Cariprazine for the Adjunctive Treatment of Major Depressive Disorder: Results of a Randomized Phase 3 Placebo-Controlled Study

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The following information concerns a use that has not been approved by the U.S. Food and Drug Administration.

OBJECTIVE

The objective of this phase 3 study was to assess the efficacy and safety of cariprazine 1.5 mg/d and 3 mg/d versus placebo in the adjunctive treatment of adults with MDD and inadequate response to ongoing antidepressant therapy

CONCLUSIONS

Cariprazine 1.5 mg/d was associated with significantly greater reductions in MADRS total score versus placebo in patients with MDD and inadequate response to antidepressant therapy alone

Cariprazine appeared to be safe and well tolerated with safety results generally consistent with previous findings

These results show that cariprazine is safe and effective as an adjunct to antidepressants in the treatment of adults with MDD

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Writing and editorial assistance was provided to the authors by Prescott Medical Communications Group (Chicago, IL), a contractor of AbbVie. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

G.S. Sachs is a full-time employee of Signant Health; has been a consultant to Abbott Laboratories, Allergan, Astellas, AstraZeneca, Blackthorn, Bristol-Myers Squibb, Intra-Cellular Therapies, Otsuka, Pfizer, Sunovion, Takeda, Wyeth, and Repligen; has served on speakers or advisory boards for Abbott Laboratories, Allergan, Astellas, Sanofi, Pfizer, Sunovion, and Takeda.

P.P. Yeung and **L. Rekeda** are employees and shareholders of AbbVie.

A. Khan was a contracted investigator and was compensated for participating in the trial.

M. Fava's disclosures can be viewed online at https://mghcme.org/faculty/.

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Supported by funding from AbbVie.

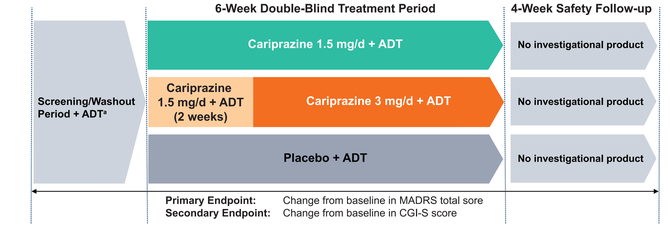
Presented at the American Psychiatric Association Annual Meeting | New Orleans, Louisiana, USA | May 21-25, 2022

INTRODUCTION

- Patients with major depressive disorder (MDD) often do not achieve remission with first line antidepressant therapy (ADT) and may require adjunctive treatment[1]
- Cariprazine, a dopamine D_3-preferring D_3/D_2 and serotonin 5-HT_{1A} receptor partial agonist approved to treat adults with schizophrenia and manic, mixed, or depressive episodes of bipolar I disorder, is under investigation as adjunctive therapy for MDD
- In a previously published placebo-controlled study, adjunctive treatment with cariprazine 2–4.5 mg/d was more effective than placebo in improving depressive symptoms in adults with MDD[2]

METHODS

- This randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study was conducted in adults (18-65 years) with MDD at 116 centers in the US and Europe
- Patients with inadequate response to ADT alone were randomized to placebo, cariprazine 1.5 mg/d, or cariprazine 3 mg/d
- MADRS total score changes from baseline to week 6 were analyzed by a mixed-effects model for repeated measures (MMRM)
  - Adjustments for multiple comparisons were made using the matched parallel gatekeeping procedure to control the overall type I error rate (alpha=0.05)



[a]Up to 14 days (with an additional 7 days if needed); key inclusion criteria included: DSM-5 diagnosis for MDD with current MDE ≥8 weeks and <24 months; HAMD-17 total score ≥22 and score ≥2 on Item 1; inadequate response (<50% improvement) to 1 to 3 ADTs during the current MDE.
ADT, antidepressant therapy; CGI-S, Clinical Global Impressions – Severity; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5th edition; HAMD-17, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode.

RESULTS

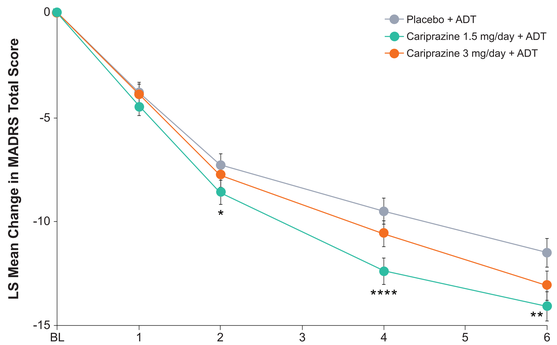
- A total of 759 patients were randomized to double-blind treatment, 757 received ≥1 dose of double-blind treatment (safety population), and 751 received ≥1 dose and completed ≥1 postbaseline MADRS assessment (modified intent-to-treat [mITT] population) (**Patient Disposition Diagram; QR code**)
- Cariprazine 1.5 mg/d resulted in significantly greater mean reductions from baseline in MADRS total score versus placebo at week 6 (nominal *P*=.0025; adjusted *P*=.0050) (**Figure 1**)
  - Significant differences from placebo were observed as early as week 2 (nominal *P*=.0453) (**Figure 1**)
- Cariprazine 3 mg/d resulted in numerically greater reductions in MADRS total score versus placebo at week 6, but the difference was not statistically significant (nominal *P*=.0691; adjusted *P*=.0727)
- Compared with placebo, a significantly higher proportion of patients receiving cariprazine 1.5 mg/d responded to treatment (**Figure 2**)
- Akathisia and nausea were the only AEs ≥5% in either cariprazine group and twice that of placebo (**Table 3**)
- Changes in weight at the end of treatment were relatively small (<1 kg) in all treatment groups; this profile is consistent with results from a previously published long-term safety study[3] of cariprazine that reported weight gain of 1.6 kg over 6 months

Table 1. Baseline Characteristics (Safety Population)

	Placebo (n=253)	Cariprazine 1.5 mg/d (n=252)	Cariprazine 3 mg/d (n=252)
Age, mean (SD), years	46.4 (11.9)	43.3 (13.6)	44.8 (13.3)
Female, n (%)	184 (72.7)	191 (75.8)	180 (71.4)
Race, n (%)			
White	203 (80.2)	205 (81.3)	215 (85.3)
Black or African American	43 (17.0)	37 (14.7)	30 (11.9)
Asian	5 (2.0)	4 (1.6)	7 (2.8)
Other	2 (0.8)	6 (2.4)	0 (0.0)
BMI, mean (SD), kg/m²	30.5 (7.9)	30.1 (7.6)	29.0 (7.0)
Psychiatric History			
Duration of current episode of MDD, n (%), months[a]	8.3 (5.3)	6.8 (4.3)	7.9 (4.8)
Number of lifetime MDD episodes, mean (SD)	6.9 (19.8)	6.2 (8.6)	6.2 (7.2)
Lifetime duration of MDD, mean (SD), years	14.8 (11.6)	12.8 (10.7)	14.0 (12.1)
Baseline Efficacy Variables[b]			
MADRS total score, mean (SD)	31.9 (5.7)	32.8 (5.0)	32.7 (4.9)

[a]Duration of current episode of MDD (months)=the number of months between the date of informed consent and the date of onset of current episode of major depressive disorder.
[b]Based on the modified intent-to-treat population.
BMI, body mass index; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; SD, standard deviation.

Figure 1. Mean Change from Baseline in MADRS Total Score (MMRM)



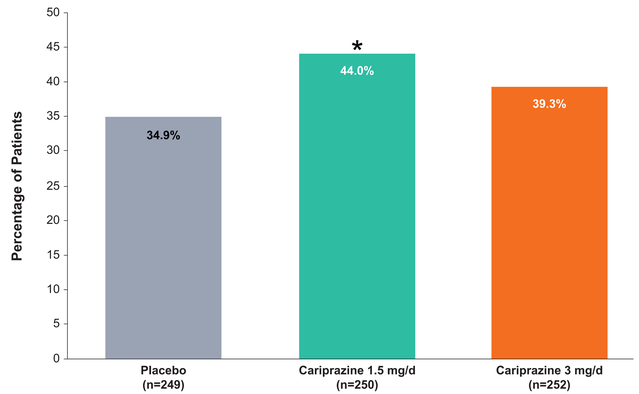
*P<.05, **P<.01, ****P<.0001 vs placebo.
ADT, antidepressant therapy; BL, baseline; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

Table 2. Efficacy Parameters (mITT population)

		Placebo (n=249)	Cariprazine 1.5 mg/d (n=250)	Cariprazine 3 mg/d (n=252)
CGI-S Score (Secondary)				
MMRM	LS mean (SE) change from baseline to week 6	-1.1 (0.1)	-1.4 (0.1)	-1.3 (0.1)
	LSMD (95% CI)		-0.3 (-0.5, -0.1)	-0.2 (-0.4, 0.0)
	P value		0.0091	0.0944
	Adjusted *P* value[a]		0.0727	0.0944
HAMD-17				
ANCOVA and LOCF[b]	LS mean (SE) change from baseline to week 6	-10.6 (0.7)	-12.7 (0.7)	-11.9 (0.7)
	LSMD (95% CI)		-2.1 (-3.3, -0.8)	-1.2 (-2.5, 0.1)
	P value		0.0014	0.0597
HAM-A				
MMRM	LS mean (SE) change from baseline to week 6	-7.8 (0.6)	-9.1 (0.6)	-8.6 (0.6)
	LSMD (95% CI)		-1.3 (-2.5, -0.1)	-0.8 (-2.0, 0.5)
	P value		0.0370	0.2219
CGI-I				
MMRM	LS mean (SE) change from baseline to week 6	2.8 (0.1)	2.6 (0.1)	2.6 (0.1)
	LSMD (95% CI)		-0.3 (-0.5, -0.1)	-0.3 (-0.5, -0.1)
	P value		0.0026	0.0076

[a]Adjustment was performed using matched parallel gatekeeping procedure to control the overall Type I error rate for multiple comparisons of 2 active doses versus placebo at week 6.
[b]Based on ANCOVA model using observed cases, with treatment group, pooled country, and ADT failure category as factors and baseline HAMD-17 total score as a covariate for between-treatment-group comparisons at week 6.
ANCOVA, analysis of covariance; CGI-I, Clinical Global Impressions–Improvement; Clinical Global Impressions – Severity; CI, confidence interval; HAM-A, Hamilton Rating Scale for Anxiety; HAMD-17, 17-item Hamilton Depression Rating Scale; LOCF, last observation carried forward; LS, least squares; LSMD, least squares mean difference; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; SE, standard error.

Figure 2. MADRS Responders[a] at Week 6 (mITT Population)



[a]Defined as ≥50% reduction from baseline in MADRS total score
*Nominal *P*<.05 versus placebo.
MADRS, Montgomery-Asberg Depression Rating Scale; mITT, modified intent-to-treat.

Table 3. Double-Blind Treatment-Emergent Adverse Events (Safety Population)

	Placebo (n=253)	Cariprazine 1.5 mg (n=252)	Cariprazine 3 mg (n=252)
Patients with ≥1 TEAE, n (%)	93 (36.8)	125 (49.6)	124 (49.2)
Patients with ≥1 SAE, n (%)	2 (0.8)	1 (0.4)	1 (0.4)
Deaths, n (%)	0	0	0
Discontinuations due to AEs, n (%)	6 (2.4)	3 (1.2)	18 (7.1)
Common TEAEs (≥5% in either cariprazine group), n (%)			
Akathisia	2 (0.8)	13 (5.2)	20 (7.9)
Nausea	6 (2.4)	20 (7.9)	16 (6.3)
Headache	15 (5.9)	22 (8.7)	11 (4.4)
Insomnia	10 (4.0)	18 (7.1)	16 (6.3)
Somnolence	7 (2.8)	13 (5.2)	11 (4.4)
Weight Changes			
Change from baseline, mean (SD), kg	0.11 (1.9)	0.68 (2.4)	0.78 (2.8)
Increase ≥7% from baseline, n (%), kg	2 (0.8)	10 (4.0)	3 (1.2)

AE, adverse event; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event.