39 ( $P = .009$ ). RSWG criteria have also been used to assess remission in an open-label, active-controlled, 2-year study that compared the efficacy of oral quetiapine and risperidone long-acting injectable (RLAI) for preventing relapse in symptomatically stable patients with schizophrenia or schizoaffective disorder; remission was a secondary, preplanned, prespecified, post hoc outcome. Sustained remission (meeting RSWG symptom severity criteria for ≥ 6 months) was reported for 51% of RLAI-treated patients and 39% of quetiapine-treated patients during the study.<sup>19</sup> Additionally, in a pooled, post hoc analysis that used RSWG criteria to analyze data from two 52-week studies, remission rates for ≥ 6 consecutive months were higher for aripiprazole- (32%) than for haloperidol-treated patients (22%), with an NNT of 10.<sup>20</sup>

Interestingly, separation of the cariprazine and placebo curves for time to loss of remission in our post hoc analysis was not evident until approximately 7 weeks after the start of double-blind treatment. In contrast, separation of the Kaplan-Meier curves estimating time to loss of remission for quetiapine and placebo in the previously summarized post hoc analysis occurred approximately 2–3 weeks after randomization.<sup>18</sup> Interestingly, a similar delay until separation of the curves for cariprazine versus placebo was also apparent in the cariprazine relapse prevention study; although different criteria were used to estimate relapse than sustained remission, separation of the cariprazine and placebo curves for cumulative rate of relapse also occurred at approximately 6–7 weeks.<sup>15</sup> Of note, other relapse prevention studies of similar design conducted using atypical antipsychotics have estimated comparatively shorter times to separation of the treatment- and placebo-group curves for incidence of relapse than what was observed for cariprazine and placebo, with separation occurring at approximately 1 week for asenapine,<sup>21</sup> 2–3 weeks for lurasidone<sup>22</sup> and olanzapine,<sup>23</sup> and 4 weeks for brexpiprazole.<sup>24</sup> The longer time to separation of the curves for cariprazine and placebo may be related to the relatively longer half-life of cariprazine compared with other antipsychotics and may suggest some persistent drug effect for patients switched to placebo at randomization. A delayed antipsychotic-placebo separation in placebo-controlled discontinuation trials has also been clearly described comparing the placebo substitution arms after stabilization with oral paliperidone, once-monthly paliperidone, or once-every-3-months paliperidone.<sup>25</sup> This effect of a longer maintenance of efficacy even after drug

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discontinuation, indicated by a delayed drug-placebo separation, could be relevant for preventing relapse and sustaining remission in cases of partial nonadherence, but additional cariprazine investigations are needed to better understand the corollaries related to its combined 1-week half-life.

However, other pharmacologic factors may also affect reported relapse rates. For example, differences in receptor binding affinity may affect symptom stability during periods of dose adjustment and medication switching. Namely, symptom destabilization can occur when agents that have strong antihistaminergic or anticholinergic effects (eg, quetiapine, olanzapine, asenapine) are changed too quickly to agents with lower affinity to these receptors or to placebo.<sup>26</sup> This abrupt change in receptor binding can result in rebound effects and symptoms (eg, anxiety, agitation) that could be interpreted as relapse. As such, patients undergoing abrupt discontinuation of a histaminergic or cholinergic antipsychotic, whether in the context of a switch to placebo in a clinical trial or for purposes of clinical management, should be monitored for rebound symptoms, and care should be taken so as not to confound relapse and rebound phenomena.

These analyses are subject to several limitations, including their post hoc nature and lack of an active comparator. As is common in post hoc analyses, *P* values were not controlled for multiple comparisons; additionally, the study was not powered to examine differences between cariprazine doses. The long open-label period in the cariprazine relapse-prevention study required patients to become

stable and maintain symptom stability on cariprazine; as such, patients for whom cariprazine was not effective were discontinued from the study before randomization. The requirement to meet strict stability criteria during the open-label stabilization phase resulted in a low number of completers during this phase, which may have led to a bias in the double-blind phase in favor of patients who improved on and tolerated cariprazine. These findings may not be generalizable to the overall patient population due to strict inclusion/exclusion criteria. Given these limitations, assessing sustained remission rates in real-world patients with significant comorbidities would be warranted to determine the naturalistic value of cariprazine for sustaining long-term remission in an effectiveness trial.

Despite these limitations, post hoc analyses of data from a long-term relapse prevention trial demonstrated that cariprazine was effective in maintaining stable, long-term remission in patients with schizophrenia who had previously responded to cariprazine in open-label treatment. Patients treated with cariprazine compared with placebo had significantly longer time to loss of remission and significantly higher rates of sustained remission for 6 consecutive months starting at double-blind baseline, at each visit for 6 consecutive months prior to a patient's last visit in remission during the double-blind period, and for 6 consecutive months preceding the patient's final study visit. These findings suggest that cariprazine may be an effective long-term treatment option for patients with schizophrenia, given that sustained remission is a necessary component of patient wellness and eventual functional recovery.

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