

# Efficacy of adjunctive low-dose cariprazine in major depressive disorder: a randomized, double-blind, placebo-controlled trial

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This 19-week, double-blind, placebo-controlled, randomized phase 2 study evaluated the efficacy, safety, and tolerability of adjunctive cariprazine (0.1–0.3 and 1.0–2.0 mg/day) as an antidepressant treatment for adults with treatment-resistant major depressive disorder (MDD) (NCT00854100). The primary endpoint was change in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score and the secondary was change in the Clinical Global Impression-Intensity score. Additional efficacy parameters were also assessed. A total of 231 patients were randomized. None of the predefined parameters reached significance for either cariprazine doses, but higher doses yielded numerically greater mean changes in MADRS and Clinical Global Impression-Intensity scores, and MADRS response and remission rates, compared with placebo. No differences were seen on any measures between cariprazine 0.1–0.3 mg/day and placebo. Cariprazine was relatively well tolerated, and common treatment-emergent adverse events (incidence  $\geq 5\%$  and twice the placebo group rate) in both dosage groups included headache, arthralgia, restlessness, fatigue, increased appetite, insomnia, dry mouth, and

constipation. In conclusion, both cariprazine doses were relatively well tolerated; although differences were not statistically significant, patients treated with cariprazine 1.0–2.0 mg/day had greater mean decreases in measures of depression symptoms compared with placebo, which is consistent with another adjunctive cariprazine MDD study, and thus warrants further investigation. *Int Clin Psychopharmacol* 33:312–321 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

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## Introduction

Major depressive disorder (MDD) is a chronic disease with a lifetime prevalence of 16.2% for adults in the USA (Kessler *et al.*, 2003). MDD is associated with significant morbidity (Baldessarini *et al.*, 2017), can lead to substantial disability, and has larger effects on disability and days out of role than most other medical conditions (Merikangas *et al.*, 2007). Despite the availability of a wide range of antidepressant treatment (ADT) options with diverse molecular targets, insufficient treatment response remains a significant problem in MDD, and patients frequently experience inadequate response to one or more ADTs of adequate dose and duration (Fava,

2003). Half of all patients with MDD fail to achieve adequate response (i.e.  $\geq 50\%$  reduction in Quick Inventory of Depressive Symptomatology-Self-Report score) (Rush *et al.*, 2003) to their initial ADT (Nemeroff, 2007). The STAR\*D study found that only 37% of patients achieved remission [score of  $\leq 7$  on the 17-item Hamilton Depression Rating Scale (HAMD<sub>17</sub>)] (Hamilton, 1960) during initial treatment with citalopram, a selective serotonin reuptake inhibitor (SSRI), and patients who did not achieve remission began a second treatment step (switching to another ADT, augmentation of citalopram with an additional ADT or cognitive therapy, or cognitive therapy alone), and 31% of them achieved remission (Rush *et al.*, 2006; Warden *et al.*, 2007). In addition, patients with MDD are less likely to respond, and they more likely to suffer a relapse, as treatment steps are added (Warden *et al.*, 2007).

Currently, treatment-resistant MDD is addressed by switching to another ADT medication from the same or different class (e.g. from an SSRI to a serotonin

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norepinephrine reuptake inhibitor) (Fava, 2000), combination strategy, which combines ADTs from different classes (Lam *et al.*, 2002), and adjunctive treatment to augment ADT efficacy with another class of medication, for example, a mood stabilizer or atypical antipsychotic (Nelson and Papakostas, 2009; Wright *et al.*, 2013). Some atypical antipsychotics can treat MDD effectively (Nelson and Papakostas, 2009; Wright *et al.*, 2013), but only brexpiprazole (Otsuka America Pharmaceutical Inc., 2015), aripiprazole (Otsuka America Pharmaceutical Inc., 2014), and quetiapine extended release (AstraZeneca Pharmaceuticals LP, 2013) are the Food and Drug Administration (FDA)-approved for adjunctive treatment with ADTs.

Cariprazine is an orally active atypical antipsychotic that was approved by the FDA in 2015 for the treatment of acute exacerbation of schizophrenia and manic or mixed episodes in bipolar I disorder I in adults (Allergan, 2016). Cariprazine is a potent dopamine D<sub>3</sub>-preferring D<sub>3</sub>/D<sub>2</sub> receptor partial agonist that exhibits high affinity and occupancy of both D<sub>3</sub> and D<sub>2</sub> receptors (Kiss *et al.*, 2012; Silfstein *et al.*, 2013). These characteristics make cariprazine a promising candidate for MDD treatment, because D<sub>3</sub> receptors are highly expressed in brain regions involved in motivation and reward-related behavior (Carnicella *et al.*, 2014), leading investigators to hypothesize that cariprazine may have positive effects on cognition (Marder *et al.*, 2016) and mood (Gross and Drescher, 2012; Nakajima *et al.*, 2013). Cariprazine is also a partial agonist of 5-HT<sub>1A</sub> receptors, which may enhance SSRI effects (Hayes *et al.*, 2011). In preclinical trials, cariprazine has exhibited antidepressant-like effects in various animal models of behavior (Duman *et al.*, 2012), and, in mice, these effects were found to be at least partially mediated by the D<sub>3</sub> receptor (Papp *et al.*, 2014).

Cariprazine 2.0–4.5 mg/day demonstrated efficacy and was relatively well tolerated as an adjunctive treatment to ADT in adult patients with treatment-resistant MDD in a previously published phase 2 study (Durgam *et al.*, 2016a). In addition, treatment with cariprazine 1.5 mg/day monotherapy in adults with bipolar depression significantly improved symptoms and was relatively well tolerated (Durgam *et al.*, 2016b). The present phase 2 study evaluated the efficacy, safety, and tolerability of two dosage ranges (0.1–0.3 and 1.0–2.0 mg/day) of adjunctive cariprazine with ADT.

## Patients and methods

### Study design

This was a 19-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of adjunctive cariprazine 0.1–0.3 and 1.0–2.0 mg/day in outpatients with MDD who had failed to respond to one or two previous ADTs given at adequate dose and titration (protocol MD-71; NCT00854100). The study was conducted from 2009 to 2010; patients were enrolled at

41 sites in the USA, and the protocol was approved by the Institutional Review Boards at each study center. ICH-E6 Good Clinical Practice guidelines were followed, and all participants provided written informed consent before study initiation.

The study period comprised a 1-week no-drug screening period followed by an 8-week prospective open-label ADT treatment phase (ADTs included citalopram, duloxetine, escitalopram, sertraline, or venlafaxine ER), an 8-week open-label ADT plus randomized double-blind adjunctive treatment (1:1:1 placebo, cariprazine 0.1–0.3 or 1–2 mg/day) phase, and a 2-week safety follow-up period. Adjustments to ADT dosage were permitted through week 4 of the open-label period, and ADT nonresponders at week 8 were randomized (Supplementary Fig., Supplemental digital content 1, <http://links.lww.com/ICP/A45>). ADT responders [i.e. those who achieved  $\geq 50\%$  improvement in HAMD<sub>17</sub> total score, HAMD<sub>17</sub> total score  $\leq 14$ , or Clinical Global Impressions-Improvement (CGI-I) score  $< 3$ ] (Guy, 1976) continued their respective open-label ADT and single-blind placebo adjunct treatment for 8 weeks.

Treatment allocation randomization codes were generated by Statistical Programming. Each drug package label had a randomization number, and each study center was provided drug supplies corresponding to a sequence of patient randomization numbers for the double-blind phase. ADT nonresponders were assigned drug supplies corresponding to the randomization sequence, as they entered the double-blind phase. Investigational product was provided as 2-week blister packs at each visit; placebo and active cariprazine capsules were identical in appearance, taste, and packaging. All patients, investigators, and study staff remained blinded to double-blind treatment allocation (while only patients were blinded during the single-blind period) for the full duration of the study, until database lock.

In the first week of the double-blind period, the cariprazine 1.0–2.0 mg/day group received 0.5 mg/day cariprazine, and was titrated to 1.0 mg/day in the second week. The cariprazine 0.1–0.3 mg/day group were treated with 0.1 mg/day cariprazine from randomization to week 12. After 4 weeks of treatment, doses could be increased to 0.3 or 2.0 mg/day for patients in the 0.1–0.3 and 1.0–2.0 mg/day groups, respectively, if inadequate response [ $< 40\%$  Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) improvement and MADRS score  $> 10$ ] and no significant tolerability problems occurred. If tolerability issues developed after a dose increase, reduction to starting dose was allowed between weeks 12 and 14. No dose adjustments were allowed during the first 4 or final 2 weeks of double-blind treatment. Randomized patients' ADT dose was the same as that of the open-label period.

To select the maximum dose of cariprazine for this first study on adjunctive cariprazine for MDD, phase 1 results

available before study initiation, which indicated a maximum tolerated dose of 1.0 mg/day in healthy individuals and 12.5 mg/day in patients with schizophrenia, were considered. Cariprazine 2.0 mg/day was hypothesized as the highest tolerated dose for patients with MDD, a previously untested population, and chosen for this study. The cariprazine 0.1–0.3 mg/day was selected on the basis of efficacy at low doses in preclinical studies (Papp *et al.*, 2014) and tolerability concerns for outpatient participants.

### Patients

Male or female outpatients (18–65 years) who met the *Diagnostic and Statistical Manual of Mental Disorders*, fourth ed., Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) criteria for moderate to severe MDD without psychotic features, on the basis of the Mini-International Neuropsychiatric Interview were eligible for inclusion (Sheehan *et al.*, 1997). Patients had a current major depressive episode of at least 8 weeks in which they failed to respond to one or two adequate trials of ADT (<50% reduction in depressive symptoms using the Antidepressant Treatment Response Questionnaire) (Fava, 2003). At screening and baseline, patients had a 17-item HAMD<sub>17</sub> score of at least 18 and 24-item HAMD (HAMD<sub>24</sub>) score of at least 2 on item 1.

Exclusion criteria included the following: a principal axis I disorder or any axis I disorder other than MDD that was the primary focus of treatment within 6 months; history of depressive episodes with psychotic features; meeting the DSM-IV-TR criteria for any manic or hypomanic episode, obsessive compulsive, psychotic, borderline, or antisocial disorders; anorexia nervosa or bulimia; and dementia or other cognitive disorder. Patients with alcohol or substance abuse or dependence in the past 6 months, risk of injuring others or self, or suicide risk [attempt within the past year, investigator's judgement, Columbia-Suicide Severity Rating Scale (Posner *et al.*, 2011) survey, or MADRS item 10 score  $\geq 5$ ] were also excluded. Patients had a BMI (kg/m<sup>2</sup>) of at least 18 to 40 or less, normal physical, laboratory, and ECG results, and no concurrent medical condition that would have interfered with the study. Patients were not permitted to have taken any antipsychotic, anticonvulsant, mood stabilizer, anxiolytic, sedative/hypnotic medication, or ADT for longer than 1 week or 5 half-lives of the medication before baseline. Electroconvulsive therapy, adjunctive antipsychotic treatment, vagus nerve or transcranial magnetic stimulation, or any experimental CNS treatment within the previous 6 months or in the current episode, or previous inadequate response to electroconvulsive therapy, monoamine oxidase inhibitor, or adjunctive antipsychotic treatment, or any depot antipsychotic use was prohibited.

### Outcome measures

Primary and secondary efficacy parameters were MADRS total and CGI-I score changes from baseline (week 8) to

end of the double-blind treatment (week 16) compared with placebo, respectively. Additional parameters included changes in CGI-Severity (CGI-S) score (Guy, 1976), HAMD<sub>17</sub> and HAMD<sub>24</sub> total and subsection scores, and, at week 16, MADRS response ( $\geq 50\%$  improvement from baseline) and remission rates (total score  $\leq 10$ ), HAMD<sub>17</sub> remission rates (total score  $\leq 7$ ), and CGI-I response rates (score  $\leq 2$ ) versus placebo. The HAMD<sub>24</sub>, MADRS, and CGI-S assessments were conducted at each visit (weeks 1, 2, 4, 6, and 8 of the double-blind phase), except screening, from baseline to end of double-blind treatment, while HAMD<sub>24</sub> was obtained at screening and each visit of the double-blind phase.

Safety assessments that occurred at every visit included adverse event (AE) reporting, and monitoring of vital signs and suicide risk. Laboratory tests, ECGs, and evaluations of extrapyramidal symptoms, using the Abnormal Involuntary Movement, Barnes Akathisia Rating (Barnes, 1989), and Simpson-Angus Scales (Simpson and Angus, 1970) were also recorded at least once during the double-blind period.

### Statistical analyses

The double-blind safety population consisted of randomized patients who received at least one dose of double-blind study medication. The intent-to-treat population included all patients in the double-blind safety population with a baseline and at least one additional MADRS assessment during double-blind treatment. Analyses of MADRS, CGI-I, CGI-S, HAMD<sub>17</sub>, and HAMD<sub>24</sub> score changes were analyzed using a mixed-effects model for repeated measures, with treatment group, study center, visit, and treatment group-by-visit interaction as fixed effects, and baseline values and baseline-by-visit interactions as covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. The analysis was performed on the basis of all postbaseline scores using only the observed cases without imputation of missing values.

For the study to be considered positive, at least one cariprazine dosage group had to show a statistically significant decrease in mean MADRS total score from baseline compared with placebo after multiplicity adjustment. A closed testing procedure was used for multiplicity adjustment across the two dose ranges and primary and secondary efficacy endpoints. The primary comparison between placebo and the average of the two dosage groups (0.0–0.3 or 1.0–2.0 mg/day) in MADRS total score was tested at the two-sided 5% significance level, and, if the primary comparison was positive, the pair-wise comparison between placebo and each of the two cariprazine flexible dosage groups was tested at the two-sided 5% significance level. Statistical hypothesis tests for all efficacy measures were two-sided at a 5% level of significance for main effects. Two-sided 95%

confidence intervals were also estimated for all applicable measures.

Analyses of response and remission rates were performed using a logistic regression model, with treatment group and the corresponding baseline values as the explanatory variables.

All safety parameters were summarized with descriptive statistics.

To determine sample size, it was estimated that 75 patients per treatment would provide ~85% power to detect a treatment effect difference of 3.8 points in MADRS score change between placebo and the mean of the two cariprazine dose groups at the two-sided significance level of 5%. This assumed a common SD of 8 for the primary efficacy parameters, a correlation coefficient of 0.5 for within-patient assessments, and a 30% patient drop-out rate.

Study raters performing MADRS assessments received training and certification in the rating scales used in this study by Concordant Rater Systems. To monitor and manage study raters, each patient completed a computerized MADRS assessment, and the data were compared against data from the study center rater assessment.

## Results

### Patient characteristics and disposition

Of 502 patients enrolled in the open-label period, 403 completed treatment (Fig. 1), and 172 (42.7%) were classified as responders. Of the 231 nonresponders who began double-blind treatment, 81, 76, and 74 were randomized to placebo, cariprazine 0.1–0.3 mg/day, and 1.0–2.0 mg/day, respectively. Of 230 safety and intent-to-treat patients, 205 (89.1%) completed treatment. Most premature discontinuations were due to protocol violations [nine (3.9%)], and causes of discontinuation were generally comparable among groups.

ADT responders ( $n=172$ ) continued ADT and adjunctive placebo, and two discontinued (one withdrew consent and one was lost to follow-up) before week 6 and were not included in this safety population. Data for responders were collected, but are not reported here.

Baseline demographics and disease history were generally similar among groups (Table 1).

### Efficacy

MADRS changes (primary endpoint) were not statistically significant in either cariprazine group, but cariprazine 1.0–2.0 mg/day showed a nonsignificant greater reduction in depressive symptoms (MADRS least squares mean difference,  $-1.8$ ;  $P=0.227$ ) compared with placebo. No improvement was observed with cariprazine 0.1–0.3 mg/day treatment (Fig. 2a).

Although not statistically significant, cariprazine 1.0–2.0 mg/day exhibited a nonsignificant greater improvement in

CGI-I scores relative to placebo (Table 2). No significant differences were observed in either group versus placebo in any additional efficacy parameters. MADRS response and remission rate differences were not statistically significant, but were nonsignificantly greater in both cariprazine dose groups relative to placebo (Fig. 2b). CGI-I response rates did not reach statistical significance, but were nonsignificantly greater with cariprazine 1.0–2.0 mg/day (Table 2).

## Safety

### Exposure

In the safety population, mean treatment duration days, were as follows: placebo, 53.8; cariprazine 0.1–0.3 mg/day, 53.4; and cariprazine 1.0–2.0 mg/day, 51.2. The mean daily cariprazine dose was 0.2 and 1.1 mg/day for cariprazine 0.1–0.3 and 1.0–2.0 mg/day treatment groups, respectively.

### Adverse events

In the open-label period, 379 (75.5%) patients reported any treatment-emergent adverse event (TEAE). A summary of commonly occurring TEAEs during this phase is presented in Supplementary Table (Supplemental digital content 2, <http://links.lww.com/ICP/A46>). Nine patients reported serious AEs, five patients reported AEs that led to treatment discontinuation, and one death occurred (completed suicide by intentional overdose with zolpidem tartrate; patient had received duloxetine for 42 days and was not randomized).

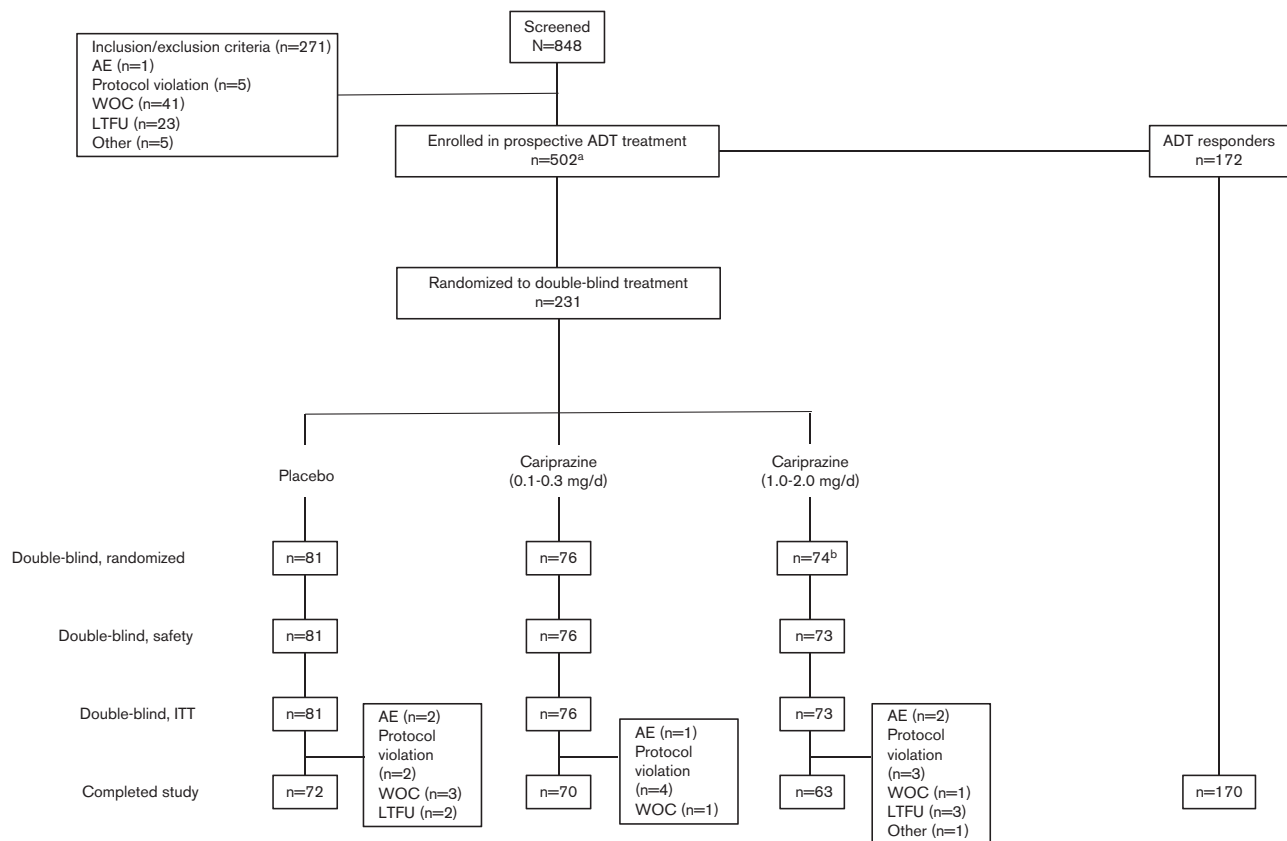
Serious AEs reported during double-blind treatment included unstable angina (placebo) and chronic obstructive pulmonary disease (1.0–2.0 mg/day group). Commonly occurring TEAEs (occurring in  $\geq 5\%$  of patients and with an incidence of at least twice the placebo rate) were headache and arthralgia with cariprazine 0.1–0.3 mg/day, and headache, restlessness, fatigue, increased appetite, insomnia, dry mouth, and constipation with cariprazine 1.0–2.0 mg/day (Table 3). Most TEAEs were mild to moderately severe (placebo, 95.1%; 0.1–0.3 mg/day, 94.7%, and 1.0–2.0 mg/day, 93.2%). Discontinuations due to AEs occurred in two (2.5%), one (1.3%), and one (2.7%) patients, respectively, in placebo, cariprazine 0.1–0.3, and 1.0–2.0 mg/day. No deaths occurred during the double-blind phase.

No newly emergent AEs were reported in more than 4% of patients in any group in the safety follow-up period.

### Extrapyramidal symptoms-related events

Akathisia occurred more frequently with cariprazine 1.0–2.0 mg/day compared with placebo, but less frequently with cariprazine 0.1–0.3 mg/day (Table 3). Treatment-emergent parkinsonism (Simpson-Angus Scales score  $> 3$ ) occurred in 2 patients in each treatment group. The incidence of treatment-emergent akathisia (Barnes Akathisia Rating score  $> 2$ ), was highest with cariprazine 1.0–2.0 mg/day, followed by placebo and then cariprazine 0.1–0.3 mg/day (Table 3).

Fig. 1



Patient disposition. ADT, antidepressant therapy; AE, adverse event; ITT, intent-to-treat; LTFU, lost to follow-up; WOC, withdrawal of consent. <sup>a</sup>Overall, 403 patients completed the prospective ADT treatment phase; of these patients, 231 patients did not respond to ADT and were randomized to the double-blind treatment group (double-blind safety population), and 172 patients did respond to ADT and continued receiving ADT treatment and placebo; one death occurred (suicide by intentional overdose) in the prospective ADT treatment period. <sup>b</sup>One randomized patient withdrew consent before receiving the investigational product.

### Laboratory parameters, vital signs, and ECG

Minimal mean changes from baseline were observed and generally comparable across treatment groups for vital signs, waist circumference, and BMI (Table 4). Fewer patients treated with cariprazine 1.0–2.0 mg/day had orthostatic hypotension (9.4%) relative to placebo (20%) or cariprazine 0.1–0.3 mg/day (15.1%). A greater number of patients had at least 7% increase in body weight with cariprazine 1.0–2.0 mg/day (15.1%) than in placebo (3.7%) or cariprazine 0.1–0.3 mg/day (1.3%).

Mean changes in laboratory parameters were generally comparable across treatments, except for insulin and prolactin levels, both of which had a greater mean increase with cariprazine 1.0–2.0 mg/day than with placebo (Table 4).

### Suicidality

No suicidal behavior was reported during double-blind treatment, and the incidence of measured suicidal ideation was higher in patients treated with placebo than either cariprazine dose as measured with the Columbia-Suicide

Severity Rating Scale (19.8%, placebo; 11.8%, cariprazine 0.1–0.3 mg/day; and 12.3%, cariprazine 1.0–2.0 mg/day).

### Discussion

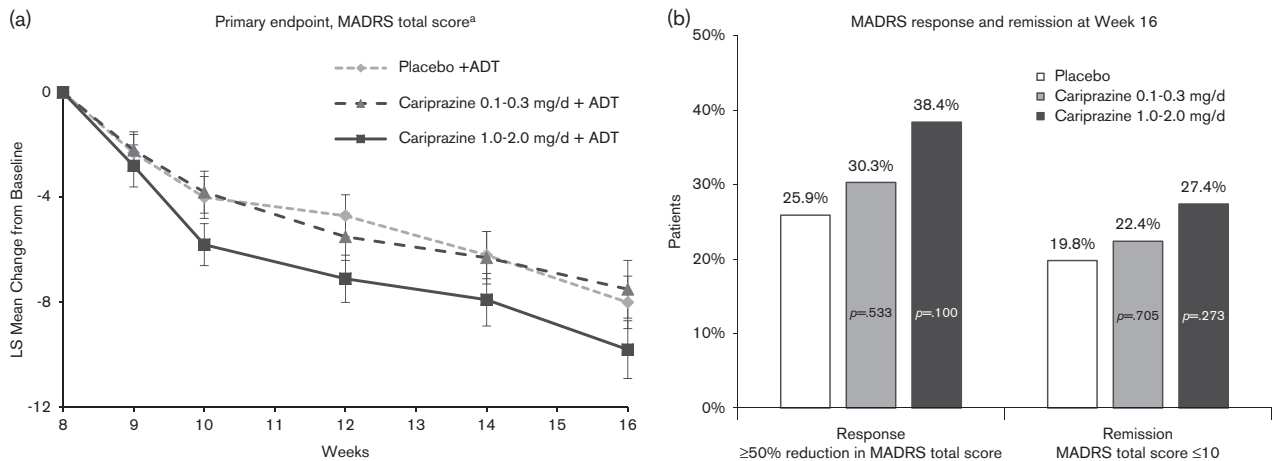
In this phase 2 study, cariprazine 0.1–0.3 and 1.0–2.0 mg/day did not show statistically significant superiority to placebo in any efficacy measures. Therefore, this was a negative study, but cariprazine 1.0–2.0 mg/day did show a nonsignificant greater reduction (i.e. improvement) in depressive symptoms compared with placebo. Both dosage ranges of cariprazine were well tolerated as an adjunctive to ADT in adult patients with MDD and previous inadequate ADT response. While cariprazine 0.1–0.3 mg/day did not separate from placebo in any predefined endpoints, cariprazine 1.0–2.0 mg/day led to a nonsignificantly higher reduction in depressive symptoms in nearly every parameter assessed compared with placebo. The MADRS treatment effect for cariprazine 1.0–2.0 mg/day was –1.8 points, which approaches the two-point threshold commonly considered clinically relevant (Montgomery and Moller, 2009). Previously, a

**Table 1** Baseline characteristics of the double-blind safety population

	Placebo + ADT (n = 81)	Cariprazine + ADT	
		0.1–0.3 mg/day (n = 76)	1.0–2.0 mg/day (n = 73)
Age [mean (SD)] (years)	45.2 (10.2)	46.6 (11.7)	44.2 (12.1)
Women [n (%)]	61 (75.3)	52 (68.4)	51 (69.9)
White [n (%)]	69 (85.2)	57 (75.0)	60 (82.2)
Black or African American [n (%)]	10 (12.3)	15 (19.7)	11 (15.1)
Asian [n (%)]	0	2 (2.6)	1 (1.4)
Weight [mean (SD)] (kg)	84.3 (15.1)	84.0 (17.8)	83.5 (16.1)
BMI [mean (SD)] (kg/m <sup>2</sup> )	30.0 (5.0)	29.5 (5.6)	29.5 (5.5)
Age at MDD onset [mean (SD)] (years)	29.0 (12.2)	30.6 (12.1)	28.6 (12.7)
Recurrent MDD [n (%)]	69 (85.2)	65 (85.5)	61 (83.6)
Duration of current episode [mean (SD)] (months)	31.9 (62.1)	25.0 (33.5)	26.5 (53.0)
Duration of MDD [n (%)] (years)			
≤ 1	5 (6.2)	6 (7.9)	6 (8.2)
> 1–3	4 (4.9)	7 (9.2)	14 (19.2)
> 3–5	7 (8.6)	7 (9.2)	2 (2.7)
> 5	65 (80.2)	56 (73.7)	51 (69.9)
Baseline MADRS total score <sup>a</sup> [mean (SD)]	26.4 (6.3)	26.6 (7.0)	26.3 (6.5)
Open-label ADT [n (%)]			
Citalopram	7 (8.6)	12 (15.8)	9 (12.3)
Duloxetine	22 (27.2)	20 (26.3)	23 (31.5)
Escitalopram	20 (24.7)	18 (23.7)	20 (27.4)
Sertraline	11 (13.6)	10 (13.2)	7 (9.6)
Venlafaxine ER	21 (25.9)	16 (21.1)	14 (19.2)

% , Proportion of patients; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; n, number of patients.  
<sup>a</sup>Six patients were enrolled twice in the study; only data from the first enrollment phase are included. Baseline for the double-blind treatment phase is the last nonmissing assessment before the first dose of double-blind investigational product.

**Fig. 2**



(a) MADRS total score changes from baseline by study visit, and (b) MADRS response and remission rates. (a) Primary endpoint, MADRS total score<sup>a</sup>. (b) MADRS response and remission at week 16. Six patients were enrolled twice in the study. Only data from the first enrollment phase are included. <sup>a</sup>Mean changes from baseline by study visit in MADRS total score (ITT population), LS mean (SE), LSMD versus placebo, and P values are based on an MMRM model with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and the baseline value and baseline-by-visit interaction as the covariates. <sup>b</sup>Response and remission at week 16 (LOCF), analyses of response and remission (LOCF) rates were performed using a logistic regression model, with treatment group and the corresponding baseline values as the explanatory variables. ITT, intent-to-treat; LOCF, last observation carried forward; LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

positive adjunctive trial of cariprazine 2.0–4.5 mg/day exhibited an MADRS treatment effect of –2.2 points (Durgam *et al.*, 2016a); however, the cariprazine mean daily dose was 2.6 mg in that study compared with 1.1 mg in this trial. These findings indicate that cariprazine doses of more than 1.0–2.0 mg/day may increase the

therapeutic response, and should therefore be investigated further.

Changes in laboratory parameters, vital signs, waist circumference, and BMI were generally small and comparable across treatment groups, while orthostatic hypotension

Table 2 Efficacy end points

Efficacy parameters at week 16	Placebo + ADT (n = 81)	Cariprazine + ADT	
		0.1–0.3 mg/day (n = 76)	1.0–2.0 mg/day (n = 73)
MADRS total score <sup>a</sup>			
Baseline [mean (SD)]	26.4 (6.3)	26.6 (7.0)	26.3 (6.5)
LS change at week 16 [mean (SE)]	-8.0 (1.0)	-7.5 (1.1)	-9.8 (1.1)
LSMD (95% CI)	-	0.5 (-2.4 to 3.4)	-1.8 (-4.8 to 1.1)
P value	-	0.746	0.227
CGI score-1 <sup>b</sup>			
Baseline [mean (SD)]	2.6 (0.1)	2.5 (0.1)	2.3 (0.1)
LS at week 16 [mean (SE)]	2.5 (0.1)	2.5 (0.1)	2.3 (0.1)
LSMD (95% CI)	-	0.0 (-0.3 to 0.3)	-0.2 (-0.6 to 0.1)
P value	-	0.918	0.167
CGI response (score ≥ 2) <sup>c</sup>			
Responders	49.4	47.4	58.9
Odds ratio vs. placebo (95% CI)	0.9 (0.5–1.7)	1.5 (0.8–2.8)	1.2 (0.7–2.0)
P value	-	0.805	0.229
CGI-S score <sup>a</sup>			
Baseline [mean (SD)]	4.0 (0.5)	4.1 (0.6)	4.2 (0.7)
LS change at week 16 [mean (SE)]	-0.9 (0.1)	-0.9 (0.1)	-1.3 (0.1)
LSMD (95% CI)	-	0.1 (-0.2 to 0.4)	-0.3 (-0.7 to 0.0)
P value	-	0.569	0.058
HAMD <sub>17</sub> total score <sup>a</sup>			
Baseline [mean (SD)]	19.7 (3.9)	20.3 (4.4)	20.2 (4.3)
LS change at week 16 [mean (SE)]	-5.9 (0.8)	-6.1 (0.8)	-7.4 (0.8)
LSMD (95% CI)	-	-0.2 (-2.3 to 1.9)	-1.5 (-3.7 to 0.6)
P value	-	0.829	0.166
HAMD <sub>24</sub> total score <sup>a</sup>			
Baseline [mean (SD)]	24.5 (5.9)	25.7 (6.6)	24.9 (6.1)
LS mean change at week 16 [mean (SE)]	-7.6 (1.0)	-7.9 (1.0)	-9.5 (1.1)
LSMD (95% CI)	-	-0.3 (-3.0 to 2.5)	-1.9 (-4.7 to 0.9)
P value	-	0.847	0.184

Six patients were enrolled twice in the study. Only data from the first enrollment phase are included.

ADT, antidepressant therapy; CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; CI, confidence interval; HAMD<sub>17</sub>, Hamilton Depression Rating Scale, 17 item; HAMD<sub>24</sub>, Hamilton Depression Rating Scale, 24 item; ITT, intent-to-treat; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures; n, number of patients.

<sup>a</sup>LS mean (SE), LSMD versus placebo, 95% CI, and P values are based on an MMRM model with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and the baseline value and baseline-by-visit interaction as the covariates.

<sup>b</sup>LS mean (SE), LSMD versus placebo, 95% CI, and P values are based on an MMRM model with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and visit two CGI-S score and visit two CGI-S score-by-visit interaction as the covariates.

<sup>c</sup>Analyses of response and remission rates were performed using a logistic regression model, with treatment group and the corresponding baseline values as the explanatory variables.

and suicidal thoughts/behaviors were lower with cariprazine 1.0–2.0 mg/day compared with placebo. In this study, the incidence of TEAEs was lower than that reported in previously published cariprazine MDD (Durgam *et al.*, 2016a) and monotherapy bipolar mania trials (Durgam *et al.*, 2015; Sachs *et al.*, 2015). A notable AE in this population, akathisia, had a generally lower occurrence (5.5%) than that observed in other adjunctive antipsychotic MDD trials: aripiprazole (25%) (Otsuka America Pharmaceutical Inc., 2014), brexpiprazole (4–14%) (Otsuka America Pharmaceutical Inc., 2015), and cariprazine (2.0–4.5 mg/day, 22.3%) (Durgam *et al.*, 2016a), but was higher than that reported for quetiapine fumarate (2%) (AstraZeneca Pharmaceuticals LP, 2013). The tolerability of cariprazine 1.0–2.0 mg/day provides additional support for assessing higher doses in future trials.

While not significant, the difference in MADRS response rates between cariprazine 1.0–2.0 mg/day and placebo was greater than the 10% threshold generally considered clinically significant (Montgomery and Moller, 2009). The mean difference in cariprazine and placebo

responders (12.5%) was greater than the difference in the previous cariprazine 2.0–4.5 mg/day aydose group in the positive trial (11.1%) (Durgam *et al.*, 2016a), and similar to SSRIs/serotonin norepinephrine reuptake inhibitors response rates (compared with placebo) in the study data submitted to the FDA (mean: 16%; range: 3.3–49.6%; Melander *et al.*, 2008).

The lack of statistical significance may be partially explained by the small sample size of ~70 patients per group for a three-way comparison of two dosage groups and placebo. The overall population (N = 230), when compared with the patient population in other adjunctive antipsychotic trials, was more than 30% smaller than that of the trials of aripiprazole, and approximately half that of quetiapine fumarate and brexpiprazole (all pivotal trials), and cariprazine 2.0–4.5 mg/day (Durgam *et al.*, 2016a). Another possible explanation for the lack of significance is the selection of a cariprazine dose too low to be effective, and delayed dose increases due to the fixed-flexible dose study design. By not allowing increases to the maximum dose until halfway through the

double-blind phase, patients may not have received potentially efficacious doses for sufficient durations to achieve clinically relevant responses. Finally, the negative results may be partly due to longer current

depressive episode duration in study participants (mean: ~2.3 years), compared with that in the participants of the positive cariprazine trial (~7.5 months) (Durgam *et al.*, 2016a) and positive aripiprazole trial (~18 months) (Berman *et al.*, 2009), given that shorter current episodes appear to increase the likelihood of positive treatment outcomes (Habert *et al.*, 2016).

**Table 3 Summary of adverse events (double-blind safety population)**

Adverse event summary	Placebo + ADT (n=81) [n (%)]	Cariprazine + ADT	
		0.1-0.3 mg/ day (n=76) [n (%)]	1.0-2.0 mg/ day (n=73) [n (%)]
Any TEAE	47 (58.0)	42 (55.3)	48 (65.8)
Serious AEs	1 (1.2)	0	1 (1.4)
Discontinuations due to AEs	2 (2.5)	1 (1.3)	2 (2.7)
Common TEAEs (reported by ≥5% of patients in any treatment group) <sup>a</sup>			
Headache	2 (2.5)	6 (7.9)	6 (8.2)
Restlessness	1 (1.2)	1 (1.3)	6 (8.2)
Dizziness	4 (4.9)	4 (5.3)	5 (6.8)
Fatigue	2 (2.5)	1 (1.3)	5 (6.8)
Increased appetite	1 (1.2)	1 (1.3)	5 (6.8)
Insomnia	2 (2.5)	1 (1.3)	5 (6.8)
Nasopharyngitis	4 (4.9)	0	5 (6.8)
Nausea	4 (4.9)	4 (5.3)	5 (6.8)
Dry mouth	1 (1.2)	2 (2.6)	4 (5.5)
Constipation	1 (1.2)	1 (1.3)	4 (5.5)
Akathisia	3 (3.7)	2 (2.6)	4 (5.5)
Diarrhea	4 (4.9)	4 (5.3)	2 (2.7)
Arthralgia	1 (1.2)	4 (5.3)	1 (1.4)

Six patients were enrolled twice in the study. Only data from the first enrollment phase are included.

Version 13.0 of MedDRA was used to code adverse events.

%, Proportion of patients with TEAE; ADT, antidepressant therapy; n, number of patients with TEAE; TEAE, treatment-emergent adverse events.

<sup>a</sup>Patients were counted only once within each preferred term.

If a patient had more than one occurrence in the same event category, only the most related occurrence was counted.

The eight-point change in the MADRS score for placebo was numerically greater than those reported in the seven aripiprazole or brexipiprazole augmentation trials with similar study designs (Berman *et al.*, 2007, 2009; Marcus *et al.*, 2008; Kamijima *et al.*, 2013; Lenze *et al.*, 2015; Thase *et al.*, 2015a, 2015b), and high placebo response can reduce signal detection, which may lead to negative results (Fava *et al.*, 2003). The magnitude of placebo response may be partially attributed to rating errors (despite the use of Concordant Rater Systems), and to the study design; as the number of treatment arms or dosage groups increase, patients' perception that they will benefit from treatment also increases (Papakostas and Fava, 2009). Another potential contributor to the placebo response was the requirement that patients take additional capsules when increasing their dose (Alphs *et al.*, 2012).

Limitations of the current study included lack of an active comparator, which prevented determination of the assay sensitivity, and low fractional doses of cariprazine, which were selected on the basis of preclinical studies that showed efficacy at low doses (Papp *et al.*, 2014) and concerns about tolerability in outpatients. However, in

**Table 4 Additional safety outcomes**

Measures	Placebo		Cariprazine 0.1–(0.3 mg/day)		Cariprazine (1.0–2.0 mg/day)	
	n	Mean change (SD)	n	Mean change (SD)	n	Mean change (SD)
<b>Vital signs</b>	81		76		73	
Systolic blood pressure (supine) (mmHg)		2.9 (9.6)		1.1 (10.8)		−0.8 (10.5)
Diastolic blood pressure (supine) (mmHg)		2.5 (8.7)		0.7 (7.6)		1.0 (7.8)
Heart rate (supine) (bpm)		−1.2 (10.7)		−0.4 (9.4)		0.5 (11.1)
Body weight (kg)		0.6 (2.6)		0.1 (2.5)		1.4 (3.6)
Waist circumference (cm)		−0.2 (4.5)		−0.4 (4.5)		0.2 (4.7)
BMI (kg/m <sup>2</sup> )		0.2 (0.9)		0.0 (0.9)		0.5 (1.3)
<b>Laboratory tests</b>						
Glucose (fasting) (mmol/l)	68	0.0 (0.6)	68	−0.1 (0.8)	58	0.1 (0.8)
Insulin (pmol/l)	78	17.7 (107.3)	75	19.5 (126.3)	66	66.9 (197.3)
Prolactin (ng/ml)	78	0.8 (3.6)	75	1.7 (3.8)	67	4.9 (9.3)
Creatine kinase (U/l)	78	10.5 (47.7)	75	5.2 (54.7)	67	6.6 (54.6)
<b>Lipids</b>	78		75		67	
Total cholesterol (mmol/l)		−0.2 (0.8)		0.0 (0.8)		−0.1 (1.1)
HDL (mmol/l)		0.0 (0.2)		0.0 (0.2)		0.0 (0.2)
LDL (mmol/l)		−0.1 (0.7)		0.0 (0.7)		−0.1 (0.8)
<b>Liver function</b>	78		75		67	
Alanine aminotransferase (U/l)		2.2 (11.0)		1.7 (18.7)		4.4 (20.9)
Alkaline phosphatase (U/l)		−0.8 (12.4)		−0.4 (13.2)		−1.5 (13.8)
Aspartate aminotransferase (U/l)		1.8 (8.3)		−0.5 (8.9)		1.9 (10.2)
Total bilirubin (μmol/l)		−1.0 (2.8)		−0.7 (4.6)		−1.3 (3.3)

Six patients were enrolled twice in the study. Only data from the first enrollment period are included.

Only patients with available baseline and at least one postbaseline value in the double-blind treatment phase are included in the analyses.

Mean change is mean change from baseline to end of treatment. Baseline was defined as the last assessment before the start of the prospective ADT phase. End of treatment is defined as the last available assessment in the double-blind treatment period.

HDL, high-density lipoprotein; LDL, low-density lipoprotein, n, number of patients.



this study, patients tolerated cariprazine 1.0–2.0 mg/day reasonably well, and, in a study initiated subsequently, no significant tolerability issues with doses up to 4.5 mg/day were reported (Durgam *et al.*, 2016a). Another limitation of the study was the fixed-flexible dose study design, which may be more representative of real-world practice, but it prevented analysis of specific dosages. As with all studies, patient characteristics and differences across treatment groups at baseline have the potential to confound results. For example, the proportion of placebo patients with MDD duration of more than 5 years was higher than in the two cariprazine groups, which might have influenced the findings (Perlis, 2013). Finally, the exclusion of patients with other primary axis I disorders may prevent generalization of these results to all patients with MDD.

The numerically greater, but not statistically significant, reduction (improvement) in depressive symptoms from baseline, compared with placebo, of cariprazine 1.0–2.0 mg/day that is reported, is consistent with the results of adjunctive cariprazine 2.0–4.5 mg/day from another placebo-controlled trial (Durgam *et al.*, 2016a). Alternatively, in that previous trial, patients with MDD who received higher doses of adjunctive cariprazine had significantly greater improvements in MADRS total score compared with placebo by week 2 that were maintained to the end of the study. CGI-I and CGI-S score improvements were also significantly greater with cariprazine 2.0–4.5 mg/day treatment than with placebo in that trial (Durgam *et al.*, 2016a), and significantly greater rates of MADRS response occurred with both cariprazine 1.0–2.0 and 2.0–4.5 mg/day treatment. Significant differences in response rates from placebo were detected at weeks 3 and 2 for the cariprazine 1.0–2.0 and 2.0–4.5 mg/day groups, respectively (Durgam *et al.*, 2016a). It is likely that the cariprazine 1.0–2.0 mg/day used in the present study was too low to reach therapeutic significance, warranting future studies to characterize the optimal therapeutic dose of cariprazine, and its efficacy, safety, and tolerability as an adjunctive treatment for adults with MDD.

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## Conflicts of interest

Drs. Durgam, Earley, Lu, and Hayes acknowledge a potential conflict of interest as employees of Allergan. Dr.

Durgam is a stock shareholder of Allergan. Drs. Laszlovszky and Németh acknowledge a potential conflict of interest as employees of Gedeon Richter Plc. Drs. Laszlovszky and Németh are patent owners of the investigational medicinal product used in this study. Dr. Fava's disclosure statement can be viewed online at [http://mghcme.org/faculty/faculty-detail/maurizio\\_fava](http://mghcme.org/faculty/faculty-detail/maurizio_fava).

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