***ORIGINAL RESEARCH***

*Key Words: major depressive disorder, antidepressant agents, antipsychotic agents, depressive disorder, treatment-resistant, randomized-placebo controlled trial, cariprazine, clinical trial, Phase 3*

# Cariprazine Augmentation to Antidepressant Therapy in Major Depressive Disorder: Results of a Randomized, Double-Blind, Placebo-Controlled Trial

*By Willie R. Earley, Hua Guo, György Németh, Judit Harsányi, Michael E. Thase*

***ABSTRACT*** *~ Cariprazine is an atypical antipsychotic currently under investigation as an adjunctive to antidepressant treatment (ADT) for patients with major depressive disorder (MDD). Here results of an 18- to 19-week randomized double-blind placebo-controlled Phase 3 study evaluating the efficacy of adjunctive cariprazine (1.5–4.5 mg/day[d]) with ADT in participants with previous inadequate response to ADT are presented. ADT response was assessed in an 8-week open-label period; inadequate responders were randomized (N = 530) to open-label ADT plus placebo (n = 261) or cariprazine (n = 269) for the 8-week double-blind phase (NCT01715805). Primary and secondary endpoints were changes at week 8 (cariprazine versus placebo) in Montgomery–Åsberg Depression Rating Scale (MADRS) total score and in Sheehan Disability Scale (SDS) score, respectively, which were analyzed by mixed-effect models for repeated measures. Cariprazine did not significantly improve scores in either compared to placebo, but non-significantly reduced depressive symptoms (MADRS least-squares mean difference [LSMD]: −0.2, P = 0.7948 and SDS LSMD: −0.7, P = 0.2784). Of additional efficacy parameters, cariprazine significantly improved Clinical Global Impressions – Improvement (CGI-I) scores versus placebo (LSMD: −0.2; P = 0.0410). A greater proportion of participants achieved MADRS response with cariprazine vs placebo, but differences were not significant. Cariprazine was generally well-tolerated, and metabolic parameters and body weight changes were not meaningfully different than placebo. Common newly-emergent adverse events included akathisia and restlessness. The lack of significant improvement in depressive symptoms with adjunctive cariprazine and ADT for MDD in inadequate responders contrasts with previously published results, therefore additional studies are needed to understand role of adjunctive cariprazine in MDD.* Psychopharmacology Bulletin. *2018;48(4):62–80.*

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## Introduction

Major depressive disorder (MDD) is common,[1,2] causes substantial disability[3,4] and high economic burden worldwide.[5] Resistance to antidepressant treatment (ADT) is associated with approximately 30% higher medical costs compared with patients who respond to treatment.[6] Insufficient response to treatment remains a significant problem in MDD despite decades of research on the relationship of neurotransmitters to depression, patients frequently lack sufficient response to 1 or more ADTs of adequate dose and duration.[7] Additionally, half of patients with MDD fail to achieve adequate response to initial ADT,[8] and as more treatment steps are added, the likelihood of response decreases while risk of relapse increases.[9] One current approach for addressing treatment-resistant MDD is switching to, or combining with, additional treatments in the same or different class as the initial ADT.[10–13] Some atypical antipsychotics have demonstrated efficacy in MDD and are one class of medication used to treat MDD adjunctively with standard ADTs.[13,14]



Cariprazine, approved in 2015 in the United States for the treatment of acute exacerbation of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adults, is an orally active and potent dopamine $D_3$-preferring $D_3/D_2$ receptor and serotonin 5-$HT_{1A}$ receptor agonist atypical antipsychotic.[15] Cariprazine is also being investigated as a potential treatment for bipolar I depression[16] and MDD.[17] Cariprazine has anti-depressive properties, potentially due to its high affinity for and occupancy of $D_3$ receptors,[18,19] which are expressed in brain regions involved in motivation and reward-related behavior.[20] The therapeutic potential of cariprazine in the treatment of depressive symptoms has been shown in various animal models,[11,21,22] and clinical studies, including a previously published Phase 2 placebo-controlled study, which demonstrated that adjunctive cariprazine 2.0–4.5 mg/day[d] and ADT were efficacious and generally well tolerated for treatment-resistant MDD in adults.[17] Here we present the results of a Phase 3 study evaluating the efficacy, safety, and tolerability of a larger dose range of adjunctive cariprazine (1.5–4.5 mg/d) with ADT in adults with previous inadequate response to ADT.

## Materials and Methods

### *Study Design*

This was an 18- to 19-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study of adjunctive cariprazine 1.5–4.5 mg/d with open-label ADT conducted from 2012 to

2016 at 66 sites in the United States (enrolled ⩾1 participant in the prospective period) in outpatients with a diagnosis of MDD who had failed to respond to 1 or 2 previous ADTs (in the current episode) given at adequate dose and duration (NCT01715805). The study was approved by the Institutional Review Board at each study center and was conducted in full compliance with the International Conference on Harmonisation Guidances on General Considerations for Clinical Trials, Good Clinical Practice, and the Declaration of Helsinki. All participants provided informed written consent prior to study involvement.

### *Open-Label ADT Phase*

After a 1- to 2-week screening period, participants entered an 8-week prospective open-label ADT phase (Supplemental Figure 1) and were prescribed and acquired a commercially available ADT (bupropion [XL], citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine [XR/IR/ER], paroxetine [CR], or vilazodone) from pharmacies, and single-blind placebo adjunct capsules, which were provided by the Sponsor in blister packs. The investigators chose the ADT to prescribe to each participant; none were prescribed an ADT that they had previously had an inadequate response in the current episode and every attempt was made to not prescribe any ADT ~>30% of participants per study center. ADT dosage could be adjusted until the end of week 4 of open-label period.

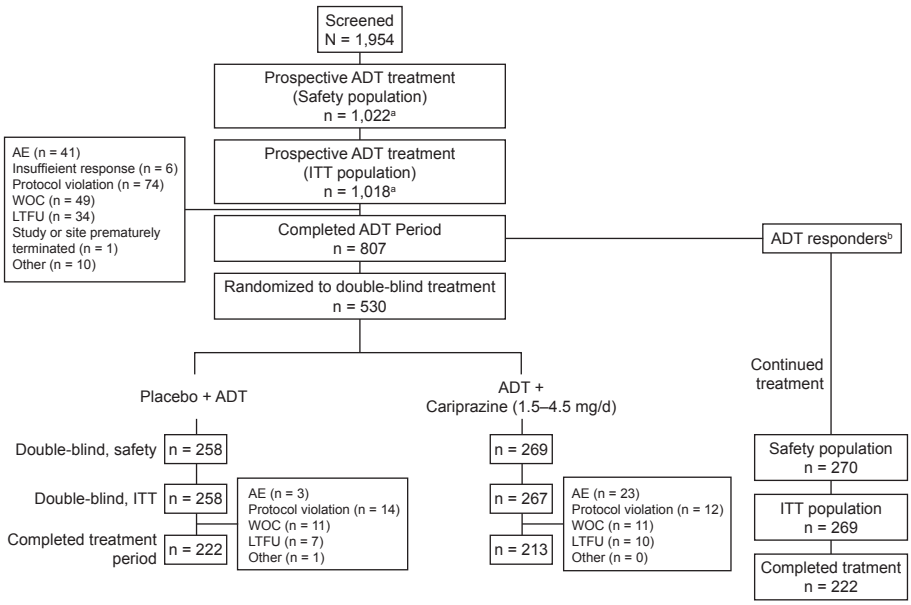


### *Double-Blind Phase*

Participants with inadequate response to ADT at the end of the open-label period (defined as not meeting any of the following 3 criteria: improvement of ⩾50% in the 17-item Hamilton Depression Rating Scale [HAMD-17] total score[23] compared to baseline/week 0, HAMD-17 total score ⩽14, or a Clinical Global Impressions–Improvement [CGI-I][24] score <3 [at least minimally improved]) entered the double-blind phase and were randomized (1:1) to double-blind placebo or cariprazine 1.5–4.5 mg/d and ADT (open label) for 8 weeks, followed by a 1-week safety follow-up period with no study drug, but investigator-judged standard treatment was permitted. Participants were supplied with blister packs of investigational product capsules (identical in appearance, taste and packaging) that contained 0.5, 1.0, 1.5 or 3.0 mg cariprazine or placebo. Participants randomized to cariprazine were titrated to a dose of 3.0 mg/d by increasing from 0.5 mg/d (day 1 of double-blind phase) to 3.0 mg/d (day 6) by 0.5 mg increments daily, and dose could be decreased from 3.0 mg/d to 1.5 mg/d if tolerability

**FIGURE 1**

**Participant Disposition**




ADT = antidepressant treatment; AE = adverse event; ITT = intent-to-treat; LTFU = lost to follow-up; WOC = withdrawal of consent.
[a]530 participants met criteria for double-blind treatment and 527 were randomized, of those 261 participants were randomized to the placebo group and 269 were randomized to the cariprazine group. [b]277 participants met criteria to enter ADT continued-treatment period and 270 entered. The prospective ADT treatment (safety population) consisted of all participants who underwent screening and took ⩾1 dose of open-label ADT plus single-blind adjunct, the prospective ADT treatment (ITT population) consisted of members of the pre-randomized safety population who had ⩾1 MADRS total score assessment during the 8-week prospective phase; ADT responders (safety population) are members of the pre-randomized safety population that were not randomized; the ADT responders (ITT population) had ⩾1 MADRS total score assessment during the 8-week prospective ADT continued-treatment period; the randomized population were those randomized to a double-blind treatment group, and the double-blind safety population consisted of all patients in the randomized population who took at least 1 dose of double-blind investigational product.

issues developed. At weeks 2, 3, and 4 of the double-blind phase participants (either treatment groups) with inadequate response (<40% Montgomery-Åsberg Depression Rating Scale [MADRS][25] total score change and >10 MADRS total score) could have their dose increased up to a maximum dose of 4.5 mg/d, and following a dose increase, participants who developed tolerability issues were permitted a dose reduction. No dose increases were permitted during the last 4 weeks of the double-blind phase. ADT responders continued to receive ADT and single-blind placebo for 8 weeks. Data for responders to ADT were collected, but not reported here.

Eligible participants were registered in an interactive voice response system or interactive web response system that assigned sequential

participant identification numbers and Statistical Programming Software randomized participants to a treatment arm and assigned the appropriate investigational product number; allocation information was not accessible by anyone involved in the study. Randomization was stratified by study center. Participants and investigators were blinded to treatment until after study completion and no randomization code was unblinded during double-blind treatment. After discontinuing or completing double-blind treatment, participants entered a 1-week safety follow-up period, and those who completed 16 weeks of treatment were eligible to enter a 26-week, open-label cariprazine extension study.

To select the cariprazine dose range for this study, the following data were considered: the maximum tolerated cariprazine dose in healthy subjects is 1.0 mg/d and in patients with schizophrenia is 12.5 mg/d;[26] along with the results from a prior Phase 2 adjunctive MDD study (RGH-MD-71, NCT00854100, Accepted for publication), which indicated cariprazine 0.1–0.3 mg/d and 1.0–2.0 mg/d were well tolerated, but did not significantly reduce depressive symptoms compared to placebo. Thus, it was concluded that the dose of cariprazine for this study should have a minimum of 1.5 mg/d and maximum exceeding 2.0 mg/d.



### *Participants*

Participants were outpatients (18–65 years) meeting the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[27] criteria for moderate to severe MDD without psychotic features and in a current major depressive episode (≥8 weeks and <12 months), and had previously failed to respond to 1 or 2 adequate ADT trials (<50% reduction in depressive symptoms during the current episode, defined by the Antidepressant Treatment Response Questionnaire [ATRQ]).[7] Participants were required to have a HAMD-17 total score of ≥20 and a score of ≥2 on Item 1, as well as a score of ≥2 on Item 1 of the 24-item HAMD (HAMD-24) scale. Physical examination, clinical laboratory, and ECG results were required to be normal or not judged to be clinically significant by investigators. Participants were excluded due to a principal axis I disorder other than MDD, any axis I disorder that was the primary focus of treatment within 6 months, any axis II disorder sufficiently severe to interfere with study participation, dementia, amnesia, other cognitive disorder, mental retardation, and secondary diagnoses of comorbid generalized anxiety disorder or social anxiety. Participants with alcohol or substance abuse or dependence (last 6 months), risk of injuring others, self, or property or suicide risk (attempt within past year, investigator's judgement, Columbia-Suicide Severity Rating Scale [C-SSRS][28] survey results, or MADRS item

10 score ⩾5) were excluded. Treatment with clozapine, any depot antipsychotic, antipsychotic or ADT augmentation (in current episode); an anticonvulsant/mood stabilizer (within previous year); electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental CNS treatment (in current episode or within 6 months prior to baseline, whichever was longer) was prohibited.

### *Efficacy Assessments*

The Structured Clinical Interview for DSM-*IV*-TR Axis I Disorders, Clinical Trials version (SCID-I-CT)[29] was used for diagnostic screening and the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ)[26] assessed participants' prior ADT failure (inclusion criteria). The primary efficacy parameter was change from baseline to week 8 (of double-blind period) in MADRS total score versus placebo, and the secondary efficacy parameter was change in Sheehan Disability Scale[30] (SDS) score versus placebo. Additional efficacy endpoints included changes in CGI-Severity (CGI-S) scores,[24] CGI-I scores, $HAMD_{17}$ total scores, Hamilton Rating Scale for Anxiety (HAM-A) scores,[31] and SDS subscale (work, social, and family life) scores, and CGI-I response (score ⩽2) and MADRS response (⩾50% improvement from baseline) and MADRS remission (MADRS total score ⩽10) rates. In the double-blind phase, assessments of MADRS total scores, CGI-S, and CGI-I were conducted at each visit (baseline, weeks 1, 2, 3, 4, 6, and 8); SDS at baseline and weeks 2, 4, 6, and 8; and HAMD-17 and HAM-A scales at weeks 4 and 8.



### *Safety Assessments*

Adverse event (AE), vital sign and suicide risk (using the C-SSRS) monitoring occurred at every visit. Laboratory tests, ophthalmologic examinations, ECG, and evaluations of extrapyramidal symptoms (EPS), using the Abnormal Involuntary Movement (AIMS),[24] Barnes Akathisia Rating (BARS),[32] and Simpson-Angus Scales (SAS),[33] were recorded at least once in the double-blind period.

### *Statistical Analyses*

The double-blind safety population consisted of randomized participants who received ⩾1 dose of study medication. Safety population participants with ⩾1 MADRS assessment during the double-blind period comprised the double-blind intent-to-treat (ITT) population. The double-blind baseline was the last non-missing efficacy assessment

before first double-blind period dose. Efficacy and safety assessments were based on the ITT and safety populations, respectively.

MADRS total score changes from baseline to week 8 were analyzed by a mixed-effects model for repeat measures (MMRM) with treatment group, study center, visit, and treatment group–by-visit interaction as fixed effects and the baseline MADRS score and baseline score-by-visit interaction as covariates. An unstructured covariance matrix was used to model the covariance of within-participant scores, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom. MMRM analysis was performed on all baseline scores using only the observed cases without imputing missing values. A sensitivity analysis was performed using a pattern-mixture model based on non-future dependent missing value restrictions[34] to assess the robustness of primary MMRM results to the possible violation of the missing-at-random assumption.

By-visit analyses using MMRM and the last-observation-carried-forward (LOCF) approach were performed for all efficacy parameters. The analysis of covariance (ANCOVA) model included treatment group and study center as factors and baseline efficacy measure as a covariate. Rates for response and remission were reported by treatment group and by visit, and a logistic regression model with LOCF was used to model the probability of response or remission as a function of treatment group and the corresponding baseline score. All statistical tests were 2-sided hypothesis tests performed at the 5% level of significance for main effects, and confidence intervals (CI) were 2-sided 95%. Statistical analyses were performed using SAS, version 9.3 or newer (SAS Institute, Cary, N.C.). Raters were provided training and certification in the rating scales used in this study by Bracket Global (Wayne, P.A.)



All safety parameters were summarized with descriptive statistics.

To select sample size, it was estimated 250 participants per randomized treatment group would have provided approximately 90% power to detect a treatment effect size of 0.30 of cariprazine vs placebo at a 2-sided significance level of 5%, assuming the correlation coefficient of within-participant assessments was 0.6 and the discontinuation rate was 15% (based on the aripiprazole adjunctive MDD studies).[35–37]

## Results

### *Participants and Disposition*

Of 1954 screened, 1022 participants were enrolled in the prospective ADT phase and 807 completed (Figure 1). ADT responders (n = 270) continued ADT and adjunctive placebo for 8 weeks, and data were

collected, but are not reported here. Inadequate responders to ADT (n = 530) were randomized to double-blind treatment, and 3 did not take double-blind treatment and were not included in the safety population (n = 527): placebo (n = 258) and cariprazine (n = 269). Of the safety population, 435 (82.5%) completed double-blind treatment. The most frequent reasons for premature discontinuation in this phase were protocol violation (n = 14; 5.4%) for placebo and AEs (n = 23; 8.6%) for cariprazine. Baseline demographics and disease history were generally comparable among groups (Table 1). In the double-blind safety population, the mean duration of treatment was 51.8 and 49.1 days in the placebo and cariprazine groups, respectively, the overall mean daily dose of cariprazine was 2.97 mg/d, and the modal daily dose was 36.1% for 4.5 mg/d, 46.1% for 3.0 mg/d dose, and 17.8% for 1.5 mg/d.

### *Efficacy*

For the primary endpoint, MADRS total score change compared to placebo, the difference was not statistically significant (least-squares mean



**TABLE 1**

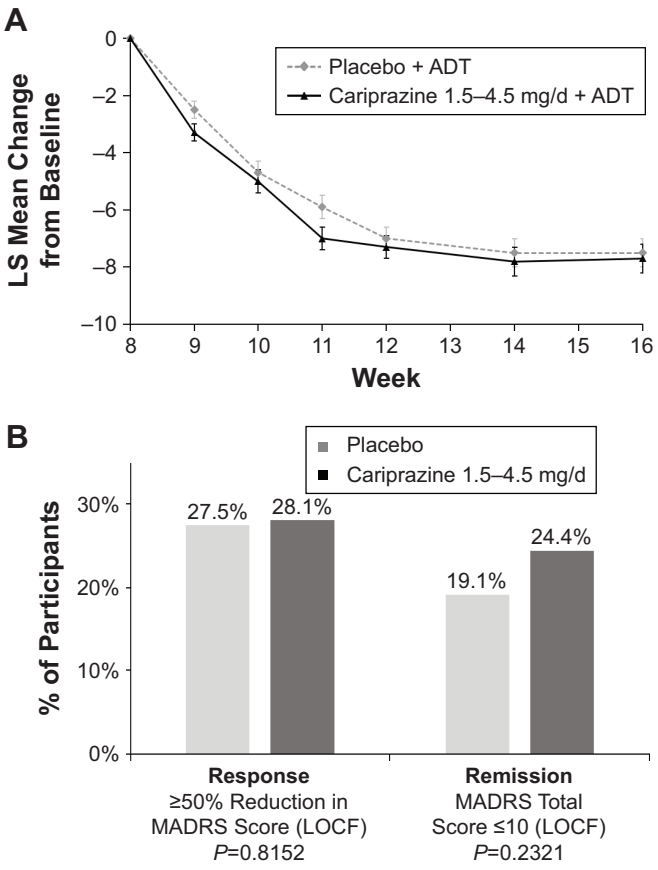
**Baseline Characteristics of the Double-Blind Safety Population**

| | PLACEBO (N = 258) | CARIPRAZINE (N = 269) |
|---|---|---|
| Age, years, mean (SD) | 43.8 (11.8) | 44.2 (11.6) |
| Women, n (%) | 170 (65.9) | 174 (64.7) |
| White, n (%) | 184 (71.3) | 196 (72.9) |
| Black or African American, n (%) | 63 (24.4) | 65 (24.2) |
| Asian, n (%) | 6 (2.3) | 7 (2.6) |
| American Indian or Alaska Native, n (%) | 2 (0.8) | 1 (0.4) |
| Native Hawaiian or Other Pacific Islander, n (%) | 2 (0.8) | 0 |
| Other | 1 (0.4) | 0 |
| Mean weight, kg (SD) | 83.97 (18.61) | 83.98 (19.08) |
| BMI, kg/m$^2$ (SD) | 29.36 (5.62) | 29.27 (5.77) |
| Age at MDD onset, year, mean (SD) | 30.7 (12.4) | 31.2 (12.0) |
| Recurrent MDD, n (%) | 246 (95.3) | 261 (97.0) |
| Mean duration of current episode, weeks (SD) | 27.75 (11.56) | 29.45 (11.90) |
| Duration of MDD, n (%) | | |
| ⩽1 year | 27 (10.5) | 21 (7.8) |
| >1–3 years | 28 (10.9) | 21 (7.8) |
| >3–5 years | 24 (9.3) | 33 (12.3) |
| >5 years | 179 (69.4) | 193 (71.7) |
| Baseline MADRS Total Score[a], mean (SD) | 25.2 (6.1) | 25.4 (5.5) |

SD = standard deviation, BMI = body mass index, MDD = major depressive disorder, MADRS = Montgomery-Åsberg Depression Rating Scale.
[a]Baseline for the double-blind treatment phase is the last nonmissing assessment before the first dose of double-blind investigational product.

FIGURE 2

**MADRS A) Mean (Sd) Changes from Baseline by Study Visit in MADRS Total Score (ITT Population); Mixed Effect Model for Repeat Measures (MMRM); B) Response and Remission Rates**




MADRS = Montgomery-Åsberg Depression Rating Scale; SD = standard deviation; ITT = intent-to-treat; MMRM = mixed-effects model for repeated measures; LS = least squares; LOCF = last-observation carried forward.

MADRS total score changes from baseline to week 8 were analyzed by a MMRM with treatment group, study center, visit, and treatment group–by-visit interaction as fixed effects, and the double-blind baseline MADRS score and double-blind baseline score-by-visit interaction as covariates. An unstructured covariance matrix was used to model the covariance of within-participant scores, and the Kenward- Roger approximation was used to estimate denominator degrees of freedom. MMRM analysis was performed only the observed cases without imputing missing values.

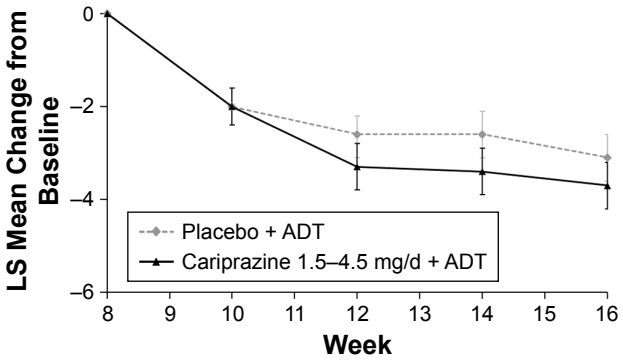
Rates for response and remission were reported by treatment group and by visit, and a logistic regression model with LOCF was used to model the probability of response or remission as a function of treatment group and the corresponding baseline score.



difference [LSMD]: −0.2; $P = 0.7948$, Figure 2a). Cariprazine 1.5–4.5 mg/d improved, but not significantly, the mean SDS total score compared to placebo at week 8 (LSMD = −0.7, $P = 0.2784$, Figure 3). MADRS response rates were not increased with cariprazine vs placebo (Figure 2b),

FIGURE 3

**SDS Total Score Mean (Sd) Changes from Baseline by Study Visit in (ITT Population); MMRM**




SDS=Sheehan Disability Scale; ITT=intent-to-treat; MMRM=mixed-effects model for repeated measures; LS=least squares.
SDS score changes from baseline to week 8 were analyzed by a MMRM with treatment group, pooled study center, visit, and treatment group–by-visit interaction as fixed effects, and the double-blind baseline value and double-blind baseline-by-visit interaction as covariates. An unstructured covariance matrix was used to model the covariance of within-participant scores.



and MADRS remission rates were improved with cariprazine (24.4% vs placebo, 19.1%), but not significantly ($P = 0.2321$, Figure 2b).

Additional efficacy parameters are reported in Table 2. CGI-I scores were reduced (symptom improvement) with cariprazine treatment compared to placebo (LSMD −0.2; $P = 0.0410$). HAMD-17 scores were reduced (LSMD = −0.7), but did not reach statistical significance ($P = 0.1967$). At week 8, cariprazine did not separate from placebo in CGI-S and HAM-A total score changes. CGI-I response rates were greater with cariprazine (53.2%) vs placebo (46.9%), but the difference was not statistically significant ($P = 0.0695$).

## *Safety*

### Adverse Events

*Open-label ADT phase*

In the open-label ADT period, 54.2% (554/1,022) of participants reported any treatment-emergent AE (TEAE). Serious adverse events (SAEs) were reported in 0.8% (n = 8) of participants and AEs leading to discontinuation occurred in 4.2% (n = 43) of participants.

*Double-blind phase*

Newly-emergent AEs (NEAEs) were reported 50.8% of placebo and 67.3% of cariprazine participants in the double-blind phase (Table 3).

TABLE 2

**Additional Efficacy Endpoints at Week 8 for the Double-Blind ITT Population**

| PARAMETER | PLACEBO (N = 258) | CARIPRAZINE (N = 267) |
|---|---|---|
| CGI-I score | n = 219 | n = 211 |
| LS mean (SE) | 2.5 (0.1) | 2.3 (0.1) |
| LSMD vs placebo | | −0.2 |
| 95% CI | | −0.4, −0.0 |
| *P*-value | | 0.0410 |
| CGI-S score | n = 219 | n = 211 |
| LS mean (SE) | −0.9 (0.1) | −1.0 (0.1) |
| LSMD vs placebo | | −0.1 |
| 95% CI | | −0.3, 0.1 |
| *P*-value | | 0.3016 |
| $HAMD_{17}$ total score | n = 219 | n = 211 |
| LS mean (SE) | −6.5 (0.4) | −7.2 (0.4) |
| LSMD vs placebo | | −0.7 |
| 95% CI | | −1.7, 0.4 |
| *P*-value | | 0.1967 |
| HAM-A score | n = 219 | n = 211 |
| LS mean (SE) | −4.2 (0.3) | −4.3 (0.3) |
| LSMD vs placebo | | −0.1 |
| 95% CI | | −1.0, 0.8 |
| *P*-value | | 0.7959 |

ITT = intent-to-treat; N = number of participants with available analysis value at both double-blind baseline and a specific time point; CGI-I = Clinical Global Impressions–Improvement; LSMD = least-squares mean difference; CI=confidence interval; CGI-S; Clinical Global Impressions–Severity; $HAMD_{17}$ = 17-item Hamilton Depression Rating Scale; HAM-A = Hamilton Rating Scale for Anxiety; MMRM = mixed-effects model for repeated measures.
P-values are from an MMRM with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and double-blind baseline value and double-blind baseline-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within-participant scores.



Most were judged by the site investigator to be mild or moderate in severity. AEs that led to discontinuations occurred in 3 placebo (1.2%) and 23 cariprazine (8.6%) participants. No deaths occurred in any phase. Commonly (⩾5% of cariprazine participants and with an incidence of at least twice the rate in the placebo) occurring newly-emergent AEs (NEAEs) included akathisia and restlessness.

Serious AEs were reported in 3 (1.2%) placebo participants (participant 1: cholelithiasis; participant 2: acute pancreatitis and worsening of migraine; participant 3: pulmonary embolism and seizure) and 1 (0.4%) cariprazine participant (suicidal ideation and worsening depression). Of those, only seizure (placebo participant) was judged by the site investigator to be related to treatment.

TABLE 3

**Treatment-Emergent Adverse Events in ⩾2% of Participants in any Group (n, %) (Double-Blind Safety Population)**

| PREFERRED TERM | PLACEBO (N = 258) | CARIPRAZINE (N = 269) |
|---|---|---|
| Participants with at least 1 NEAE | 131 (50.8) | 181 (67.3) |
| Akathisia | 8 (3.1) | 46 (17.1) |
| Restlessness | 5 (1.9) | 22 (8.2) |
| Insomnia | 16 (6.2) | 20 (7.4) |
| Headache | 9 (3.5) | 18 (6.7) |
| Nausea | 10 (3.9) | 15 (5.6) |
| Somnolence | 2 (0.8) | 13 (4.8) |
| Weight increased | 12 (4.7) | 13 (4.8) |
| Vision blurred | 2 (0.8) | 12 (4.5) |
| Anxiety | 7 (2.7) | 12 (4.5) |
| Fatigue | 5 (1.9) | 11 (4.1) |
| Dizziness | 8 (3.1) | 9 (3.3) |
| Tremor | 3 (1.2) | 7 (2.6) |
| Diarrhoea | 9 (3.5) | 7 (2.6) |
| Dry mouth | 8 (3.1) | 6 (2.2) |
| Nasopharyngitis | 7 (2.7) | 6 (2.2) |
| Back pain | 1 (0.4) | 6 (2.2) |
| Sedation | 1 (0.4) | 6 (2.2) |

NEAE = newly-emergent adverse event; SOC = system organ class; ADT = antidepressant treatment; AE = adverse event.
AE Dictionary: MedDRA Version 18.0. If >1 AE was coded to the same preferred term for a participant, the participant was counted only once for that preferred term. If >1 preferred term was coded to the same SOC for a participant, the participant was counted only once for that SOC. An AE that occurred >30 days after the date of the last dose of the open-label ADT was not summarized.



### *EPS-related events*

Akathisia occurred more frequently in participants in the cariprazine group (17.1%) compared to placebo (3.1%). Treatment-emergent parkinsonism (SAS score ⩽3 at baseline and >3 postbaseline) was observed more often in cariprazine participants (4.5%) than placebo (0.4%). Treatment-emergent akathisia (BARS score ⩽2 at baseline and >2 postbaseline), occurred more frequently in cariprazine (21.7%) vs placebo (2.7%) participants.

### *Vital signs, ECG, orthostatic hypotension*

Mean changes in clinical laboratory parameters and vital signs were generally small and comparable across the treatment groups (Table 4); potentially clinically significant differences in laboratory values were observed in values for fasting triglycerides (5.2% cariprazine; 3.2% placebo), blood urea nitrogen (1.6% cariprazine; 0.8% placebo), and uric acid (3.6% cariprazine; 0.8% placebo). Mean increases in body weight occurred in both treatment groups: placebo (0.45 kg) and cariprazine (1.11 kg). A similar

TABLE 4

**Changes in Additional Safety Measures from Double-Blind Baseline to End of Double-Blind Treatment (Double-Blind Safety Population)**

| Measurement, unit | Placebo N | Placebo mean change (SD) | Cariprazine N | Cariprazine mean change (SD) |
|---|---|---|---|---|
| Vital signs | | | | |
| Supine systolic blood pressure, mm Hg | 258 | 0.6 (9.4) | 267 | −1.2 (10.8) |
| Supine dystolic blood pressure, mm Hg | | −0.4 (7.6) | | −0.6 (7.4) |
| Supine pulse rate, bpm | | 1.7 (10.1) | | 0.7 (9.3) |
| Body weight, kg | | 0.45 (2.30) | | 1.11 (2.09) |
| Laboratory tests | | | | |
| Glucose (fasting), mg/dL | 226 | 0.78 (17.7) | 218 | 3.36 (22.1) |
| Prolactin, ng/mL | 245 | 0.69 (5.85) | 251 | 1.38 (8.98) |
| Creatine kinase, U/L | 242 | 14.7 (126.6) | 251 | −4.8 (287.1) |
| Lipids, mg/dL | | | | |
| Total cholesterol | 242 | 2.35 (26.0) | 251 | −0.65 (27.2) |
| HDL | 241 | −0.06 (9.35) | 251 | −0.29 (8.61) |
| LDL | 240 | 1.18 (23.1) | 251 | −1.48 (24.2) |
| Liver function | | | | |
| Alanine aminotransferase, U/L | 242 | 0.3 (11.1) | 251 | 0.6 (15.6) |
| Alkaline phosphatase, U/L | 238 | 0.3 (11.5) | 251 | −0.1 (9.8) |
| Aspartate aminotransferase, U/L | 242 | 0.5 (6.7) | 251 | −0.1 (11.1) |
| Total bilirubin, μmol/L | 242 | −0.337 (2.919) | 251 | −0.106 (3.245) |

n = number of participants with an available value at the specified time point; SD = standard deviation; Hg = mercury; bpm = beats per minute; U = units; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Double-blind baseline defined as the last assessment before the first dose of double-blind investigational product. Only participants with double-blind baseline and at least 1 postbaseline assessment during double-blind treatment are included.



incidence of weight changes ⩾7% of body weight occurred in both groups: decreases (placebo: 0.8% and cariprazine: 0.4%) and increases (placebo: 3.1% and cariprazine: 3.0%). A lower incidence of orthostatic hypotension occurred in cariprazine (11.6%) vs placebo (16.7%) participants.

### *Suicidality*

No suicidal behavior was reported in the double-blind phase, but suicidal ideation was reported in 8.1% and 10.9% of placebo and cariprazine participants, respectively.

## Discussion

The predefined primary endpoint was not met in this Phase 3 trial; therefore, this was a negative study. Cariprazine 1.5–4.5 mg/d did not show statistically significant improvement in the primary (MADRS

total score) or secondary (SDS score) efficacy endpoints compared with placebo. The 7.5-point MADRS decrease with placebo was greater than observed in the placebo participants in the adjunctive MDD trials of brexpiprazole[38,39] and aripiprazole,[35–37,40] but lower than those observed in quetiapine fumarate[41] and previous cariprazine[17] trials. The high placebo response in this population may have prevented a detection of efficacy on MADRS total scores of cariprazine compared to placebo.

Although not significant, cariprazine did demonstrate a numerically greater reduction (improvement) in mean SDS scores relative to placebo. A delay in psychosocial and functional improvement following a reduction of depressive symptoms has been previously observed,[42] and the relatively short duration of this study may have prevented the detection of significant changes in SDS scores. Similar to the primary endpoint, placebo participants also exhibited a large numerical change in SDS total score (−3.1), which exceeded the treatment group SDS score changes observed in other positive adjunctive atypical antipsychotic trials.[35–39] This high placebo response may have inhibited the ability to detect SDS score changes in the cariprazine group.



CGI-I score improvements (reduction in symptoms) with cariprazine treatment would have been considered statistically significant versus placebo had the prior endpoint been met. The HAMD-17 scores were reduced to a greater extent with cariprazine treatment than placebo, but did not reach significance. A similar trend to the primary and secondary endpoints was observed in the high HAMD-17 score decreases with placebo treatment, which was larger than in adjunctive brexpiprazole trials.[38,39] Rates of MADRS remission were higher for cariprazine than placebo, but differences were not statistically significant, which may be due to the short duration of this study that was designed to assay acute MDD treatment and not powered to detect remission.

The efficacy results of this study contrast with a similarly designed study of cariprazine in participants with MDD and previous inadequate response to ADTs, in which the cariprazine 2.0–4.5 mg/d group significantly improved MADRS, SDS, CGI-I and CGI-S scores relative to placebo.[17] Possible explanations for these contrasting results may be the increased treatment resistance (more persistent disease) in the current study as indicated by a higher rate of participants reporting recurrent MDD. In the present study, participants were also younger at MDD onset compared to the previous study (30.7 − 32.1 vs 33.2 − 34.4 years, respectively), and had MDD for a longer time (13.0 vs 11.7 − 11.9 years). Participants randomized in the current study also had a lower baseline MADRS score (mean: ~25) compared to the previous positive study (mean: ~29), which may have prevented a significant separation from

placebo because treatment effects may be reduced as baseline symptom severity decreases. [Kornstein et al. 2018/submitted for publication].

To identify inadequate response to ADT, the previous study defined it by a minimum antidepressant resistance rating score of 3 on the Antidepressant Treatment History Form, while the criteria for this study was a ⩾50% reduction in HAMD-17 total score from baseline. The differing criteria may have inadvertently resulted in the selection of a participant population with greater resistance, which also had decreased response to adjunctive cariprazine treatment in the current study.

Cariprazine was relatively well tolerated in this participant population, and changes in laboratory parameters, vital signs, waist circumference, and BMI were generally small and comparable across treatments. Incidences of TEAEs in the cariprazine group (67.3%) were generally lower than in the previously published cariprazine MDD[17] and monotherapy bipolar mania trials.[43,44] The incidence of akathisia (17.3%) was similar to that reported in other adjunctive MDD trials: aripiprazole (25%),[45] brexpiprazole (4%–14%),[46] and cariprazine (2–4.5 mg/d, 22.3%),[17] but higher than reported for quetiapine fumarate (2%).[47] Mean weight change was lower than reported in some aripiprazole studies[36,40] and for brexpiprazole 2 mg and 3 mg.[38,39]



## Limitations

Limitations of the study included relatively short duration of the randomized phase, absence of active comparator to determine assay sensitivity, and lack of generalizability to subpopulations of patients with MDD with comorbid psychiatric disorders. The fixed-flexible dose study design prevents drawing conclusions regarding a specific dosage, but nevertheless is more representative of actual clinical practice. Study enrollment required identification of an inadequate ADT response in a prospective phase using standardized rating scales, which have inherent limitations and difficulties.[48] The requirement that participants fail to respond to ADT treatment in a prospective phase compared to those who reported previous failure increased the length and burden of trial for participants, which may have affected the accuracy of measurements taken at later study visits. Participants also had a relatively low baseline MADRS total scores leaving a decreased margin for measuring potential change with treatment.

## Conclusions

Adult participants with MDD and inadequate response to ADT who were treated with adjunctive cariprazine and ADT did not have statistically significant improvement in depression symptoms compared

to placebo, but non-significant greater reductions in symptoms compared to placebo was observed in some efficacy measures. The lack of statistically significant MADRS score changes compared to placebo contrasts with a previous positive study,[17] but is comparable to the lower dose phase 2 study (Allergan, submitted for publication). Cariprazine was generally well tolerated and no new safety signals were observed. Due to the limitations of the study design and the potential confounding of results, additional trials of cariprazine augmentation of ADT are needed to further assess its role in the treatment of MDD. ✤

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## Role of the Sponsors

Allergan and Gedeon Richter Plc. were involved in the study design, collection (via contracted clinical investigator sites), analysis and interpretation of data, and decision to present these results.



## Disclosures

Drs. Earley and Guo acknowledge a potential conflict of interest as employees of Allergan. Dr. Earley owns stock in Allergan, AstraZeneca, and Eli Lilly. Dr. Guo owns stock in Allergan. Drs. Harsányi and Németh acknowledge a potential conflict of interest as employees of Gedeon Richter Plc. Dr. Németh is a patent owner of the investigational medicinal product used in this study. Dr. Thase has received grants from the Agency for Healthcare Research and Quality, Alkermes, Forest Laboratories (an Allergan affiliate), National Institute of Mental Health, Otsuka, PharmaNeuroboost, and Roche; has acted as an advisor or a consultant for Alkermes, AstraZeneca, Bristol-Myers Squibb, Cerecor, Eli Lilly, Forest Laboratories, Gerson Lehman Group, GlaxoSmithKline, Guidepoint Global, Lundbeck, MedAvante, Merck, Neuronetics, Novartis, Ortho-McNeil Pharmaceuticals, Otsuka, Pamlab, Pfizer, Shire, Sunovion, and Takeda; has received royalties from American Psychiatric Association, Guilford Publications, Herald House, and W.W. Norton & Company; and holds equity in MedAvante Inc.

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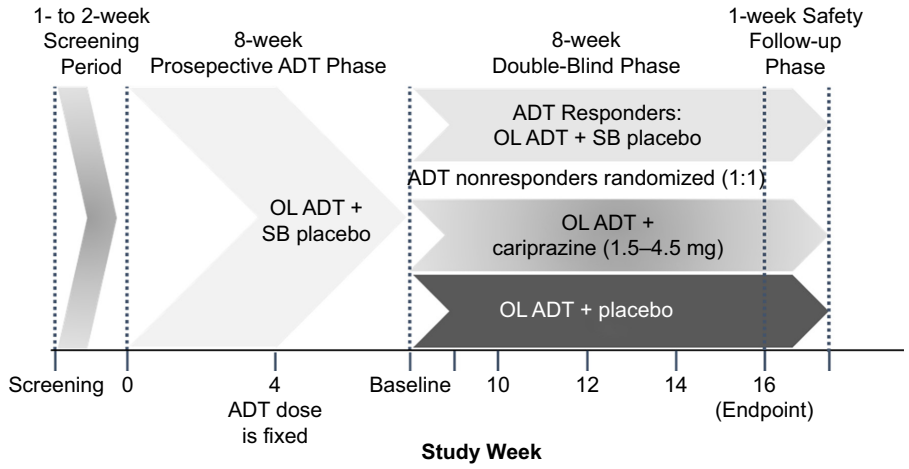
## Supplementary Material

**FIGURE S1**

### Study Design




ADT = antidepressant treatment; OL = open-label; SB = single-blind.
At baseline ADT response was assessed, and only nonresponders were randomized to either placebo or cariprazine plus ADT.
During the 1-week safety follow-up, participants did not continue treatment with cariprazine, but were permitted to continue with standard treatment, as judged by the investigator.



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