CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204370Orig1s009

Trade Name:	VRAYLAR
Generic or Proper Name:	cariprazine
Sponsor:	ABBVIE INC
Approval Date:	December 16, 2022
Indication:	VRAYLAR is an atypical antipsychotic indicated for: • Treatment of schizophrenia in adults. • Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. • Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults. • Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 204370/S-009

SUPPLEMENT APPROVAL

Allergan Sales, LLC
Attention: Guang Yang, MS
Associate Director, Regulatory Affairs
1 N. Waukegan Road, Dept. PA72, Bldg. AP30
North Chicago, IL 60064

Dear Ms. Yang:

Please refer to your supplemental new drug application (sNDA) dated and received February 18, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vraylar (cariprazine) capsules.

This Prior Approval supplemental new drug application provides for a new indication of adjunctive therapy to antidepressants for the treatment of major depressive disorder in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Sarah Seung, Regulatory Project Manager, at sarah.seung@fda.hhs.gov or (240) 402-3879.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIFFANY R FARCHIONE
12/16/2022 02:56:36 PM

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LABELING

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VRAYLAR safely and effectively. See full prescribing information for VRAYLAR.

VRAYLAR® (cariprazine) capsules, for oral use
Initial U.S. Approval: 2015

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis. (5.1)**
- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of VRAYLAR have not been established in pediatric patients (5.2, 8.4)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2022
Dosage and Administration (2.5)	12/2022
Warnings and Precautions (5.7, 5.12)	12/2022

----------INDICATIONS AND USAGE----------

VRAYLAR is an atypical antipsychotic indicated for:

- Treatment of schizophrenia in adults (1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults (1)
- Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults (1)
- Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults (1)

----------DOSAGE AND ADMINISTRATION----------

- Administer VRAYLAR once daily with or without food (2)

	Starting Dose	Recommended Dose
Schizophrenia (2.2)	1.5 mg daily	1.5 mg to 6 mg daily
Bipolar Mania (2.3)	1.5 mg daily	3 mg to 6 mg daily
Bipolar Depression (2.4)	1.5 mg daily	1.5 mg or 3 mg daily
Adjunctive therapy to antidepressants for MDD (2.5)	1.5 mg daily	1.5 mg or 3 mg daily

- Schizophrenia and Bipolar Mania: Maximum recommended daily dosage is 6 mg. Dosages above 6 mg daily do not confer significant benefit, but increase the risk of dose-related adverse reactions (2.2, 2.3)
- Bipolar Depression: Maximum recommended daily dosage is 3 mg (2.4)
- Adjunctive therapy for treatment of MDD: Maximum recommended daily dosage is 3 mg (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 1.5 mg, 3 mg, 4.5 mg, and 6 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to VRAYLAR (4)

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) (5.3)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (5.4)
- *Tardive Dyskinesia*: Discontinue if appropriate (5.5)
- *Late-Occurring Adverse Reactions:* Because of VRAYLAR's long half-life, monitor for adverse reactions and patient response for several weeks after starting VRAYLAR and with each dosage change (5.6)
- *Metabolic Changes*: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts (CBC) in patients with pre-existing low white blood cell counts (WBC) or history of leukopenia or neutropenia. Consider discontinuing VRAYLAR if a clinically significant decline in WBC occurs in absence of other causative factors (5.8)
- *Orthostatic Hypotension and Syncope*: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.11)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery (5.12)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) were (*6.1*):

- Schizophrenia: extrapyramidal symptoms and akathisia
- Bipolar mania: extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness
- Bipolar depression: nausea, akathisia, restlessness, and extrapyramidal symptoms
- Adjunctive treatment of MDD: akathisia, restlessness, fatigue, constipation, nausea, insomnia, increased appetite, dizziness, and extrapyramidal symptoms

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Strong CYP3A4 inhibitors: Reduce VRAYLAR dosage by half (2.6, 7.1)
- CYP3A4 inducers: Concomitant use is not recommended (2.6, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for the emergence of suicidal thoughts and behaviors [*see Warnings and Precautions (5.2)*]. The safety and effectiveness of VRAYLAR have not been established in pediatric patients *[see Use in Specific Populations (8.4)]*.

1. INDICATIONS AND USAGE

VRAYLAR® is indicated for:

- Treatment of schizophrenia in adults *[see Clinical Studies (14.1)]*
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults *[see Clinical Studies (14.2)]*
- Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults *[see Clinical Studies (14.3)]*
- Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults *[see Clinical Studies (14.4)]*

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

VRAYLAR is given orally once daily and can be taken with or without food.

Because of the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks. Prescribers should monitor patients for adverse reactions and treatment response for several weeks after starting VRAYLAR and after each dosage change *[see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)]*.

2.2 Recommended Dosage in Schizophrenia

The starting dosage of VRAYLAR is 1.5 mg once daily. The recommended dosage range is 1.5 mg to 6 mg once daily. The dosage can be increased to 3 mg on Day 2. Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments. The maximum recommended dosage is 6 mg daily. In short-term controlled trials, dosages above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions [*see Adverse Reactions (6.1), Clinical Studies (14.1)*].

2.3 Recommended Dosage in Manic or Mixed Episodes Associated with Bipolar I Disorder

The starting dosage of VRAYLAR is 1.5 mg once daily and should be increased to 3 mg once daily on Day 2. The recommended dosage range is 3 mg to 6 mg once daily. Depending upon clinical response and

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tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments. The maximum recommended dosage is 6 mg daily. In short-term controlled trials, dosages above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions *[see Adverse Reactions (*6.1*), Clinical Studies (*14.2*)]*.

2.4 Recommended Dosage in Depressive Episodes Associated with Bipolar I Disorder (Bipolar Depression)

The starting dosage of VRAYLAR is 1.5 mg once daily. Depending upon clinical response and tolerability, the dosage can be increased to 3 mg once daily on Day 15. Maximum recommended dosage is 3 mg once daily.

2.5 Recommended Dosage for Adjunctive Therapy to Antidepressants in Treatment of Major Depressive Disorder

The starting dosage of VRAYLAR is 1.5 mg once daily. Depending upon clinical response and tolerability, the dosage can be increased to 3 mg once daily on Day 15. In clinical trials, dosage titration at intervals of less than 14 days resulted in a higher incidence of adverse reactions *[see Adverse Reactions* (*6.1)*]. Maximum recommended dosage is 3 mg once daily.

2.6 Dosage Adjustments for CYP3A4 Inhibitors and Inducers

Dosage recommendation for patients initiating a strong CYP3A4 inhibitor while on a stable dose of VRAYLAR: If a strong CYP3A4 inhibitor is initiated, reduce the current dosage of VRAYLAR by half. For patients taking 4.5 mg daily, the dosage should be reduced to 1.5 mg or 3 mg daily. For patients taking 1.5 mg daily, the dosing regimen should be adjusted to every other day. When the CYP3A4 inhibitor is withdrawn, VRAYLAR dosage may need to be increased *[see Drug Interactions (7.1)]*.

Dosage recommendation for patients initiating VRAYLAR therapy while already on a strong CYP3A4 inhibitor: Patients should be administered 1.5 mg of VRAYLAR on Day 1 and on Day 3 with no dose administered on Day 2. From Day 4 onward, the dose should be administered at 1.5 mg daily, then increased to a maximum dose of 3 mg daily. When the CYP3A4 inhibitor is withdrawn, VRAYLAR dosage may need to be increased *[see Drug Interactions (7.1)]*.

Dosage recommendation for patients concomitantly taking VRAYLAR with CYP3A4 inducers:
Concomitant use of VRAYLAR and a CYP3A4 inducer has not been evaluated and is not recommended because the net effect on active drug and metabolites is unclear *[see Dosage and Administration (2.1), Warnings and Precautions (5.6), Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

2.7 Treatment Discontinuation

Following discontinuation of VRAYLAR, the decline in plasma concentrations of active drug and metabolites may not be immediately reflected in patients' clinical symptoms; the plasma concentration of cariprazine and its active metabolites will decline by 50% in ~1 week *[see Clinical Pharmacology (12.3)]*. There are no systematically collected data to specifically address switching patients from VRAYLAR to other antipsychotics or concerning concomitant administration with other antipsychotics.

3. DOSAGE FORMS AND STRENGTHS

VRAYLAR (cariprazine) capsules are available in four strengths.

- 1.5 mg capsules: White cap and body imprinted with "FL 1.5"
- 3 mg capsules: Green to blue-green cap and white body imprinted with "FL 3"
- 4.5 mg capsules: Green to blue-green cap and body imprinted with "FL 4.5"

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- 6 mg capsules: Purple cap and white body imprinted with "FL 6"

4. CONTRAINDICATIONS

VRAYLAR is contraindicated in patients with history of a hypersensitivity reaction to cariprazine. Reactions have ranged from rash, pruritus, urticaria, and reactions suggestive of angioedema (e.g., swollen tongue, lip swelling, face edema, pharyngeal edema, and swelling face).

5. WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Antipsychotic drugs increase the all-cause risk of death in elderly patients with dementia-related psychosis. Analyses of 17 dementia-related psychosis placebo-controlled trials (modal duration of 10 weeks and largely in patients taking atypical antipsychotic drugs) revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.3)]*.

5.2 Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18-24 years old	5 additional patients
	Decreases Compared to Placebo
25-64 years old	1 fewer patient
≥65 years old	6 fewer patients

* VRAYLAR is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

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Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing VRAYLAR, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.3 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials in elderly patients with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.

5.4 Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue VRAYLAR and provide intensive symptomatic treatment and monitoring.

5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs, including VRAYLAR. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of tardive dyskinesia is unknown.

Given these considerations, VRAYLAR should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and 2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on VRAYLAR, drug discontinuation should be considered. However, some patients may require treatment with VRAYLAR despite the presence of the syndrome.

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5.6 Late-Occurring Adverse Reactions

Adverse reactions may first appear several weeks after the initiation of VRAYLAR treatment, probably because plasma levels of cariprazine and its major metabolites accumulate over time. As a result, the incidence of adverse reactions in short-term trials may not reflect the rates after longer term exposures *[see Dosage and Administration (2.1), Adverse Reactions (6.1), Clinical Pharmacology (12.3)]*.

Monitor for adverse reactions, including extrapyramidal symptoms (EPS) or akathisia, and patient response for several weeks after a patient has begun VRAYLAR and after each dosage increase. Consider reducing the dose or discontinuing the drug.

5.7 Metabolic Changes

Atypical antipsychotic drugs, including VRAYLAR, have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. There have been reports of hyperglycemia in patients treated with VRAYLAR. Although all drugs in the class to date have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication and monitor periodically during long-term treatment.

Schizophrenia

In the 6-week, placebo-controlled trials of adult patients with schizophrenia, the proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high were similar in patients treated with VRAYLAR and placebo. In the long-term, open-label schizophrenia studies, 4% patients with normal hemoglobin A1c baseline values developed elevated levels (≥ 6.5%).

Bipolar Disorder

In six placebo-controlled trials up to 8-weeks of adult patients with bipolar disorder (mania or depression), the proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high were similar in patients treated with VRAYLAR and placebo. In the long-term, open-label bipolar disorder studies, 4% patients with normal hemoglobin A1c baseline values developed elevated levels (≥ 6.5%).

Adjunctive Treatment of Major Depressive Disorder

In two 6-week placebo-controlled trials of adult patients with major depressive disorder, the proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) was greatest in the VRAYLAR 3 mg per day + antidepressant therapy arm (3.2%) compared with those taking VRAYLAR 1.5 mg per day + antidepressant therapy (2%) or those placebo-treated (1.3%). The proportion of patients with shifts from normal to borderline (≥100 and <126 mg/dL) or from borderline to high were similar in patients treated with VRAYLAR and placebo. In a long-term, open-label adjunctive treatment of MDD study, 7% patients with normal hemoglobin A1c baseline values developed elevated levels (> 6%).

In one 8-week placebo-controlled trial of adult patients with major depressive disorder, the changes from baseline to end of the trial in fasting glucose were similar among the VRAYLAR and placebo + antidepressant therapy treatment groups. During the 8-week trial, serum insulin levels increased by 12 pmol/L in the VRAYLAR 1 mg to 2 mg per day group, 20 pmol/L in the VRAYLAR 2 mg to 4.5 mg per day group, and 8.5 pmol/L in the placebo group.

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Dyslipidemia

Atypical antipsychotics cause adverse alterations in lipids. Before or soon after initiation of antipsychotic medication, obtain a fasting lipid profile at baseline and monitor periodically during treatment.

Schizophrenia

In the 6-week, placebo-controlled trials of adult patients with schizophrenia, the proportion of patients with shifts in fasting total cholesterol, LDL, HDL, and triglycerides were similar in patients treated with VRAYLAR and placebo.

Bipolar Disorder

In six placebo-controlled trials up to 8-weeks of adult patients with bipolar disorder (mania or depression), the proportion of patients with shifts in fasting total cholesterol, LDL, HDL, and triglycerides were similar in patients treated with VRAYLAR and placebo.

Adjunctive Treatment of Major Depressive Disorder

In two 6-week placebo-controlled trials of adult patients with major depressive disorder, the proportion of patients with shifts in total cholesterol, fasting LDL, HDL, and fasting triglycerides were similar in patients treated with VRAYLAR and placebo.

Weight Gain

Weight gain has been observed with use of atypical antipsychotics, including VRAYLAR. Monitor weight at baseline and frequently thereafter. Tables 2, 3, 4, and 5 show the change in body weight occurring from baseline to endpoint in 6-week trials of schizophrenia, 3-week bipolar mania trials, 6-week and 8-week bipolar depression trials, and 6-week and 8-week trials of adjunctive treatment for major depressive disorder, respectively.

Table 2. Change in Body Weight (kg) in 6-Week Schizophrenia Trials

		VRAYLAR*		
	Placebo (N=573)	1.5 - 3 mg/day (N=512)	4.5 - 6 mg/day (N=570)	9 - 12◦ mg/day (N=203)
Mean Change at Endpoint	+0.3	+0.8	+1	+1
Proportion of Patients with Weight Increase (≥7%)	5%	8%	8%	17%

*Data shown by modal daily dose, defined as most frequently administered dose per patient

◦The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

In long-term, uncontrolled trials with VRAYLAR in schizophrenia, the mean changes from baseline in weight at 12, 24, and 48 weeks were 1.2 kg, 1.7 kg, and 2.5 kg, respectively.

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Table 3. Change in Body Weight (kg) in 3-Week Bipolar Mania Trials

		VRAYLAR*	
	Placebo (N=439)	3 - 6 mg/day (N=259)	9 - 12◦ mg/day (N=360)
Mean Change at Endpoint	+0.2	+0.5	+0.6
Proportion of Patients with Weight Increase (≥7%)	2%	1%	3%

*Data shown by modal daily dose, defined as most frequently administered dose per patient
◦The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Table 4. Change in Body Weight (kg) in two 6-Week and one 8-Week Bipolar Depression Trials

		VRAYLAR	
	Placebo (N=463)	1.5 mg/day (N=467)	3 mg/day (N=465)
Mean Change at Endpoint	-0.1	+0.7	+0.4
Proportion of Patients with Weight Increase (≥7%)	1%	3%	3%

Table 5. Change in Body Weight (kg) in two 6-Week and one 8-Week Adjunctive Treatment for Major Depressive Disorder Trials

		VRAYLAR	
6-week Trials	Placebo +ADT (N=503)	1.5 mg/day +ADT (N=502)	3 mg/day +ADT (N=503)
Mean Change at Endpoint	+0.2	+0.7	+0.7
Proportion of Patients with Weight Increase (≥7%)	1%	2%	2%
8-week Trial	Placebo + ADT (N=266)	1 to 2 mg/day + ADT (N=273)	2 to 4.5 mg/day + ADT (N=273)
Mean Change at Endpoint	0	+0.9	+0.9
Proportion of Patients with Weight Increase (≥7%)	2%	2%	3%

In the long-term, open-label adjunctive treatment of MDD trial, 2 patients (0.6%) discontinued due to weight increase. VRAYLAR was associated with mean change from baseline in weight of 1.7 kg at Week 26. In the long-term, open-label adjunctive treatment of MDD trial, 19% of patients demonstrated a ≥7% increase in body weight, and 5% demonstrated a ≥7% decrease in body weight.

5.8 Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including VRAYLAR. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients

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with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of VRAYLAR at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue VRAYLAR in patients with absolute neutrophil count < 1000/mm^3 and follow their WBC until recovery.

5.9 Orthostatic Hypotension and Syncope

Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose titration and when increasing the dose. Symptomatic orthostatic hypotension was infrequent in trials of VRAYLAR and was not more frequent on VRAYLAR than placebo. Syncope was not observed.

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, and concomitant treatment with antihypertensive medications), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. VRAYLAR has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from pre-marketing clinical trials.

5.10 Falls

Antipsychotics, including VRAYLAR, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.11 Seizures

Like other antipsychotic drugs, VRAYLAR may cause seizures. This risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

5.12 Potential for Cognitive and Motor Impairment

VRAYLAR, like other antipsychotics, may cause somnolence and has the potential to impair judgment, thinking, or motor skills.

In 6-week schizophrenia trials, somnolence (hypersomnia, sedation, and somnolence) was reported in 7% of VRAYLAR-treated patients compared to 6% of placebo-treated patients. In 3-week bipolar mania trials, somnolence was reported in 8% of VRAYLAR-treated patients compared to 4% of placebo-treated patients. In two 6-week and one 8-week trials of depressive episodes of bipolar I disorder, VRAYLAR-treated patients reported 7% somnolence and 4% in the placebo-treated patients. In 6-week adjunctive treatment of major depressive disorder trials, somnolence was reported in 6% of VRAYLAR-treated patients compared to 4% of placebo-treated patients. In one 8-week adjunctive treatment of major depressive disorder trial, somnolence was reported in 11% of VRAYLAR-treated patients compared to 6% of placebo-treated patients.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with VRAYLAR does not affect them adversely.

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5.13 Body Temperature Dysregulation

Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use VRAYLAR with caution in patient who may experience these conditions.

5.14 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Dysphagia has been reported with VRAYLAR. VRAYLAR and other antipsychotic drugs should be used cautiously in patients at risk for aspiration.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Suicidal Thoughts and Behaviors *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis *[see Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Late Occurring Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Metabolic Changes *[see Warnings and Precautions (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.8)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.9)]*
- Falls *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.12)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.13)]*
- Dysphagia *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The information below is derived from an integrated clinical study database for VRAYLAR consisting of 6,722 adult patients exposed to one or more doses of VRAYLAR for the treatment of schizophrenia, manic or mixed episodes associated with bipolar I disorder, bipolar depression, and adjunctive treatment of major depressive disorder in placebo-controlled studies. This experience corresponds with a total experience of 1,182.8 patient-years. A total of 4,329 VRAYLAR-treated patients had at least 6 weeks and 296 VRAYLAR-treated patients had at least 48 weeks of exposure.

Patients with Schizophrenia

The following findings are based on four placebo-controlled, 6-week schizophrenia trials with VRAYLAR doses ranging from 1.5 to 12 mg once daily. The maximum recommended dosage is 6 mg daily.

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Adverse Reactions Associated with Discontinuation of Treatment: There was no single adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in VRAYLAR-treated patients and at least twice the rate of placebo.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): extrapyramidal symptoms and akathisia.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo, at any dose are shown in Table 6.

Table 6. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in 6-Week Schizophrenia Trials

System Organ Class / Preferred Term	Placebo (N= 584) (%)	VRAYLAR* 1.5 to 3 mg/day (N=539) (%)	VRAYLAR* 4.5 to 6 mg/day (N=575) (%)	VRAYLAR* 9 to 12 mg/day (N=203) (%)
Cardiac Disorders				
Tachycardia[a]	1	2	2	3
Gastrointestinal Disorders				
Abdominal pain[b]	5	3	4	7
Constipation	5	6	7	10
Diarrhea[c]	3	1	4	5
Dry Mouth	2	1	2	3
Dyspepsia	4	4	5	5
Nausea	5	5	7	8
Toothache	4	3	3	6
Vomiting	3	4	5	5
General Disorders/Administration Site Conditions				
Fatigue[d]	1	1	3	2
Infections and Infestations				
Nasopharyngitis	1	1	1	2
Urinary tract infection	1	1	<1	2
Investigations				
Blood creatine phosphokinase increased	1	1	2	3
Hepatic enzyme increased[e]	<1	1	1	2
Weight increased	1	3	2	3
Metabolism and Nutrition Disorders				
Decreased appetite	2	1	3	2
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	1	2	1	2
Back pain	2	3	3	1
Pain in extremity	3	2	2	4
Nervous System Disorders				
Akathisia	4	9	13	14

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Table 6. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in 6-Week Schizophrenia Trials

System Organ Class / Preferred Term	Placebo (N= 584) (%)	VRAYLAR* 1.5 to 3 mg/day (N=539) (%)	VRAYLAR* 4.5 to 6 mg/day (N=575) (%)	VRAYLAR* 9 to 12 mg/day (N=203) (%)
Extrapyramidal symptoms[f]	8	15	19	20
Headache[g]	13	9	11	18
Somnolence[h]	5	5	8	10
Dizziness	2	3	5	5
Psychiatric Disorders				
Agitation	4	3	5	3
Insomnia[i]	11	12	13	11
Restlessness	3	4	6	5
Anxiety	4	6	5	3
Respiratory, Thoracic and Mediastinal disorders				
Cough	2	1	2	4
Skin and Subcutaneous Disorders				
Rash	1	<1	1	2
Vascular Disorders				
Hypertension[j]	1	2	3	6

Note: Figures rounded to the nearest integer

* Data shown by modal daily dose, defined as most frequently administered dose per patient

[a] **Tachycardia terms:** heart rate increased, sinus tachycardia, tachycardia

[b] **Abdominal pain terms:** abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain

[c] **Diarrhea terms**: diarrhea, frequent bowel movements

[d] **Fatigue terms**: asthenia, fatigue

[e] **Hepatic enzyme increase terms:** alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased

[f] **Extrapyramidal Symptoms terms:** bradykinesia, cogwheel rigidity, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, masked facies, muscle rigidity, muscle tightness, Musculoskeletal stiffness, oculogyric crisis, oromandibular dystonia, parkinsonism, salivary hypersecretion, tardive dyskinesia, torticollis, tremor, trismus

[g] **Headache terms:** headache, tension headache

[h] **Somnolence terms:** hypersomnia, sedation, somnolence

[i] **Insomnia terms:** initial insomnia, insomnia, middle insomnia, terminal insomnia

[j] **Hypertension terms:** blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased, hypertension

◦ The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Patients with Bipolar Mania

The following findings are based on three placebo-controlled, 3-week bipolar mania trials with VRAYLAR doses ranging from 3 to 12 mg once daily. The maximum recommended dosage is 6 mg daily.

Adverse Reactions Associated with Discontinuation of Treatment: The adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in VRAYLAR-treated patients and at least twice the rate of placebo was akathisia (2%). Overall, 12% of the patients who received VRAYLAR discontinued treatment due to an adverse reaction, compared with 7% of placebo-treated patients in these trials.

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Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at any dose are shown in Table 7.

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Table 7. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in 3-Week Bipolar Mania Trials

System Organ Class / Preferred Term	Placebo (N= 442) (%)	VRAYLAR* 3 to 6 mg/day (N=263) (%)	VRAYLAR* 9 to 12 mg/day° (N=360) (%)
Cardiac Disorders			
Tachycardia[a]	1	2	1
Eye Disorders			
Vision blurred	1	4	4
Gastrointestinal Disorders			
Nausea	7	13	11
Constipation	5	6	11
Vomiting	4	10	8
Dry mouth	2	3	2
Dyspepsia	4	7	9
Abdominal pain[b]	5	6	8
Diarrhea[c]	5	5	6
Toothache	2	4	3
General Disorders/Administration Site Conditions			
Fatigue[d]	2	4	5
Pyrexia[e]	2	1	4
Investigations			
Blood creatine phosphokinase increased	2	2	3
Hepatic enzymes increased[f]	<1	1	3
Weight increased	2	2	3
Metabolism and Nutrition Disorders			
Decreased appetite	3	3	4
Musculoskeletal and Connective Tissue Disorders			
Pain in extremity	2	4	2
Back pain	1	1	3
Nervous System Disorders			
Akathisia	5	20	21
Extrapyramidal Symptoms[g]	12	26	29
Headache[h]	13	14	13
Dizziness	4	7	6
Somnolence[i]	4	7	8
Psychiatric Disorders			
Insomnia[j]	7	9	8
Restlessness	2	7	7

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Table 7. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in 3-Week Bipolar Mania Trials

System Organ Class / Preferred Term	Placebo (N= 442) (%)	VRAYLAR* 3 to 6 mg/day (N=263) (%)	VRAYLAR* 9 to 12 mg/day◦ (N=360) (%)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	2	1	3
Vascular Disorders			
Hypertension[k]	1	5	4

Note: Figures rounded to the nearest integer
*Data shown by modal daily dose, defined as most frequently administered dose per patient
[a]**Tachycardia terms:** heart rate increased, sinus tachycardia, tachycardia
[b]**Abdominal pain terms:** abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness,
[c]**Diarrhea:** diarrhea, frequent bowel movements
[d]**Fatigue terms:** asthenia, fatigue
[e]**Pyrexia terms:** body temperature increased, pyrexia
[f]**Hepatic enzymes increased terms:** alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased
[g]**Extrapyramidal Symptoms terms:** bradykinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, musculoskeletal stiffness, oromandibular dystonia, parkinsonism, salivary hypersecretion, tremor
[h]**Headache terms:** headache, tension headache
[i]**Somnolence terms:** hypersomnia, sedation, somnolence
[j]**Insomnia terms:** initial insomnia, insomnia, middle insomnia
[k]**Hypertension terms:** blood pressure diastolic increased, blood pressure increased, hypertension
◦ The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Patients with Bipolar Depression

The following findings are based on three placebo-controlled, two 6-week and one 8-week bipolar depression trials with VRAYLAR doses of 1.5 mg and 3 mg once daily.

Adverse Reactions Associated with Discontinuation of Treatment: There were no adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in VRAYLAR-treated patients and at least twice the rate of placebo. Overall, 6% of the patients who received VRAYLAR discontinued treatment due to an adverse reaction, compared with 5% of placebo-treated patients in these trials.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): nausea, akathisia, restlessness, and extrapyramidal symptoms.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at 1.5 mg or 3 mg doses are shown in Table 8.

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Table 8. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in Two 6-Week and One 8-Week Bipolar Depression Trials

	Placebo (N=468) (%)	VRAYLAR 1.5 mg/day (N=470) (%)	VRAYLAR 3 mg/day (N=469) (%)
Restlessness	3	2	7
Akathisia	2	6	10
Extrapyramidal symptoms[a]	2	4	6
Dizziness	2	4	3
Somnolence[b]	4	7	6
Nausea	3	7	7
Increased appetite	1	3	3
Weight increase	<1	2	2
Fatigue[c]	2	4	3
Insomnia[d]	7	7	10

[a]**Extrapyramidal symptoms terms**: akinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle tightness, musculoskeletal stiffness, myoclonus, oculogyric crisis, salivary hypersecretion, tardive dyskinesia, tremor
[b]**Somnolence terms**: hypersomnia, sedation, somnolence
[c]**Fatigue terms**: asthenia, fatigue, malaise
[d]**Insomnia terms**: initial insomnia, insomnia, insomnia related to another mental condition, middle insomnia, sleep disorder, terminal insomnia

Adjunctive Therapy in Major Depressive Disorder

The following findings are based on two placebo-controlled, fixed-dose 6-week trials with VRAYLAR doses of 1.5 and 3 mg once daily plus an antidepressant and one placebo-controlled, flexible-dose 8-week trial with VRAYLAR doses of (1 to 2 mg) and (2 to 4.5 mg) once daily plus an antidepressant for adjunctive therapy in MDD.

Adverse Reactions Associated with Discontinuation of Treatment: The adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in VRAYLAR-treated patients and at least twice the rate of placebo was akathisia (2%). Overall, 6% of the patients who received VRAYLAR discontinued treatment due to an adverse reaction, compared with 3% of placebo-treated patients in these trials.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): Akathisia, nausea, and insomnia occurred in two 6-week, fixed-dose trials. Akathisia, restlessness, fatigue, constipation, nausea, increased appetite, dizziness, insomnia, and extrapyramidal symptoms occurred in one 8-week flexible-dose trial.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at 1.5 mg or 3 mg doses are shown in Table 9.

Table 9. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-Treated Patients and > Placebo-Treated Adult Patients in Two Fixed-Dose 6-Week

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Placebo-Controlled Trials of Adjunctive Treatment of Major Depressive Disorder

System Organ Class/ Preferred Term	Placebo + ADT (N=503) (%)	VRAYLAR 1.5 mg/day + ADT (N=502) (%)	VRAYLAR 3 mg/day + ADT (N=503) (%)
Eye Disorders			
Vision Blurred	<1	<1	2
Gastrointestinal Disorders			
Nausea	3	7	6
Dry Mouth	2	3	3
Constipation	1	2	2
Vomiting	1	1	2
General Disorders			
Fatigue	2	3	3
Investigations			
Weight increased	1	2	2
Nervous System Disorders			
Akathisia[a]	2	7	10
Somnolence[b]	4	5	7
Extrapyramidal Symptoms[c]	4	5	6
Psychiatric Disorders			
Insomnia[d]	5	9	10
Restlessness	2	4	4
Anxiety	1	2	1
Skin and Subcutaneous Tissue Disorders			
Hyperhidrosis	1	1	2

Note: Figures rounded to the nearest integer

[a] **Akathisia terms:** akathisia**,** psychomotor hyperactivity, feeling jittery, nervousness, tension

[b] **Somnolence terms**: hypersomnia, sedation, lethargy, somnolence

[c] **Extrapyramidal symptoms terms**: drooling, dyskinesia, extrapyramidal disorder, hypotonia, muscle contractions involuntary, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, myoclonus, oromandibular

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dystonia, parkinsonism, resting tremor, restless legs syndrome, stiff leg syndrome, salivary hypersecretion, stiff tongue, tardive dyskinesia, tremor, trismus

[d]**Insomnia terms**: initial insomnia, insomnia, middle insomnia, poor sleep quality, sleep disorder, terminal insomnia

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at 1 mg to 2 mg per day or 2 mg to 4.5 mg per day doses are shown in Table 10.

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Table 10. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-Treated Patients and > Placebo-Treated Adult Patients in a Flexible-dose 8-Week Placebo-Controlled Trial of Adjunctive Treatment of Major Depressive Disorder

System Organ Class/ Preferred Term	Placebo + ADT (N=266) (%)	VRAYLAR 1 to 2 mg/day + ADT (N=273) (%)	VRAYLAR 2 to 4.5 mg/day + ADT (N=273) (%)
Cardiac disorders			
Palpitations	1	2	<1
Eye disorders			
Vision blurred	1	1	4
Gastrointestinal disorders			
Nausea	5	7	13
Constipation	2	2	5
Dry mouth	3	5	4
Vomiting	<1	1	3
General disorders			
Fatigue	4	7	10
Edema	<1	2	1
Infections			
Nasopharyngitis	2	4	1
Investigations			
Increased appetite	2	2	5
Weight increased	1	2	3
Musculoskeletal and Connective Tissue disorders			
Back pain	1	2	3
Myalgia	0	1	2
Nervous System disorders			
Akathisia[a]	3	8	23
Extrapyramidal symptoms[b]	5	12	18
Somnolence[c]	6	10	11
Dizziness	2	4	5
Psychiatric disorders			
Insomnia[d]	8	14	16
Restlessness	3	8	8
Agitation	<1	<1	3
Anxiety	<1	1	3

[a] **Akathisia terms:** akathisia, feeling jittery, nervousness, tension

[b] **Extrapyramidal symptoms terms**: cogwheel rigidity, drooling, dyskinesia, extrapyramidal disorder, hypertonia, jaw stiffness, muscle contractions involuntary, muscle disorder, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, nuchal rigidity, parkinsonism, psychomotor retardation, reduced facial expression, resting tremor, restless legs syndrome, sensation of heaviness, salivary hypersecretion, tremor

[c] **Somnolence terms**: hypersomnia, sedation, lethargy, somnolence

[d] **Insomnia terms**: initial insomnia, insomnia, middle insomnia, terminal insomnia, sleep disorder, poor sleep quality

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Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. Although these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Extrapyramidal Symptoms (EPS) and Akathisia

In schizophrenia, bipolar mania, bipolar depression and adjunctive treatment of major depressive disorder trials, data were objectively collected using the Simpson Angus Scale (SAS) for treatment-emergent EPS (parkinsonism) (SAS total score ≤ 3 at baseline and > 3 post-baseline) and the Barnes Akathisia Rating Scale (BARS) for treatment-emergent akathisia (BARS total score ≤ 2 at baseline and > 2 post-baseline).

In 6-week schizophrenia trials, the incidence of reported adverse reactions related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness was 17% for VRAYLAR-treated patients versus 8% for placebo-treated patients. These reactions led to discontinuation in 0.3% of VRAYLAR-treated patients versus 0.2% of placebo-treated patients. The incidence of akathisia was 11% for VRAYLAR-treated patients versus 4% for placebo-treated patients. These reactions led to discontinuation in 0.5% of VRAYLAR-treated patients versus 0.2% of placebo-treated patients.

In 3-week bipolar mania trials, the incidence of reported adverse reactions related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 28% for VRAYLAR-treated patients versus 12% for placebo-treated patients. These reactions led to a discontinuation in 1% of VRAYLAR-treated patients versus 0.2% of placebo-treated patients. The incidence of akathisia was 20% for VRAYLAR-treated patients versus 5% for placebo-treated patients. These reactions led to discontinuation in 2% of VRAYLAR-treated patients versus 0% of placebo-treated patients.

In the two 6-week and one 8-week bipolar depression trials, the incidence of reported adverse reactions related to EPS, excluding akathisia and restlessness was 4% for VRAYLAR-treated patients versus 2% for placebo-treated patients. These reactions led to discontinuation in 0.4% of VRAYLAR-treated patients versus 0% of placebo-treated patients. The incidence of akathisia was 8% for VRAYLAR-treated patients versus 2% for placebo-treated patients. These reactions led to discontinuation in 1.5% of VRAYLAR-treated patients versus 0% of placebo-treated patients.

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In the two 6-week adjunctive treatment of major depressive disorder trials, the incidence of reported adverse reactions related to EPS, excluding akathisia and restlessness, was 6% for VRAYLAR-treated patients versus 4% for placebo-treated patients. These reactions led to discontinuation in 0.3% of VRAYLAR-treated patients versus 0.6% of placebo-treated patients. The combined incidence of akathisia and restlessness was 12% for VRAYLAR-treated patients versus 4% for placebo-treated patients. These reactions led to discontinuation in 2% of VRAYLAR-treated patients versus 0.4% of placebo-treated patients.

In one 8-week adjunctive treatment of major depressive disorder trial, the incidence of reported adverse reactions related to EPS, excluding akathisia and restlessness, was 12% for VRAYLAR-treated patients versus 5% for placebo-treated patients. These reactions led to discontinuation in 1% of VRAYLAR-treated patients versus 0.4% of placebo-treated patients. The incidence of akathisia and restlessness was 22% for VRAYLAR-treated patients versus 6% for placebo-treated patients. These reactions led to discontinuation in 3% of VRAYLAR-treated patients versus 0.0% of placebo-treated patients.

Cataracts

The development of cataracts was observed in nonclinical studies *[see Nonclinical Toxicology (13.2)]*. Cataracts were reported during the premarketing clinical trials of cariprazine; however, the duration of trials was too short to assess any association to cariprazine usage.

Vital Signs Changes

There were no clinically meaningful differences between VRAYLAR-treated patients and placebo-treated patients in mean change from baseline to endpoint in supine blood pressure parameters except for an increase in supine diastolic blood pressure in the 9 - 12 mg/day VRAYLAR-treated patients with schizophrenia.

Pooled data from 6-week schizophrenia trials are shown in Table 11, and from 3-week bipolar mania trials are shown in Table 12.

Table 11. Mean Change in Blood Pressure at Endpoint in 6-Week Schizophrenia Trials

		VRAYLAR*		
	Placebo (N=574)	1.5 - 3 mg/day (N=512)	4.5 - 6 mg/day (N=570)	9- 12 mg/day° (N=203)
Supine Systolic Blood Pressure (mmHg)	+0.9	+0.6	+1.3	+2.1
Supine Diastolic Blood Pressure (mmHg)	+0.4	+0.2	+1.6	+3.4

* Data shown by modal daily dose, defined as most frequently administered dose per patient

° The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

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Table 12. Mean Change in Blood Pressure at Endpoint in 3-Week Bipolar Mania Trials

	Placebo (N=439)	VRAYLAR*	
		3 - 6 mg/day (N=259)	9 – 12 mg/day° (N=360)
Supine Systolic Blood Pressure (mmHg)	-0.5	+0.8	+1.8
Supine Diastolic Blood Pressure (mmHg)	+0.9	+1.5	+1.9

* Data shown by modal daily dose, defined as most frequently administered dose per patient
° The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

In the two 6-week and one 8-week bipolar depression trials, there were no clinically meaningful differences between VRAYLAR-treated patients and placebo-treated patients in mean change from baseline to endpoint in supine systolic and diastolic blood pressure. VRAYLAR-treated patients' supine blood pressure increased by 0.1 to 0.3 mmHg; placebo-treated patients' supine blood pressure increased by 0.2 mmHg.

In two 6-week and one 8-week adjunctive treatment of major depressive disorder trials, there were no clinically meaningful differences between VRAYLAR-treated patients and placebo-treated patients in mean change from baseline to endpoint in supine systolic and diastolic blood pressure. At the end of the 6-week trials, VRAYLAR-treated patients' supine systolic blood pressure decreased by 0.1 to 0.7 mmHg; placebo-treated patients' supine systolic blood pressure decreased by 0.1 mmHg. VRAYLAR-treated patients' supine diastolic blood pressure increased by 0.1 mmHg and placebo-treated patients' supine diastolic blood pressure increased by 0.2 mmHg.

Changes in Laboratory Tests

The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in 6-week schizophrenia trials ranged between 1% and 2% for VRAYLAR-treated patients, increasing with dose, and was 1% for placebo-treated patients. The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in 3-week bipolar mania trials ranged between 2% and 4% for VRAYLAR-treated patients depending on dose group administered and 2% for placebo-treated patients. The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in 6-week and 8-week bipolar depression trials ranged between 0% and 0.5% for VRAYLAR-treated patients depending on dose group administered and 0.4% for placebo-treated patients. The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in two 6-week adjunctive treatment of major depressive disorder trials ranged between 0% and 1% for VRAYLAR-treated patients depending on dose group administered and 0% for placebo-treated patients.

The proportions of patients with elevations of creatine phosphokinase (CPK) greater than 1000 U/L in 6-week schizophrenia trials ranged between 4% and 6% for VRAYLAR-treated patients, increasing with dose, and was 4% for placebo-treated patients. The proportions of patients with elevations of CPK greater than 1000 U/L in 3-week bipolar mania trials was about 4% in VRAYLAR and placebo-treated patients. The proportions of patients with elevations of CPK greater than 1000 U/L in 6-week and 8-week bipolar depression trials ranged between 0.2% and 1% for VRAYLAR-treated patients versus 0.2% for placebo-treated patients. The proportions of patients with elevations of CPK greater than 1000 U/L in two 6-week

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adjunctive treatment of major depressive disorder trials ranged between 0.6% and 0.8% for VRAYLAR-treated patients versus 0% for placebo-treated patients.

Other Adverse Reactions Observed During the Pre-marketing Evaluation of VRAYLAR

Adverse reactions listed below were reported by patients treated with VRAYLAR at doses of ≥ 1.5 mg once daily within the premarketing database of 5,763 VRAYLAR-treated patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions that appear elsewhere in the VRAYLAR label are not included.

Reactions are further categorized by organ class and listed in order of decreasing frequency, according to the following definition: those occurring in at least 1/100 patients (frequent) [only those not already listed in the tabulated results from placebo-controlled studies appear in this listing]; those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1,000 patients (rare).

Gastrointestinal Disorders: ***Infrequent****: gastroesophageal reflux disease, gastritis*
Hepatobiliary Disorders: ***Rare:*** *hepatitis*
Metabolism and Nutrition Disorders: ***Frequent****: decreased appetite;* ***Rare****: hyponatremia*
Musculoskeletal and Connective Tissue Disorders: ***Rare****: rhabdomyolysis*
Nervous System Disorders: ***Rare****: ischemic stroke*
Psychiatric Disorders: ***Infrequent:*** *suicide ideation;* ***Rare****: completed suicide, suicide attempts*
Renal and Urinary Disorders: ***Infrequent****: pollakiuria*
Skin and Subcutaneous Tissue Disorders: ***Infrequent:*** *hyperhidrosis*

6.2 Postmarketing Experience

The following adverse reaction has been identified during post approval use of VRAYLAR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders – Stevens-Johnson syndrome

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7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with VRAYLAR

Table 13. Clinically Important Drug Interactions with VRAYLAR

Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of VRAYLAR with a strong CYP3A4 inhibitor increases the exposures of cariprazine and its major active metabolite, didesmethylcariprazine (DDCAR), compared to use of VRAYLAR alone *[see Clinical Pharmacology (12.3)]*.
Intervention:	If VRAYLAR is used with a strong CYP3A4 inhibitor, reduce VRAYLAR dosage *[see Dosage and Administration (2.6)]*.
CYP3A4 Inducers	
Clinical Impact:	CYP3A4 is responsible for the formation and elimination of the active metabolites of cariprazine. The effect of CYP3A4 inducers on the exposure of VRAYLAR has not been evaluated, and the net effect is unclear *[see Clinical Pharmacology (12.3)]*.
Intervention:	Concomitant use of VRAYLAR with a CYP3A4 inducer is not recommended *[see Dosage and Administration (2.1, 2.6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VRAYLAR during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. There are no available data on VRAYLAR use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. The major active metabolite of cariprazine, DDCAR, has been detected in adult patients up to 12 weeks after discontinuation of VRAYLAR *[see Clinical Pharmacology (12.3)]*. Based on animal data, VRAYLAR may cause fetal harm.

Administration of cariprazine to rats during the period of organogenesis caused malformations, lower pup survival, and developmental delays at drug exposures less than the human exposure at the maximum recommended human dose (MRHD) of 6 mg/day. However, cariprazine was not teratogenic in rabbits at doses up to 4.6 times the MRHD of 6 mg/day *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and

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miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Advise pregnant women of the potential risk to a fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates whose mothers were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

Data

Animal Data

Administration of cariprazine to pregnant rats during the period of organogenesis at oral doses of 0.5, 2.5, and 7.5 mg/kg/day, which are 0.2 to 3.5 times the maximum recommended human dose (MRHD) of 6 mg/day based on AUC of total cariprazine (i.e. sum of cariprazine, DCAR, and DDCAR), caused fetal developmental toxicity at all doses, which included reduced body weight, decreased male anogenital distance, and skeletal malformations of bent limb bones, scapula, and humerus. These effects occurred in the absence or presence of maternal toxicity. Maternal toxicity, observed as a reduction in body weight and food consumption, occurred at doses 1.2 and 3.5-times the MRHD of 6 mg/day based on AUC of total cariprazine. At these doses, cariprazine caused fetal external malformations (localized fetal thoracic edema), visceral variations (undeveloped/underdeveloped renal papillae and/or distended urethrae), and skeletal developmental variations (bent ribs, unossified sternebrae). Cariprazine had no effect on fetal survival.

Administration of cariprazine to pregnant rats during pregnancy and lactation at oral doses of 0.1, 0.3, and 1 mg/kg/day, which are 0.03 to 0.4 times the MRHD of 6 mg/day based on AUC of total cariprazine, caused a decrease in postnatal survival, birth weight, and post-weaning body weight of first generation pups at the dose that is 0.4 times the MRHD of 6 mg/day based on AUC of total cariprazine in absence of maternal toxicity. First generation pups also had pale, cold bodies and developmental delays (renal papillae not developed or underdeveloped and decreased auditory startle response in males). Reproductive performance of the first generation pups was unaffected; however, the second generation pups had clinical signs and lower body weight similar to those of the first generation pups.

Administration of cariprazine to pregnant rabbits during the period of organogenesis at oral doses of 0.1, 1, and 5 mg/kg/day, which are 0.02 to 4.6 times the MRHD of 6 mg/day based on AUC of total cariprazine, was not teratogenic. Maternal body weight and food consumption were decreased at 4.6 times the MRHD of 6 mg/day based on AUC of total cariprazine; however, no adverse effects were observed on pregnancy parameters or reproductive organs.

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8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of cariprazine in human milk, the effects on the breastfed infant, or the effects on milk production. Cariprazine is present in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for VRAYLAR and any potential adverse effects on the breastfed infant from VRAYLAR or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Pediatric studies of VRAYLAR have not been conducted. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning, Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

Clinical trials of VRAYLAR did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. VRAYLAR is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1, 5.3)]*.

8.6 Hepatic Impairment

No dosage adjustment for VRAYLAR is required in patients with mild to moderate hepatic impairment (Child-Pugh score between 5 and 9) [*see Clinical Pharmacology (12.3)*]. Usage of VRAYLAR is not recommended in patients with severe hepatic impairment (Child-Pugh score between 10 and 15). VRAYLAR has not been evaluated in this patient population.

8.7 Renal Impairment

No dosage adjustment for VRAYLAR is required in patients with mild to moderate (CrCL ≥ 30 mL/minute) renal impairment [*see Clinical Pharmacology (12.3)*].

Usage of VRAYLAR is not recommended in patients with severe renal impairment (CrCL < 30 mL/minute). VRAYLAR has not been evaluated in this patient population.

8.8 Smoking

No dosage adjustment for VRAYLAR is needed for patients who smoke. VRAYLAR is not a substrate for CYP1A2; smoking is not expected to have an effect on the pharmacokinetics of VRAYLAR.

8.9 Other Specific Populations

No dosage adjustment is required based on patient's age, sex, or race. These factors do not affect the pharmacokinetics of VRAYLAR [*see Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

VRAYLAR is not a controlled substance.

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9.2 Abuse

VRAYLAR has not been systematically studied in animals or humans for its abuse potential or its ability to induce tolerance.

9.3 Dependence

VRAYLAR has not been systematically studied in animals or humans for its potential for physical dependence.

10 OVERDOSAGE

10.1 Human Experience

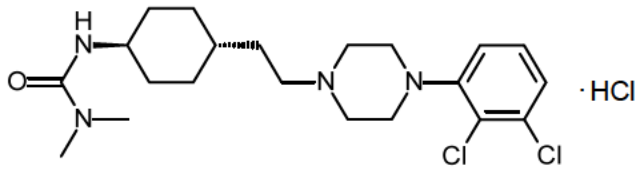
In pre-marketing clinical trials involving VRAYLAR in approximately 5000 patients or healthy subjects, accidental acute overdosage (48 mg/day) was reported in one patient. This patient experienced orthostasis and sedation. The patient fully recovered the same day.

10.2 Management of Overdosage

No specific antidotes for VRAYLAR are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. In case of an overdose, consult a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice.

11 DESCRIPTION

The active ingredient of VRAYLAR is cariprazine, an atypical antipsychotic, in hydrochloride salt form. The chemical name is *trans*-N-{4-[2-[4-(2,3-dichlorophenyl)piperazine-1-yl]ethyl]cyclohexyl}-N',N'-dimethylurea hydrochloride; its empirical formula is $C_{21}H_{32}Cl_2N_4O$•HCl and its molecular weight is 463.9 g/mol. The chemical structure is:



VRAYLAR capsules are intended for oral administration only. Each hard gelatin capsule contains a white to off-white powder of cariprazine HCl, which is equivalent to 1.5, 3, 4.5, or 6 mg of cariprazine base. In addition, capsules include the following inactive ingredients: gelatin, magnesium stearate, pregelatinized starch, shellac, and titanium dioxide. Colorants include black iron oxide (1.5, 3, and 6 mg), FD&C Blue 1 (3, 4.5, and 6 mg), FD&C Red 3 (6 mg), FD&C Red 40 (3 and 4.5 mg), or yellow iron oxide (3 and 4.5 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of cariprazine is unknown. However, the efficacy of cariprazine could be mediated through a combination of partial agonist activity at central dopamine D_2 and serotonin $5\text{-}HT_{1A}$ receptors and antagonist activity at serotonin $5\text{-}HT_{2A}$ receptors. Cariprazine forms two major metabolites, desmethylcariprazine (DCAR) and didesmethylcariprazine (DDCAR), that have *in vitro* receptor binding profiles similar to the parent drug.

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12.2 Pharmacodynamics

Cariprazine acts as a partial agonist at the dopamine D_3 and D_2 receptors with high binding affinity (K_i values 0.085 nM, and 0.49 nM (D_{2L}) and 0.69 nM (D_{2S}), respectively) and at the serotonin 5-HT_{1A} receptors (K_i value 2.6 nM). Cariprazine acts as an antagonist at 5-HT_{2B} and 5-HT_{2A} receptors with high and moderate binding affinity (Ki values 0.58 nM and 18.8 nM respectively) as well as it binds to the histamine H_1 receptors (K_i value 23.2 nM). Cariprazine shows lower binding affinity to the serotonin 5-HT_{2C} and α_{1A}- adrenergic receptors (K_i values 134 nM and 155 nM, respectively) and has no appreciable affinity for cholinergic muscarinic receptors (IC_{50}>1000 nM).

Effect on QTc Interval

At a dose three-times the maximum recommended dose, cariprazine does not prolong the QTc interval to clinically relevant extent.

12.3 Pharmacokinetics

VRAYLAR activity is thought to be mediated by cariprazine and its two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), which are pharmacologically equipotent to cariprazine.

After multiple dose administration of VRAYLAR, mean cariprazine and DCAR concentrations reached steady state at around Week 1 to Week 2 and mean DDCAR concentrations appeared to be approaching steady state at around Week 4 to Week 8 in a 12-week study (Figure 1). The half-lives based on time to reach steady state, estimated from the mean concentration-time curves, are 2 to 4 days for cariprazine, about 1 to 2 days for DCAR, and approximately 1 to 3 weeks for DDCAR. The time to reach steady state for the major active metabolite DDCAR was variable across patients, with some patients not achieving steady state at the end of the 12 week treatment *[see Dosage and Administration (2.1), Warnings and Precautions (5.6)]*. Mean concentrations of DCAR and DDCAR are approximately 30% and 400%, respectively, of cariprazine concentrations by the end of 12-week treatment.

After discontinuation of VRAYLAR, cariprazine, DCAR, and DDCAR plasma concentrations declined in a multi-exponential manner. Mean plasma concentrations of DDCAR decreased by about 50% 1 week after the last dose, and mean cariprazine and DCAR concentration dropped by about 50% in about 1 day. There was an approximately 90% decline in plasma exposure within 1 week for cariprazine and DCAR, and at about 4 weeks for DDCAR. Following a single dose of 1 mg of cariprazine administration, DDCAR remained detectable 8 weeks post-dose.

After multiple dosing of VRAYLAR, plasma exposure of cariprazine, DCAR, and DDCAR increases approximately proportionally over the therapeutic dose range.

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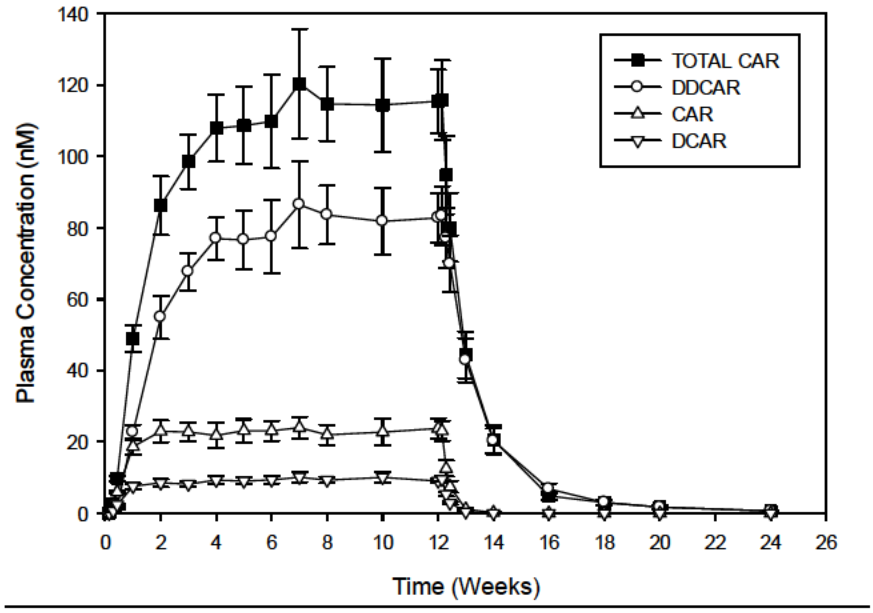
Figure 1. Plasma Concentration (Mean ± SE)-Time Profile During and Following 12-weeks of Treatment with Cariprazine 6 mg/day[a]



[a] Trough concentrations shown during treatment with cariprazine 6 mg/day.
SE: standard error; TOTAL CAR: sum concentration of cariprazine, DCAR and DDCAR; CAR: cariprazine

Absorption

After single dose administration of VRAYLAR, the peak plasma cariprazine concentration occurred in approximately 3-6 hours.

Administration of a single dose of 1.5 mg VRAYLAR capsule with a high-fat meal did not significantly affect the C_{max} and AUC of cariprazine or DCAR.

Distribution

Cariprazine and its major active metabolites are highly bound (91 to 97%) to plasma proteins.

Elimination

Metabolism
Cariprazine is extensively metabolized by CYP3A4 and, to a lesser extent, by CYP2D6 to DCAR and DDCAR. DCAR is further metabolized into DDCAR by CYP3A4 and CYP2D6. DDCAR is then metabolized by CYP3A4 to a hydroxylated metabolite.

Excretion
Following administration of 12.5 mg/day cariprazine to patients with schizophrenia for 27 days, about 21% of the daily dose was found in urine, with approximately 1.2% of the daily dose excreted in urine as unchanged cariprazine.

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Studies in Specific Populations

Hepatic Impairment
Compared to healthy subjects, exposure (C_{max} and AUC) in patients with either mild or moderate hepatic impairment (Child-Pugh score between 5 and 9) was approximately 25% higher for cariprazine and 20% to 30% lower for the major metabolites (DCAR and DDCAR) following daily doses of 0.5 mg cariprazine for 14 days *[see Use in Specific Populations (8.6)]*.

Renal Impairment
Cariprazine and its major active metabolites are minimally excreted in urine. Pharmacokinetic analyses indicated no significant relationship between plasma clearance and creatinine clearance *[see Use in Specific Populations (8.7)]*.

CYP2D6 Poor Metabolizers
CYP2D6 poor metabolizer status does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR.

Age, Sex, Race
Age, sex, or race does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR.

Drug Interaction Studies

In vitro studies
Cariprazine and its major active metabolites did not induce CYP1A2 and CYP3A4 enzymes and were weak inhibitors of CYP1A2, CYP2C9, CYP2D6, and CYP3A4 *in vitro*. Cariprazine was also a weak inhibitor of CYP2C19, CYP2A6, and CYP2E1 *in vitro.*

Cariprazine and its major active metabolites are not substrates of P-glycoprotein (P-gp), the organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3), or the breast cancer resistance protein (BCRP).

Cariprazine and its major active metabolites were poor or non-inhibitors of transporters OATP1B1, OATP1B3, BCRP, organic cation transporter 2 (OCT2), and organic anion transporters 1 and 3 (OAT1 and OAT3) *in vitro*. The major active metabolites were also poor or non-inhibitors of transporter P-gp although cariprazine was probably a P-gp inhibitor based on the theoretical GI concentrations at high doses *in vitro*.

Based on in vitro studies, VRAYLAR is unlikely to cause clinically significant pharmacokinetic drug interactions with substrates of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E, and CYP3A4, or OATP1B1, OATP1B3, BCRP, OCT2, OAT1 and OAT3.

In vivo studies

CYP3A4 inhibitors
Co-administration of ketoconazole (400 mg/day), a strong CYP3A4 inhibitor, with VRAYLAR (0.5 mg/day) increased cariprazine C_{max} and AUC_{0-24h} by about 3.5-fold and 4-fold, respectively; increased DDCAR C_{max} and AUC_{0-24h} by about 1.5-fold; and decreased DCAR C_{max} and AUC_{0-24h} by about one-third. The impact of moderate CYP3A4 inhibitors has not been studied.

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CYP3A4 inducers

CYP3A4 is responsible for the formation and elimination of the active metabolites of cariprazine. The effect of CYP3A4 inducers on the plasma exposure of cariprazine and its major active metabolites has not been evaluated, and the net effect is unclear.

CYP2D6 inhibitors

CYP2D6 inhibitors are not expected to influence pharmacokinetics of cariprazine, DCAR, or DDCAR based on the observations in CYP2D6 poor metabolizers.

Proton pump inhibitors

Co-administration of pantoprazole (40 mg/day), a proton pump inhibitor, with VRAYLAR (6 mg/day) in patients with schizophrenia for 15 days did not affect cariprazine exposure at steady-state, based on C_{max} and AUC_{0-24}. Similarly, no significant change in exposure to DCAR and DDCAR was observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There was no increase in the incidence of tumors following daily oral administration of cariprazine to rats for 2 years and to Tg.rasH2 mice for 6 months at doses which are up to 4 and 19 times respectively, the MRHD of 6 mg/day based on AUC of total cariprazine, (i.e. sum of AUC values of cariprazine, DCAR and DDCAR).

Rats were administered cariprazine at oral doses of 0.25, 0.75, and 2.5 (males)/1, 2.5, and 7.5 mg/kg/day (females) which are 0.2 to 1.8 (males)/ 0.8 to 4.1 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine.

Tg.rasH2 mice were administered cariprazine at oral doses of 1, 5, and 15 (males)/5, 15, and 50 mg/kg/day (females) which are 0.2 to 7.9 (males)/2.6 to 19 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine.

Mutagenesis

Cariprazine was not mutagenic in the *in vitro* bacterial reverse mutation assay, nor clastogenic in the in vitro human lymphocyte chromosomal aberration assay or in the *in vivo* mouse bone marrow micronucleus assay. However, cariprazine increased the mutation frequency in the *in vitro* mouse lymphoma assay under conditions of metabolic activation. The major human metabolite DDCAR was not mutagenic in the *in vitro* bacterial reverse mutation assay, however, it was clastogenic and induced structural chromosomal aberration in the *in vitro* human lymphocyte chromosomal aberration assay.

Impairment of Fertility

Cariprazine was administered orally to male and female rats before mating, through mating, and up to day 7 of gestation at doses of 1, 3, and 10 mg/kg/day which are 1.6 to 16 times the MRHD of 6 mg/day based on mg/m^2. In female rats, lower fertility and conception indices were observed at all dose levels which are equal to or higher than 1.6 times the MRHD of 6 mg/day based on mg/m^2. No effects on male fertility were noted at any dose up to 4.3 times the MRHD of 6 mg/day based on AUC of total cariprazine.

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13.2 Animal Toxicology and/or Pharmacology

Cariprazine caused bilateral cataract and cystic degeneration of the retina in the dog following oral daily administration for 13 weeks and/or 1 year and retinal degeneration/atrophy in the rat following oral daily administration for 2 years. Cataract in the dog was observed at 4 mg/kg/day which is 7.1 (male) and 7.7 (female) times the MRHD of 6 mg/day based on AUC of total cariprazine. The NOEL for cataract and retinal toxicity in the dog is 2 mg/kg/day which is 5 (males) to 3.6 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine. Increased incidence and severity of retinal degeneration/atrophy in the rat occurred at all doses tested, including the low dose of 0.75 mg/kg/day, at total cariprazine plasma levels less than clinical exposure (AUC) at the MRHD of 6 mg/day. Cataract was not observed in other repeat dose studies in pigmented mice or albino rats.

Phospholipidosis was observed in the lungs of rats, dogs, and mice (with or without inflammation) and in the adrenal gland cortex of dogs at clinically relevant exposures (AUC) of total cariprazine. Phospholipidosis was not reversible at the end of the 1-2 month drug-free periods. Inflammation was observed in the lungs of dogs dosed daily for 1 year with a NOEL of 1 mg/kg/day which is 2.7 (males) and 1.7 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine. No inflammation was observed at the end of 2-month drug free period following administration of 2 mg/kg/day which is 5 (males) and 3.6 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine; however, inflammation was still present at higher doses.

Hypertrophy of the adrenal gland cortex was observed at clinically relevant total cariprazine plasma concentrations in rats (females only) and mice following daily oral administration of cariprazine for 2 years and 6 months, respectively. Reversible hypertrophy/hyperplasia and vacuolation/vesiculation of the adrenal gland cortex were observed following daily oral administration of cariprazine to dogs for 1 year. The NOEL was 2 mg/kg/day which is 5 (males) and 3.6 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine. The relevance of these findings to human risk is unknown.

14 CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of VRAYLAR for the treatment of schizophrenia was established in three, 6-week, randomized, double-blind, placebo-controlled trials in patients (mean age of 37 years, aged 18 to 60 years; 31% were female; and 45% were Caucasian) who met Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text Revision (DSM-IV-TR) criteria for schizophrenia. An active control arm (risperidone or aripiprazole) was included in two trials to assess assay sensitivity. In all three trials, VRAYLAR was superior to placebo.

Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI-S) rating scales were used as the primary and secondary efficacy measures, respectively, for assessing psychiatric signs and symptoms in each trial:

- PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme). The PANSS total score may range from 30 to 210 with the higher score reflecting greater severity.

- The CGI-S is a validated clinician-related scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

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In each study, the primary endpoint was change from baseline in PANSS total score at the end of week 6. The change from baseline for VRAYLAR and active control groups was compared to placebo. The results of the trials are shown in Table 14. The time course of efficacy results of Study 2 is shown in Figure 2.

Study 1: In a 6-week, placebo-controlled trial (N = 711) involving three fixed doses of VRAYLAR (1.5, 3, or 4.5 mg/day) and an active control (risperidone), all VRAYLAR doses and the active control were superior to placebo on the PANSS total score and the CGI-S.

Study 2: In a 6-week, placebo-controlled trial (N = 604) involving two fixed doses of VRAYLAR (3 or 6 mg/day) and an active control (aripiprazole), both VRAYLAR doses and the active control were superior to placebo on the PANSS total score and the CGI-S.

Study 3: In a 6-week, placebo-controlled trial (N = 439) involving two flexible-dose range groups of VRAYLAR (3 to 6 mg/day or 6 to 9 mg/day), both VRAYLAR groups were superior to placebo on the PANSS total score and the CGI-S.

The efficacy of VRAYLAR was demonstrated at doses ranging from 1.5 to 9 mg/day compared to placebo. There was, however, a dose-related increase in certain adverse reactions, particularly above 6 mg. Therefore, the maximum recommended dose is 6 mg/day.

Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

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Table 14. Primary Analysis Results from Schizophrenia Trials

Study Number	Treatment Group (# ITT patients)	Primary Efficacy Endpoint: PANSS Total		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	VRAYLAR (1.5 mg/day)* (n=140)	97.1 (9.1)	-19.4 (1.6)	-7.6 (-11.8, -3.3)
	VRAYLAR (3 mg/day)* (n=140)	97.2 (8.7)	-20.7 (1.6)	-8.8 (-13.1, -4.6)
	VRAYLAR (4.5 mg/day)* (n=145)	96.7 (9.0)	-22.3 (1.6)	-10.4 (-14.6, -6.2)
	Placebo (n=148)	97.3 (9.2)	-11.8 (1.5)	--
Study 2	VRAYLAR (3 mg/day)* (n=151)	96.1 (8.7)	-20.2 (1.5)	-6.0 (-10.1, -1.9)
	VRAYLAR (6 mg/day)* (n=154)	95.7 (9.4)	-23.0 (1.5)	-8.8 (-12.9, -4.7)
	Placebo (n=149)	96.5 (9.1)	-14.3 (1.5)	--
Study 3	VRAYLAR (3-6 mg/day)* (n=147)	96.3 (9.3)	-22.8 (1.6)	-6.8 (-11.3, -2.4)
	VRAYLAR (6-9 mg/day)*[b] (n=147)	96.3 (9.0)	-25.9 (1.7)	-9.9 (-14.5, -5.3)
	Placebo (n=145)	96.6 (9.3)	-16.0 (1.6)	--

ITT: intent-to-treat; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval
[a]Difference (drug minus placebo) in least-squares mean change from baseline
*Doses that are statistically significantly superior to placebo
[b]The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

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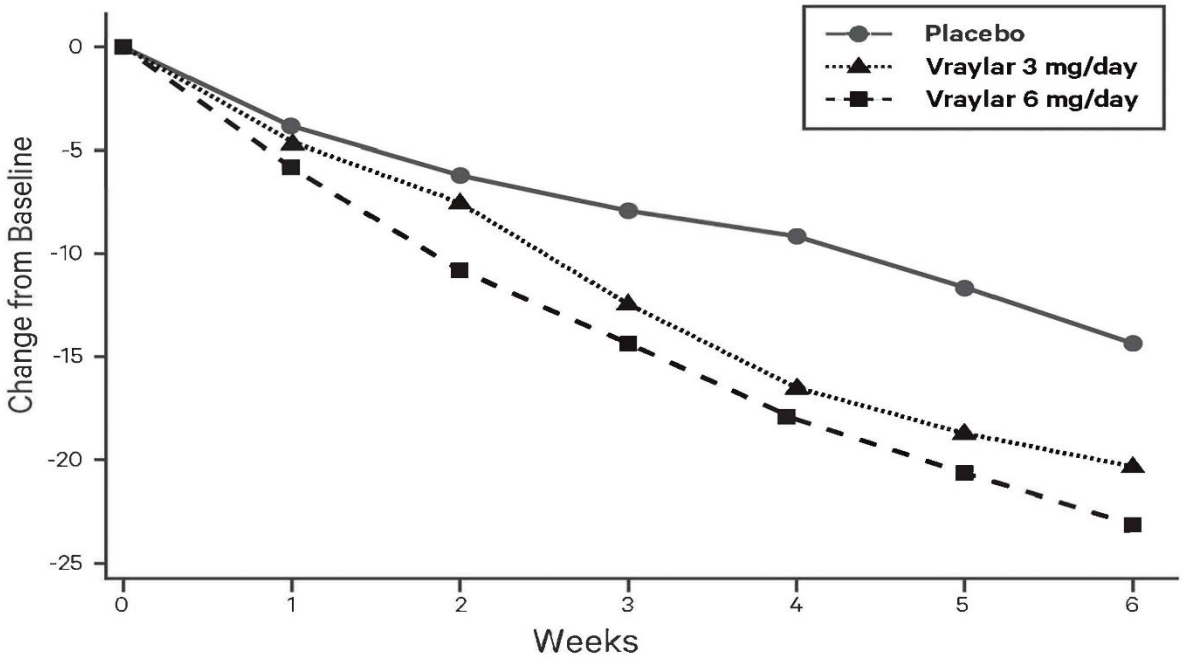
Figure 2. Change from Baseline in PANSS total score by weekly visits (Study 2)



The safety and efficacy of VRAYLAR as maintenance treatment in adults with schizophrenia were demonstrated in a randomized withdrawal trial that included 200 patients meeting DSM-IV criteria for schizophrenia who were clinically stable following 20 weeks of open-label cariprazine at doses of 3 to 9 mg/day. Patients were randomized to receive either placebo or cariprazine at the same dose for up to 72 weeks for observation of relapse. The primary endpoint was time to relapse. Relapse during the double-blind phase (DBP) was defined as meeting any one of the following criteria: hospitalization due to worsening of schizophrenia, increase in the PANSS total score by ≥ 30%, increase in CGI-S score by ≥ 2 points, deliberate self-injury, aggressive or violent behavior, clinically significant suicidal or homicidal ideation, or score >4 on one or more of the following PANSS items: delusions (P1), conceptual disorganization (P2), hallucination (P3), suspiciousness or persecution (P6), hostility (P7), uncooperativeness (G8), or poor impulse control (G14).

The efficacy of VRAYLAR was demonstrated at doses ranging from 3 to 9 mg/day compared to placebo. There was, however, a dose-related increase in certain adverse reactions, particularly above 6 mg. Therefore, the maximum recommended dose is 6 mg/day.

The Kaplan-Meier curves of the time to relapse during the double-blind, placebo-controlled, randomized withdrawal phase of the long-term trial are shown in Figure 3. Time to relapse was statistically significantly longer in the VRAYLAR-treated group compared to the placebo group.

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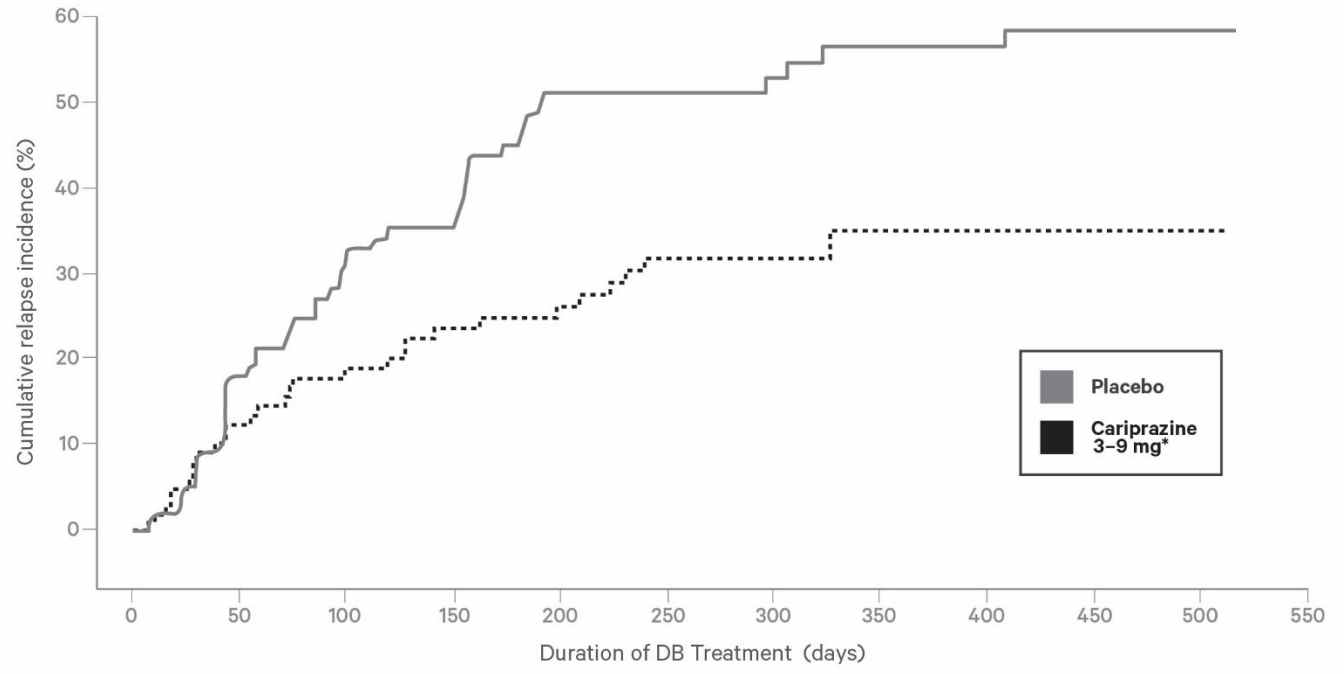
Figure 3. Kaplan-Meier Curves of Cumulative Rate of Relapse During the Double-Blind Treatment Period



At Risk	Cariprazine 3-9 mg*	101	81	72	64	54	48	44	38	32	26	18	0
	Placebo	99	75	58	54	38	32	28	23	23	21	16	0
Event	Cariprazine 3-9 mg*	0	12	18	22	24	28	28	30	30	30	30	30
	Placebo	0	17	30	32	45	45	46	48	48	49	49	49

DB = double-blind
*The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

14.2 Manic or Mixed Episodes Associated with Bipolar I Disorder

The efficacy of VRAYLAR in the acute treatment of bipolar mania was established in three, 3-week placebo-controlled trials in patients (mean age of 39 years, range 18 to 65 years; 40% were female; and 48% were Caucasian) who met DSM-IV-TR criteria for bipolar 1 disorder with manic or mixed episodes with or without psychotic features. In all three trials, VRAYLAR was superior to placebo.

Young Mania Rating Scale (YMRS) and Clinical Global Impressions-Severity scale (CGI-S) were used as the primary and secondary efficacy measures, respectively, for assessing psychiatric signs and symptoms in each trial:

- The YMRS is an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology. YMRS total score may range from 0 to 60 with a higher score reflecting greater severity.

- The CGI-S is validated clinician-related scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

In each study, the primary endpoint was decrease from baseline in YMRS total score at the end of week 3. The change from baseline for each VRAYLAR dose group was compared to placebo. The results of the trials are shown in Table 15. The time course of efficacy results is shown in Figure 4.

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Study 4: In a 3-week, placebo-controlled trial (N = 492) involving two flexible-dose range groups of VRAYLAR (3 to 6 mg/day or 6 to 12 mg/day), both VRAYLAR dose groups were superior to placebo on the YMRS total score and the CGI-S. The 6 to 12 mg/day dose group showed no additional advantage.

Study 5: In a 3-week, placebo-controlled trial (N = 235) involving a flexible-dose range of VRAYLAR (3 to 12 mg/day), VRAYLAR was superior to placebo on the YMRS total score and the CGI-S.

Study 6: In a 3-week, placebo-controlled trial (N = 310) involving a flexible-dose range of VRAYLAR (3 to 12 mg/day), VRAYLAR was superior to placebo on the YMRS total score and the CGI-S.

The efficacy of VRAYLAR was established at doses ranging from 3 to 12 mg/day. Doses above 6 mg did not appear to have additional benefit over lower doses (Table 15), and there was a dose-related increase in certain adverse reactions. Therefore, the maximum recommended dose is 6 mg/day.

Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

Table 15. Primary Analysis Results from Manic or Mixed Episodes Associated with Bipolar I Disorder Trials

Study Number	Treatment Group (# ITT patients)	Primary Efficacy Endpoint: YMRS Total		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 4	VRAYLAR (3-6 mg/day)* (n=165)	33.2 (5.6)	-18.6 (0.8)	-6.1 (-8.4, -3.8)
	VRAYLAR (6-12 mg/day)*[b] (n=167)	32.9 (4.7)	-18.5 (0.8)	-5.9 (-8.2, -3.6)
	Placebo (n=160)	32.6 (5.8)	-12.5 (0.8)	--
Study 5	VRAYLAR (3-12 mg/day)*[b] (n=118)	30.6 (5.0)	-15.0 (1.1)	-6.1 (-8.9, -3.3)
	Placebo (n=117)	30.2 (5.2)	-8.9 (1.1)	--
Study 6	VRAYLAR (3-12 mg/day)*[b] (n=158)	32.3 (5.8)	-19.6 (0.9)	-4.3 (-6.7, -1.9)
	Placebo (n=152)	32.1 (5.6)	-15.3 (0.9)	--

ITT: intent-to-treat; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval
[a]Difference (drug minus placebo) in least-squares mean change from baseline
*Doses that are statistically significantly superior to placebo
[b]The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

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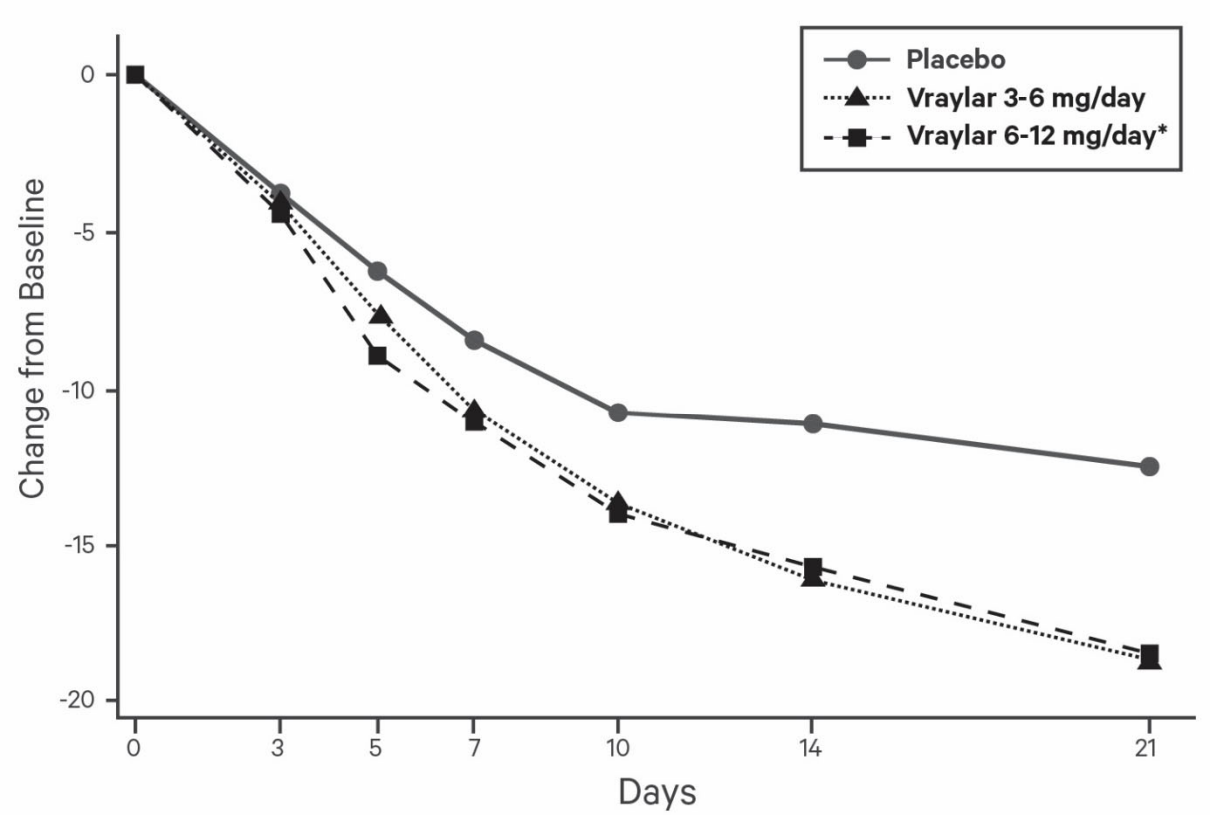
Figure 4. Change from Baseline in YMRS total score by study visit (Study 4)



* The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

14.3 Depressive Episodes Associated with Bipolar I Disorder (Bipolar Depression)

The efficacy of VRAYLAR in the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) was established in one 8-week and two 6-week placebo-controlled trials in patients (mean age of 43 years, range 18 to 65 years; 61% were female; and 75% were Caucasian) who met DSM-IV-TR or DSM-5 criteria for depressive episodes associated with bipolar I disorder.

In each study, the primary endpoint was change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at the end of Week 6. The MADRS is a 10-item clinician-rated scale with total scores ranging from 0 (no depressive features) to 60 (maximum score). The MADRS total score change from baseline for VRAYLAR compared to placebo is shown in Table 16. The time course of efficacy results of Study 8 is shown in Figure 5. In each study, the VRAYLAR 1.5 mg dose demonstrated statistical significance over placebo. The secondary endpoint was change from baseline to Week 6 in CGI-S. The CGI-S is validated clinician-related scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

Study 7: In an 8-week, placebo-controlled trial (N = 571) involving three-fixed doses of VRAYLAR (0.75 mg/day, 1.5 mg/day, and 3 mg/day), VRAYLAR 1.5 mg was superior to placebo at end of Week 6 on the MADRS total score and the CGI-S.

Study 8: In a 6-week, placebo-controlled trial (N = 474) involving two-fixed doses of VRAYLAR (1.5 mg/day and 3 mg/day), VRAYLAR 1.5 mg and 3 mg were superior to placebo at end of Week 6 on the MADRS total score.

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Study 9: In a 6-week, placebo-controlled trial (N = 478) involving two-fixed doses of VRAYLAR (1.5 mg/day and 3 mg/day), VRAYLAR 1.5 mg was superior to placebo at end of Week 6 on the MADRS total score and the CGI-S.

Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

Table 16. Primary Analysis Results from Bipolar Depression Trials

Study Number	Treatment Group (# ITT patients)	Primary Efficacy Endpoint: MADRS Total		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 7				
	VRAYLAR (1.5 mg/day)* (n=145)	30.3 (4.4)	-15.1 (0.8)	-4.0 (-6.3, -1.6)
	VRAYLAR (3 mg/day) (n=145)	30.6 (4.7)	-13.7 (0.9)	-2.5 (-4.9, -0.1)
	Placebo (n=141)	30.4 (4.6)	-11.1 (0.9)	
Study 8	VRAYLAR (1.5 mg/day)* (n=154)	30.7 (4.3)	-15.1 (0.8)	-2.5 (-4.6, -0.4)
	VRAYLAR (3 mg/day)* (n=164)	31.0 (4.9)	-15.6 (0.8)	-3.0 (-5.1, -0.9)
	Placebo (n=156)	30.2 (4.4)	-12.6 (0.8)	
Study 9	VRAYLAR (1.5 mg/day)* (n=162)	31.5 (4.3)	-14.8 (0.8)	-2.5 (-4.6, -0.4)
	VRAYLAR (3 mg/day) (n=153)	31.5 (4.8)	-14.1 (0.8)	-1.8 (-3.9, 0.4)
	Placebo (n=163)	31.4 (4.5)	-12.4 (0.8)	

ITT: intent-to-treat; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval
[a]Difference (drug minus placebo) in least-squares mean change from baseline
*Doses that are statistically significantly superior to placebo

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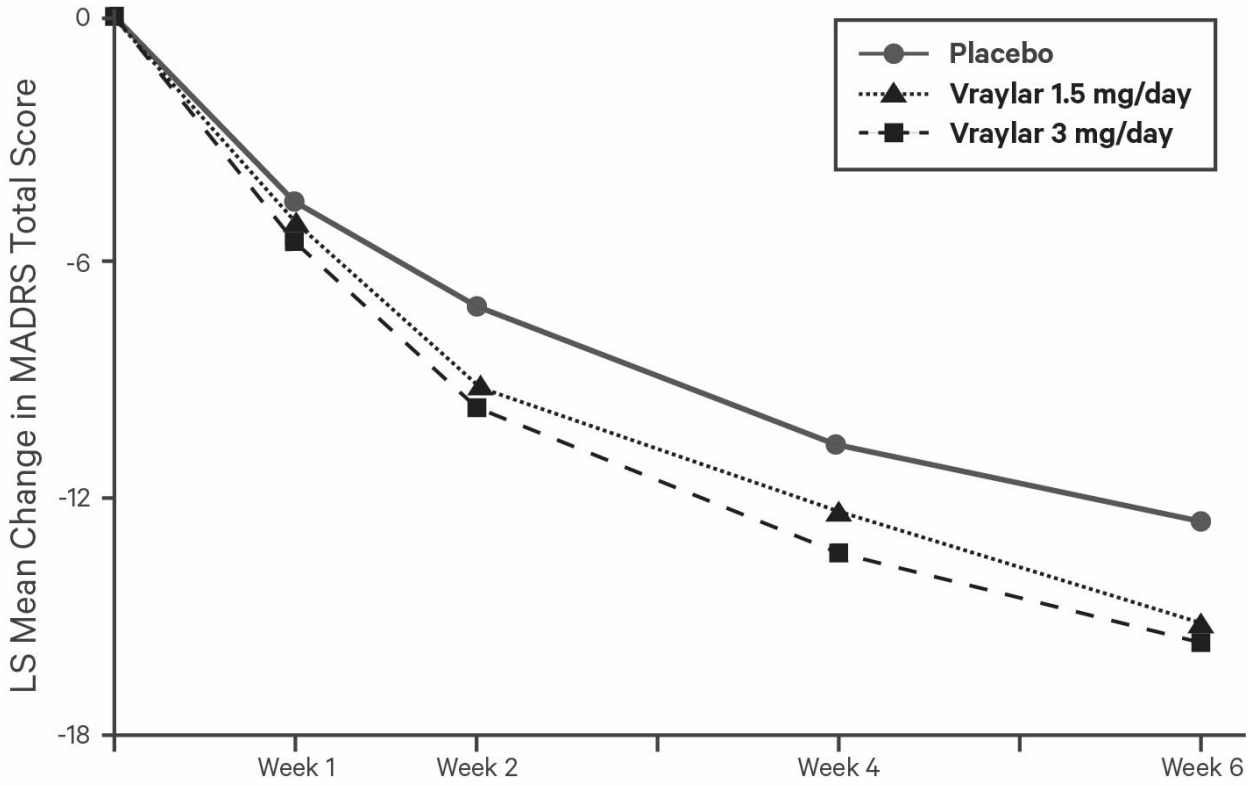
Figure 5. LS Mean* Change from Baseline in MADRS Total Score by Visits (Study 8)



*LS Mean: least-squares mean

14.4 Adjunctive Treatment of Major Depressive Disorder

The efficacy of VRAYLAR as adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) was evaluated in 2 trials in adult patients (mean age of 45 years, range 18 to 65 years; 72% were female; and 85% were Caucasian) who met DSM-IV-TR or DSM-5 criteria for MDD, with or without symptoms of anxiety, who had an inadequate response to 1 to 3 courses of prior antidepressant (ADT) therapy. Inadequate response during antidepressant treatment was defined as less than 50% improvement to antidepressant treatment of adequate dose and adequate duration.

In each study, the primary endpoint was change from baseline to Week 6 (Study 10) or Week 8 (Study 11) in the Montgomery-Asberg Depression Rating Scale (MADRS) total score, a 10-item clinician-rated scale used to assess the degree of depressive symptomatology, with 0 representing no symptoms and 60 representing worst symptoms.

Study 10: In a 6-week, placebo-controlled trial (N = 751) involving two fixed doses of VRAYLAR (1.5 mg per day or 3 mg per day) + ADT, VRAYLAR 1.5 mg + ADT was superior to placebo + ADT at end of Week 6 on the MADRS total score. The treatment effect in the VRAYLAR 3 mg per day + ADT group (vs. placebo + ADT) was not statistically significant.

Study 11: An 8-week, placebo-controlled trial (N = 808) involved flexible doses of VRAYLAR 1 to 2 mg per day + ADT or 2 to 4.5 mg per day + ADT. VRAYLAR 2 to 4.5 mg (mean dose was 2.6 mg) + ADT was superior to placebo + ADT at end of Week 8 on the MADRS total score. The treatment effect in the VRAYLAR 1 to 2 mg per day + ADT group (vs. placebo + ADT) was not statistically significant.

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Results from the primary efficacy parameters for both trials (Studies 10 and 11) are shown below in Table 17. Figure 6 below shows the time course of response based on the primary efficacy measure (MADRS total score) in Study 10.

Table 17: Primary Analysis Results from Adjunctive Treatment of Major Depressive Disorder Trials

Study Number	Treatment Group (# ITT patients)	Primary Efficacy Endpoint: MADRS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 10	VRAYLAR (1.5 mg/day) + ADT* (n=250)	32.8 (5.0)	-14.1 (0.7)	-2.5(-4.2, -0.9)
	VRAYLAR (3 mg/day) + ADT (n=252)	32.7 (4.9)	-13.1 (0.7)	-1.5 (-3.2, 0.1)
	Placebo + ADT (n=249)	31.9 (5.7)	-11.5 (0.7)	
Study 11	VRAYLAR (1 to 2 mg/day) + ADT (n=273)	29.0 (4.3)	-13.4 (0.5)	-0.9 (-2.4, 0.6)
	VRAYLAR (2 to 4.5 mg/day) + ADT* (n=271)	29.3 (4.1)	-14.6 (0.6)	-2.2 (-3.7, -0.6)
	Placebo + ADT (n=264)	28.9 (4.3)	-12.5 (0.5)	

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval
* Dosages statistically significantly superior to placebo
[a] Difference (drug minus placebo) in least-squares mean change from baseline

Examination of population subgroups based on age, sex, and race did not suggest any clear evidence of differential responsiveness.

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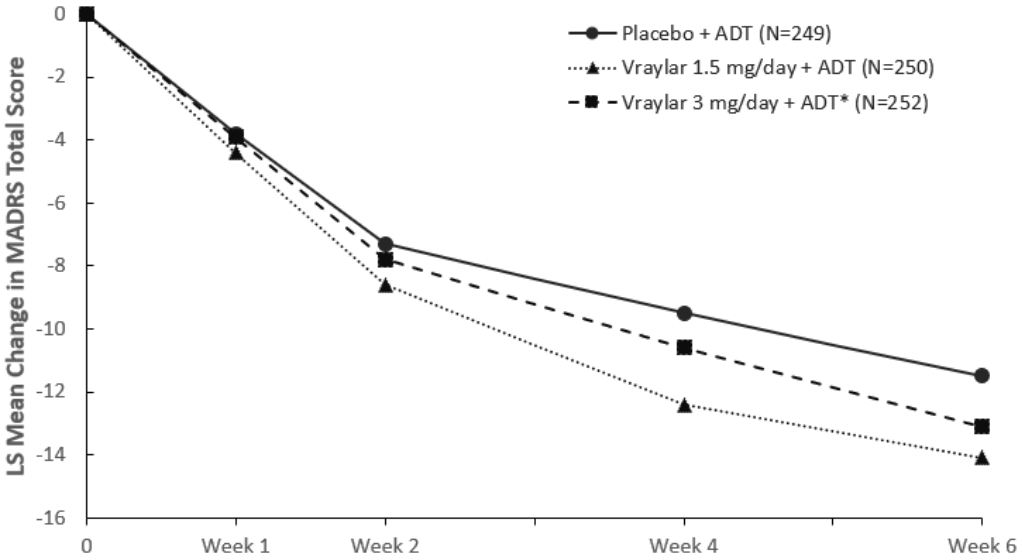
Figure 6. LS Mean‡ Change from Baseline to Week 6 in MADRS Total Score in Adjunctive Treatment of Major Depressive Disorder (Study 10)



Placebo + ADT (N)	249	246	246	238	231
Vraylar 1.5 mg/day+ADT (N)	250	250	242	237	231
Vraylar 3 mg/day+ADT* (N)	252	252	245	235	223

‡ LS Mean: least-squares mean
* Dose was not statistically significant.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VRAYLAR (cariprazine) capsules are supplied as follows:

Capsule Strength	Imprint Codes	Capsule Color	Package Configuration	NDC Code
1.5 mg	FL 1.5	White cap and body	Blister pack of 7	61874-115-17
			Bottle of 30	61874-115-30
			Bottle of 90	61874-115-90
			Box of 20 (Hospital Unit Dose)	61874-115-20
3 mg	FL 3	Green to blue-green cap and white body	Bottle of 30	61874-130-30
			Bottle of 90	61874-130-90
			Box of 20 (Hospital Unit Dose)	61874-130-20
4.5 mg	FL 4.5	Green to blue-green cap and body	Bottle of 30	61874-145-30
			Bottle of 90	61874-145-90
6 mg	FL 6	Purple cap and white body	Bottle of 30	61874-160-30
			Bottle of 90	61874-160-90
(1) 1.5 mg, (6) 3 mg	FL 1.5, FL 3		Mixed Blister pack of 7	61874-170-08

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) *[see USP Controlled Room Temperature]*. Protect 3 mg and 4.5 mg capsules from light to prevent potential color fading.

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17. PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors
Advise patients and caregivers to look for the emergence of suicidal thoughts and behaviors, especially early during treatment and when the dosage is adjusted up or down and instruct them to report such symptoms to their healthcare provider *[see Box Warning and Warnings and Precautions (5.2)]*.

Dosage and Administration
Advise patients that VRAYLAR can be taken with or without food. Counsel them on the importance of following dosage escalation instructions *[see Dosage and Administration (2)]*.

Neuroleptic Malignant Syndrome (NMS)
Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS), that has been reported in association with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact the healthcare provider or to report to the emergency room if they experience signs and symptoms of NMS *[see Warnings and Precautions (5.4)]*.

Tardive Dyskinesia
Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their health care provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

Late-Occurring Adverse Reactions
Counsel patients that adverse reactions may not appear until several weeks after the initiation of VRAYLAR treatment *[see Warnings and Precautions (5.6)]*.

Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain)
Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.7)]*.

Leukopenia/Neutropenia
Advise patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia that they should have their CBC monitored while taking VRAYLAR *[see Warnings and Precautions (5.8)]*.

Orthostatic Hypotension and Syncope
Counsel patients on the risk of orthostatic hypotension and syncope, especially early in treatment, and also at times of re-initiating treatment or increases in dose *[see Warnings and Precautions (5.9)]*.

Interference with Cognitive and Motor Performance
Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that VRAYLAR therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

Heat Exposure and Dehydration
Educate patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.13)]*.

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Concomitant Medications
Advise patients to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs since there is a potential for interactions *[see Drug Interactions (7.1)]*.

Pregnancy
Advise patients that third trimester use of VRAYLAR may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients to notify their healthcare provider with a known or suspected pregnancy [*see Use in Specific Populations (8.1)]*.

Pregnancy Registry
Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VRAYLAR during pregnancy *[see Use in Specific Populations (8.1)]*.

Licensed from Gedeon Richter Plc.

Manufactured by:
Forest Laboratories Ireland Limited
Dublin, IE.

Distributed by:
Allergan USA, Inc.
Madison, NJ 07940

VRAYLAR® is a registered trademark of Forest Laboratories Holdings Ltd., an Allergan affiliate.

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v5.0USPI115

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MEDICATION GUIDE

VRAYLAR® (VRAY-lar)
(cariprazine)
capsules

What is the most important information I should know about VRAYLAR?

VRAYLAR may cause serious side effects, including:

- **Increased risk of death in elderly people with dementia related psychosis.** Medicines like VRAYLAR can raise the risk of death in elderly who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). VRAYLAR is not approved for the treatment of patients with dementia-related psychosis.
- **Increased risk of suicidal thoughts and actions.** VRAYLAR and antidepressant medicines may increase suicidal thoughts or actions in some children and young adults **especially within the first few months of treatment or when the dose is changed.**
  - Depression and other mental illnesses are the most important causes of suicidal thoughts and actions.

  How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?
  - Pay close attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when VRAYLAR or the antidepressant medicine is started or when the dose is changed.
  - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions.
  - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

    Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:
    - thoughts about suicide or dying
    - new or worse depression
    - feeling very agitated or restless
    - trouble sleeping (insomnia)
    - acting aggressive, being angry, or violent
    - an extreme increase in activity and talking (mania)
    - attempts to commit suicide
    - new or worse anxiety
    - panic attacks
    - new or worse irritability
    - acting on dangerous impulses
    - other unusual changes in behavior or mood

What is VRAYLAR?

VRAYLAR is a prescription medicine used in adults:

- to treat schizophrenia
- for short-term (acute) treatment of manic or mixed episodes that happen with bipolar I disorder
- to treat depressive episodes that happen with bipolar I disorder (bipolar depression)
- along with antidepressant medicines to treat major depressive disorder (MDD)

It is not known if VRAYLAR is safe and effective in children.

Do not take VRAYLAR if you are allergic to cariprazine. See the end of this Medication Guide for a complete list of ingredients in VRAYLAR.

Before taking VRAYLAR, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had heart problems or a stroke
- have or have had low or high blood pressure
- have or have had diabetes or high blood sugar, or a family history of diabetes or high blood sugar. Your healthcare provider should check your blood sugar before you start and during treatment with VRAYLAR.
- have or have had high levels of total cholesterol, LDL cholesterol, or triglycerides or low levels of HDL cholesterol.
- have or had seizures (convulsions)
- have or have had kidney or liver problems
- have or had a low white blood cell count
- are pregnant or plan to become pregnant. VRAYLAR may harm your unborn baby. Taking VRAYLAR during your third trimester of pregnancy may cause your baby to have abnormal muscle movements or withdrawal symptoms after birth. Talk to your healthcare provider about the risk to your unborn baby if you take VRAYLAR during pregnancy.
  - Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with VRAYLAR.
  - If you become pregnant during treatment with VRAYLAR, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or go to http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.
- are breastfeeding or plan to breastfeed. It is not known if VRAYLAR passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with VRAYLAR.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
VRAYLAR and other medicines may affect each other causing possible serious side effects. VRAYLAR may affect the way other medicines work, and other medicines may affect how VRAYLAR works.

Your healthcare provider can tell you if it is safe to take VRAYLAR with your other medicines. Do not start or stop any medicines while taking VRAYLAR without talking to your healthcare provider first.

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I take VRAYLAR?

- Take VRAYLAR exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking VRAYLAR without first talking to your healthcare provider.
- Take VRAYLAR 1 time each day with or without food.
- If you take too much VRAYLAR, call your healthcare provider or Poison Control Center at 1-800-222-1222 or go to the nearest hospital emergency room, right away.

What should I avoid while taking VRAYLAR?

- Do not drive, operate machinery, or do other dangerous activities until you know how VRAYLAR affects you. VRAYLAR may make you drowsy.
- Do not become too hot or dehydrated during treatment with VRAYLAR.
  - Do not exercise too much.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun.
  - Do not wear too much clothing or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of VRAYLAR?

VRAYLAR may cause serious side effects, including:

- **See "What is the most important information I should know about VRAYLAR?"**
- **Stroke (cerebrovascular problems) in elderly people with dementia-related psychosis that can lead to death.**
- **Neuroleptic malignant syndrome (NMS) is a serious condition that can lead to death.** Call your healthcare provider or go to the nearest hospital emergency room right away if you have some or all of the following signs and symptoms of NMS:
  - high fever
  - confusion
  - changes in your breathing, heart rate, and blood pressure
  - stiff muscles
  - increased sweating
- **Uncontrolled body movements (tardive dyskinesia).** VRAYLAR may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking VRAYLAR. Tardive dyskinesia may also start after you stop taking VRAYLAR.
- **Late occurring side effects**. VRAYLAR stays in your body for a long time. **Some side effects may not happen right away and can start a few weeks after you start taking VRAYLAR, or if your dose of VRAYLAR increases**. Your healthcare provider should monitor you for side effects for several weeks after you start and after any increase in your dose of VRAYLAR.
- **Problems with your metabolism such as:**
  - **high blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who take VRAYLAR. Extremely high blood sugar can lead to coma or death. Your healthcare provider should check your blood sugar before you start, or soon after you start VRAYLAR, and then regularly during long-term treatment with VRAYLAR.

    Call your healthcare provider if you have any of these symptoms of high blood sugar during treatment with VRAYLAR:
    - feel very thirsty
    - feel very hungry
    - feel sick to your stomach
    - need to urinate more than usual
    - feel weak or tired
    - feel confused, or your breath smells fruity
  - **increased fat levels (cholesterol and triglycerides) in your blood.** Your healthcare provider should check the fat levels in your blood before you start, or soon after you start VRAYLAR, and then periodically during treatment with VRAYLAR.
  - **weight gain.** You and your healthcare provider should check your weight before you start and often during treatment with VRAYLAR.
- **Low white blood cell count**. Your healthcare provider may do blood tests during the first few months of treatment with VRAYLAR.

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For current labeling information, please visit https://www.fda.gov/drugsatfda

- **Decreased blood pressure (orthostatic hypotension).** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
- **Falls.** VRAYLAR may make you sleepy or dizzy, may cause a decrease in your blood pressure when changing position (orthostatic hypotension), and can slow your thinking and motor skills which may lead to falls that can cause fractures or other injuries.
- **Seizures (convulsions).**
- **Sleepiness, drowsiness, feeling tired, difficulty thinking and doing normal activities.** See "What should I avoid while taking VRAYLAR?"
- **Problems controlling your body temperature so that you feel too warm.** See "What should I avoid while taking VRAYLAR?"
- **Difficulty swallowing** that can cause food or liquid to get into your lungs.

The most common side effects of VRAYLAR include: difficulty moving or slow movements, tremors, uncontrolled body movements, restlessness and feeling like you need to move around, sleepiness, nausea, vomiting, indigestion, constipation, feeling tired, trouble sleeping, increased appetite, and dizziness

These are not all the possible side effects of VRAYLAR.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VRAYLAR?

- Store VRAYLAR at room temperature, between 68°F to 77°F (20°C to 25°C).

Keep VRAYLAR and all medicines out of the reach of children.

General information about the safe and effective use of VRAYLAR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VRAYLAR for a condition for which it was not prescribed. Do not give VRAYLAR to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about VRAYLAR that is written for healthcare professionals.

What are the ingredients in VRAYLAR?

Active ingredient: cariprazine

Inactive ingredients: gelatin, magnesium stearate, pregelatinized starch, shellac, and titanium dioxide.

Colorants include: black iron oxide, FD&C Blue 1, FD&C Red 3, FD&C Red 40, or yellow iron oxide.

Manufactured by: Forest Laboratories Ireland Limited, Dublin, IE.
Distributed by: Allergan USA, Inc. Madison, NJ 07940
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For more information, go to www.VRAYLAR.com or call 1-800-678-1605.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised 12/2022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204370Orig1s009

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Statistical Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	204370/S-009
Priority or Standard	Standard
Submit Date(s)	February 18, 2022
Received Date(s)	February 18, 2022
PDUFA Goal Date	December 18, 2022
Division/Office	Division of Psychiatry/Office of Neuroscience
Review Completion Date	December 15, 2022
Established/Proper Name	Cariprazine
(Proposed) Trade Name	Vraylar
Pharmacologic Class	Atypical antipsychotic
Code name	N/A
Applicant	Allergan Sales, LLC
Dosage form	Capsule
Applicant proposed Dosing Regimen	The starting dosage for VRAYLAR as adjunctive treatment is 1.5 mg once daily. Depending upon clinical response and tolerability, the dosage can be increased to 3 mg once daily on Day 15.
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	370143000 | Major depressive disorder (disorder) |
Recommendation on Regulatory Action	Approve

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Reference ID: 5095782

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Sarah Seung, PharmD, MS
Nonclinical Reviewer	Darren Fegley, PhD
Nonclinical Team Leader	Aisar Atrakchi, PhD
Office of Clinical Pharmacology Reviewer(s)	Atul Bhattaram, PhD Huixia Zhang, PhD
Office of Clinical Pharmacology Team Leader(s)	Sreedharan Sabarinath, PhD
Clinical Reviewer	Nancy Dickinson, PharmD
Clinical Team Leader	Jean Kim, MD
Statistical Analyst	Emily Nguyen, MS
Statistical Reviewer	Andrew Potter, PhD
Statistical Team Leader	Peiling Yang, PhD
Cross-Disciplinary Team Leader	Jean Kim, MD
Division Director (DP)	Tiffany R. Farchione, MD

Additional Reviewers of Application

OPQ	Lin Qi/Joyce Crich
Microbiology	NA
OPDP	Domenic D'Alessandro, PharmD, MBA, CDE
OSI	John Lee/Jenn Sellers/Phillip Kronstein
OSE/DEPI	NA
OSE/DMEPA	Loretta Holmes, BSN, PharmD (Safety Evaluator) Madhuri R. Patel, PharmD (Team Leader (Acting))
OSE/DRISK	NA
Other	Laurie Buonaccorsi, PharmD (Patient Labeling Reviewer)

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

Please refer to uploaded memos for each discipline in DARRTS.

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Glossary

ADT	standard antidepressant therapy
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
AR	adverse reaction
ATHF	Antidepressant Treatment History Form
CDER	Center for Drug Evaluation and Research
CDF	cumulative distribution function
CFB	change from baseline
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression- Improvement scale
CGI-S	Clinical Global Impression- Severity scale
CRF	case report form
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia Suicide Severity Rating Scale
DDCAR	didesmethylcariprazine
ECG	electrocardiogram
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
GCP	good clinical practice
HAMD-17	17-item Hamilton Depression Rating Scale
HDL	high-density lipoprotein
ICH	International Conference on Harmonisation
IND	Investigational New Drug
iPSP	Initial Pediatric Safety Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LDL	low-density lipoprotein
LOE	lack of efficacy
LOCS	Lens Opacity Classification System
MADRS	Montgomery Åsberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MPPRC	Medical Policy and Program Review Committee
NDA	new drug application
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics

PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SDS	Sheehan Disability Scale
SI	suicidal ideation
SI/B	suicidal ideation and/or behavior
SOC	system organ class
TEAE	treatment emergent adverse event
U.S.	United States of America

1 Executive Summary

1.1. Product Introduction

Vraylar (cariprazine) is an atypical antipsychotic with partial agonist activity at central dopamine D2 and serotonin 5-HT1A receptors and antagonist activity at serotonin 5-HT2A receptors. The drug was approved on September 17, 2015, for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adult subjects. Capsule dosage strengths of 1.5, 3, 4.5, and 6 mg are approved for oral ingestion once daily with or without food.

(b) (4) The original NDA application was issued a Complete Response on November 19, 2013. The NDA resubmission provided clinical data for doses 1.5 to 6 mg per day, which had fewer adverse events (AEs).

On May 24, 2019, the indication of treatment of depressive episodes of bipolar I depression was approved for doses of 1.5 and 3 mg once daily.

Cariprazine has many active metabolites. One of the major active metabolites, didesmethylcariprazine (DDCAR), has a half-life of 3 weeks and contributes to late-occurring AEs, such as EPS, somnolence, and akathisia.

On February 18, 2022, the Applicant, Allergan (a subsidiary of AbbVie), submitted their supplemental efficacy NDA 204370/S-009 for the (b) (4).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Overall, we have determined that the Applicant has provided substantial evidence of effectiveness by having two positive adequate and well-controlled studies, even though the efficacy of the low-dose and high-dose arms initially did not appear to be replicated. Statistics noted that due to a small overall average treatment effect on the MADRS (placebo subtracted change around -1 to -2.5) with cariprazine in the studies reviewed, the dose response could overlap if the studies were insufficiently powered while substantiation of efficacy was still occurring. Also, an analysis by clinical pharmacology noted that there was substantial overlap in the PK exposure levels for the two positive studies between 1.5 and 3 mg, indicating that while dose response for efficacy was flat for the two doses, this PK overlap also meant that the two doses were essentially functioning similarly in the study populations. Therefore, efficacy for the total dosage range of 1.5 to 3 mg daily was, indeed, substantiated. We also determined that the small treatment effect was clinically meaningful, given that it is similar to the effect observed in other atypical antipsychotics approved for adjunctive treatment for MDD.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

We recommend approval of cariprazine 1.5 and 3 mg/day as adjunctive treatment in conjunction with an antidepressant for MDD in adults.

The review team had initial reservations due to inconsistent and marginal efficacy results from two positive studies (Study 75, a flexible-dose study, and Study 301, a fixed-dose study) out of five total phase 3 trials (with Study 75, Study 301, and Study 302 examined in depth for this review), and dose-related safety issues of cariprazine in the MDD population. Our statistical team then determined that indeed there was substantiation of efficacy with the two positive adequate and well-controlled studies, even though the efficacy of the low-dose and high-dose arms in different studies initially did not appear to be replicated. Statistics noted that due to a small overall average treatment effect on the MADRS (placebo subtracted change around -1 to -2.5 in the two positive studies) with cariprazine in the studies reviewed, the dose response could overlap if the studies were insufficiently powered while substantiation of efficacy was still occurring. Also, an analysis by clinical pharmacology noted that there was substantial overlap in the PK exposure levels for the two positive studies between 1.5 and 3 mg, indicating that while dose response for efficacy was flat for the two doses, this PK overlap also meant that the two doses were essentially functioning similarly in the positive study populations. Therefore, efficacy for the total dosage range of 1.5 to 3 mg daily was, indeed, substantiated. We also determined that the small treatment effect was clinically meaningful, given that it is similar to the effect observed in other atypical antipsychotics approved for adjunctive treatment for MDD.

In terms of safety, a dose response was more clearly evident for AEs and dropouts in the three studies reviewed. Our safety analysis revealed that the steep cariprazine titration over 1 week in the flexible-dose Study RGH-MD-75 was likely responsible for its higher AE and dropout rates as compared to the fixed-dose studies (which titrated dosing over 2 weeks). Cariprazine is not well-tolerated with a rapid titration, with higher rates of early akathisia which causes agitation and anxiety, followed by accumulating AEs from cariprazine's long-acting major metabolites. With the slower fixed-dose study titration, it appears that the 3-mg dose, while having more AEs than 1.5 mg, was still better tolerated than the high dose arm of the flexible dose study. The rate and types of AEs for both 1.5 and 3 mg remain within a similar range to other approved antipsychotics, and to those seen for other cariprazine indications. Accordingly, both doses of 1.5 and 3 mg will still be recommended as safe and effective for the adjunctive treatment of MDD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• MDD is a common, chronic, and serious disease. If left untreated, MDD may be life-threatening. • MDD is characterized by low mood, anhedonia, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms. • Partial response to pharmacologic treatment is common, with about 30% of patients achieving remission during first line treatment with a selective serotonin reuptake inhibitor (SSRI).	Any additional treatments for MDD may be clinically important.
Current Treatment Options	• Antidepressants of various classes are the mainstay of pharmacotherapy for MDD. Patients who experience partial response to treatment with these first-line drugs may benefit from an adjunctive treatment option. • There are three atypical antipsychotics (quetiapine XR, aripiprazole, brexpiprazole) approved for adjunctive treatment of MDD. • Other strategies commonly used for an inadequate response to antidepressant treatment include maximizing the current antidepressant dose, changing to a different antidepressant, adding or changing psychotherapy, or augmentation with other (off-label) medications.	Like other medications approved for adjunctive treatment of MDD, cariprazine is an atypical antipsychotic.
Benefit	• In a 6-week, placebo-controlled trial (N = 751) involving two fixed doses of cariprazine (1.5 mg per day or 3 mg per day) added to antidepressant (ADT) treatment, cariprazine 1.5 mg + ADT was superior to placebo + ADT at end of Week 6 on the MADRS total score. The treatment effect in the cariprazine 3 mg per day + ADT group (vs. placebo + ADT) was not statistically significant. • An 8-week, placebo-controlled trial (N = 808) involved flexible doses of cariprazine 1 to 2 mg per day + ADT or 2 to 4.5 mg per day + ADT. Cariprazine 2 to 4.5 mg (mean dose was 2.6 mg) + ADT was superior	indicating that while dose response for efficacy was flat for the two doses, this PK overlap also meant that the two doses were essentially functioning similarly in the study populations. Therefore, efficacy for the total dosage range of 1.5 to 3 mg daily was, indeed, substantiated. We also determined that the small treatment effect was clinically meaningful, given that it is similar to the effect observed in other atypical

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to placebo + ADT at end of Week 8 on the MADRS total score. The treatment effect in the VRAYLAR 1 to 2 mg per day + ADT group (vs. placebo + ADT) was not statistically significant. • The overall LS means treatment effect across the positive studies was -1 to 2.5 points on the MADRS. • None of the prespecified secondary endpoints were supportive of efficacy. • There was no clear dose response for efficacy between cariprazine 1.5 and 3 mg. • PK exposures overlapped to a significant degree for the 1.5 and 3-mg dose arms in the studies reviewed. • The inclusion criteria for two fixed-dose studies (3111-301-001, 3111-302-001) allowed for subjects with more severe depression to be enrolled compared to trials of other antipsychotics approved for adjunctive MDD. Thus, these studies had a sicker and perhaps more treatment-resistant population leading to a smaller overall treatment effect.	antipsychotics approved for adjunctive treatment for MDD.
Risk and Risk Management	• The flexible dose study high-dose arm had many more AEs than the other studies, with a 21% discontinuation rate. These results were likely related to rapid titration over 1 week (as compared to the 2-week titration in the fixed-dose studies with lower AE rates). • AE rates were higher in the higher-dose arms than lower-dose arms for the fixed-dose studies. • DDCAR and DCAR are the long-lasting major metabolites that contribute to the incidence of late-occurring AEs weeks after a dose increase due to their accumulation to steady state. • Akathisia was the most common AE and reason for study discontinuation.	Safety results of cariprazine are similar to the results seen in studies for the other approved indications and similar to other antipsychotics approved for adjunctive treatment of MDD. AEs appear to be dose-dependent. A 2-week titration schedule is key to minimize rates of AEs like anxiety and akathisia. The AEs are adequately addressed in the PI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Long-term open-label safety data indicate somewhat higher rates of metabolic changes like weight gain and a higher rate of glucose intolerance (increased hemoglobin A1c) than seen in studies for the other cariprazine indications.	

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	8.1.2
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Major depressive disorder (MDD) is a serious, chronic disease characterized by one or more major depressive episodes. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines an episode of major depression as a period lasting at least 2 weeks, with five or more of the following symptoms: depressed mood, loss of interest or pleasure in most activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, decreased energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide (American Psychiatric Association, 2013). If left untreated, MDD may be life-threatening due to death by suicide.

Depression affects approximately 21 million adults (8.4% of all adults) in the United States. (National Institute of Mental Health, 2022) The total economic burden of treating depression in the United States was $83.1 billion in 2000; and workplace costs, including missed days and lack of productivity due to illness, accounted for most of the total economic burden (62%). Lack of full to adequate treatment remains a critical problem in the management of patients with MDD. Up to half of patients treated with first-line antidepressant monotherapy do not reach full remission, and as many as a third are treatment-resistant. Present strategies available to treat patients who do not respond to first-line antidepressant monotherapy include switching of the antidepressant (either within or between classes) or polypharmacy. Antidepressants are often combined with non-pharmacologic treatments.

2.2. Analysis of Current Treatment Options

The FDA has approved many medications for treatment of MDD, as shown in Table 1. Oral pharmacotherapies are first-line treatment. When pharmacotherapies are administered with psychotherapy, subjects have greater response than either alone (Hollon, Jarrett, & Nierenberg, 2005). Esketamine, an intranasal spray listed in Table 1, is indicated for the treatment of treatment-resistant depression (TRD) in adults and for the treatment of depressive symptoms in adults with MDD and acute suicidal ideation or behavior. Approved non-pharmacological therapies for MDD and TRD include electroconvulsive therapy and transcranial magnetic stimulation. Approved adjunctive treatments for partial response to MDD include aripiprazole, brexpiprazole, and extended-release quetiapine. Off label adjunctive treatments include ketamine, lithium, liothyronine sodium, modafinil, pindolol, (Kleeblatt, Betzler, Kilarski, & al., 2017) and ziprasidone (Papakostas, M, L, & al., 2015).

Table 1: FDA Approved Pharmacotherapy for Treatment of Depression

FDA Approved Pharmacotherapies	
	Citalopram

FDA Approved Pharmacotherapies	
Selective serotonin reuptake inhibitors (SSRIs)	Escitalopram
	Fluoxetine
	Fluvoxamine
	Paroxetine
	Sertraline
Selective serotonin and norepinephrine reuptake inhibitors (SNRIs)	Desvenlafaxine
	Duloxetine
	Levomilnacipran
	Milnacipran (approved for fibromyalgia)
Monoamine oxidase inhibitors	Isocarboxazid
	Phenelzine
	Selegiline transdermal
	Tranylcypromine
Tricyclic antidepressants (TCAs)	Amitriptyline
	Amoxapine
	Clomipramine
	Desipramine
	Doxepin
	Imipramine
	Maprotiline
	Nortriptyline
	Protriptyline
	Trimipramine
Atypical antidepressants	Buproprion
	Buproprion-dextromethorphan
	Mirtazapine
Serotonin modulators	Trazodone
	Vilazodone
	Vortioxetine
N-Methyl-D-Aspartate (NMDA) Receptor Antagonist	Esketamine
Atypical antipsychotics (as adjunct or monotherapy)	Aripiprazole
	Brexpiprazole
	Quetiapine extended-release
	Olanzapine/fluoxetine (monotherapy for treatment-resistant depression)

Source: Clinical Reviewer created 9/14/2022

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Cariprazine is marketed in the United States and in other countries. FDA approved cariprazine for the following indications in adults:

- September 17, 2015: Schizophrenia; mixed or manic episodes associated with bipolar I disorder
- May 24, 2019: Depressive episodes associated with bipolar I disorder (bipolar depression).

3.2. Summary of Presubmission/Submission Regulatory Activity

- **March 19, 2009:** Forest Laboratories opened IND 104466 with protocol RGH-MD-71 for the treatment of depression as an adjunct to antidepressants for those with an inadequate response.

- **June 18, 2012:** FDA and the Applicant held a Type C guidance meeting to discuss the phase 3 study design to support their future indication. FDA advised the Applicant that two positive adequate and well-controlled studies of cariprazine as adjunctive therapy with antidepressants in MDD would be needed to support the indication, and noted that the study designs of RGH-MD-75 and RGH-MD-72 were adequate. The Agency also advised the Applicant to conduct an open-label extension study to obtain long-term safety data and that 6 months of exposure data on 100 subjects taking cariprazine as adjunctive therapy to antidepressants would be acceptable.

- **May 5, July 25, October 18, November 3, 2016:** The Applicant submitted their Initial Pediatric Study Plan (iPSP) followed by their Agreed iPSP for a full waiver in all pediatric age groups for cariprazine for the adjunctive MDD indication. The Agency issued the letter of agreement on November 3, 2016.

- **April 16, May 7, June 7, 2021:** The Applicant submitted a Type C meeting request to discuss their amended statistical analysis plans (SAP) for the phase 3 studies, 3111-301-001 and 3111-302-001. On April 19, 2021, our statistics team requested that the Applicant submit the SAPs separately to the IND for our review. We received the SAP amendment on May 7 and issued comments to the Applicant on June 7, 2021.

- **June 28, 2021:** FDA issued answers to Allergan's Type C Written Response Only. The guidance provided input on the Applicant's proposed SAPs (already answered on June 7, 2021) and the proposed integrated summaries of efficacy and safety (ISE). At the time, four studies were completed, RGH-MD-71, -72, -75, and -76. The Agency had no objection to the proposed plan for the ISE, noting the exploratory nature of the ISE, and

reminded the Applicant that any efficacy demonstration for cariprazine should be based on the results of individual studies (not a pooled analysis).

- **July 29, October 7, November 12, 2021:** The Applicant submitted statistical information for review. Refer to Dr. Peiling Yang's review dated November 8, 2021.

- **December 15, 2021:** The Applicant responded to our statistical comments. Refer to Dr. Peiling Yang's review dated December 28, 2021. The statistical discussion in the latter half of 2021 was related to the fifth phase 3 trial, 3111-302-001, which was negative. The Applicant added the Clinical Global Impression-Severity (CGI-S) scale as the secondary endpoint for their registration trials, instead of the previously proposed HAM-A.

- **January 6, 2022:** FDA issued Preliminary Comments for the Applicant's Type B Pre-NDA meeting request. The Applicant proposed that their two registration trials would be RGH-MD-75 and 3111-301-001 with the other three phase 3 trials (RGH-MD-71, -72, 3111-302-001) and one long-term safety trial (RGH-MD-76) being supportive data for the supplemental NDA package. The Applicant canceled the meeting on January 11, 2022, after receiving the Agency's comments.

- **February 18, 2022:** Allergan submitted sNDA 204370/S-009, which is the subject of this review.

- **April 5, 2022:** The Sponsor of IND 104466 changed from Allergan to AbbVie. Allergan is a subsidiary of AbbVie.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Review Team requested field inspections for the Applicant's registration trials, RGH-MD-75 and 3111-301-001. Two clinical sites were chosen from each clinical trial using OSI's site selection tool.

Primary Investigator	Rationale for Inspection
Study 3111-301-001, Site #14 Kunovac, Jelena	High enrollment, good efficacy, no SAEs reported, no recent inspection
Study 3111-301-001, Site #40 Booker, Gary J.	Moderate enrollment, good efficacy
Study RGH-MD-75, Site #27 Horwitz, Alexander	Moderate enrollment, United States site is greatest driver of efficacy
Study RGH-MD-75, Site #66 Shiovitz, Thomas	Moderate enrollment, United States site helping drive efficacy favoring IP

Source: Clinical Reviewer modified from Request for Inspections in DARRTS dated 4/7/22

Per OSI's inspection report from John Lee, all four sites examined appear to be GCP-compliant, and no significant problems were observed. Please refer to OSI's review for more details.

4.2. Product Quality

Not applicable. No new product quality information was submitted with this supplement.

4.3. Clinical Microbiology

Not applicable. No new microbiology information was submitted with this supplement.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Not applicable. No new nonclinical information was submitted with this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

Cariprazine is currently approved by the FDA for use in adults for the treatment of schizophrenia, the acute treatment of manic or mixed episodes associated with bipolar I disorder, and the treatment of depressive episodes associated with bipolar I disorder (bipolar depression).

In this efficacy supplement (S-09), the Applicant is seeking approval for use of cariprazine as (b) (4)

In this supplement, a summary of the population pharmacokinetic (popPK) and pharmacokinetic/pharmacodynamic (PK/PD) analyses of data collected from two phase 3 clinical trials (Study 3111-301-001 and Study 3111-302-001) is provided to support the use of cariprazine as (b) (4). No new clinical pharmacology studies were conducted. There are no proposed labeling changes in clinical pharmacology related sections.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Same as current labeling.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The starting dosage for cariprazine is 1.5 mg once daily. Depending upon clinical response and tolerability, the dosage can be increased to 3 mg once daily on Day 15. Maximum recommended dosage is 3 mg once daily.

Therapeutic Individualization

Same as current labeling.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

No new information is provided in this supplement. Refer to current labeling for information.

6.3.2. Clinical Pharmacology Questions

Considering the totality of evidence, is there adequate support for the proposed cariprazine dose range of 1.5 to 3 mg as (b) (4) and what are the potential clinical pharmacology-based reasons that can explain the observed heterogeneity in treatment response at the dose levels being sought for approval?

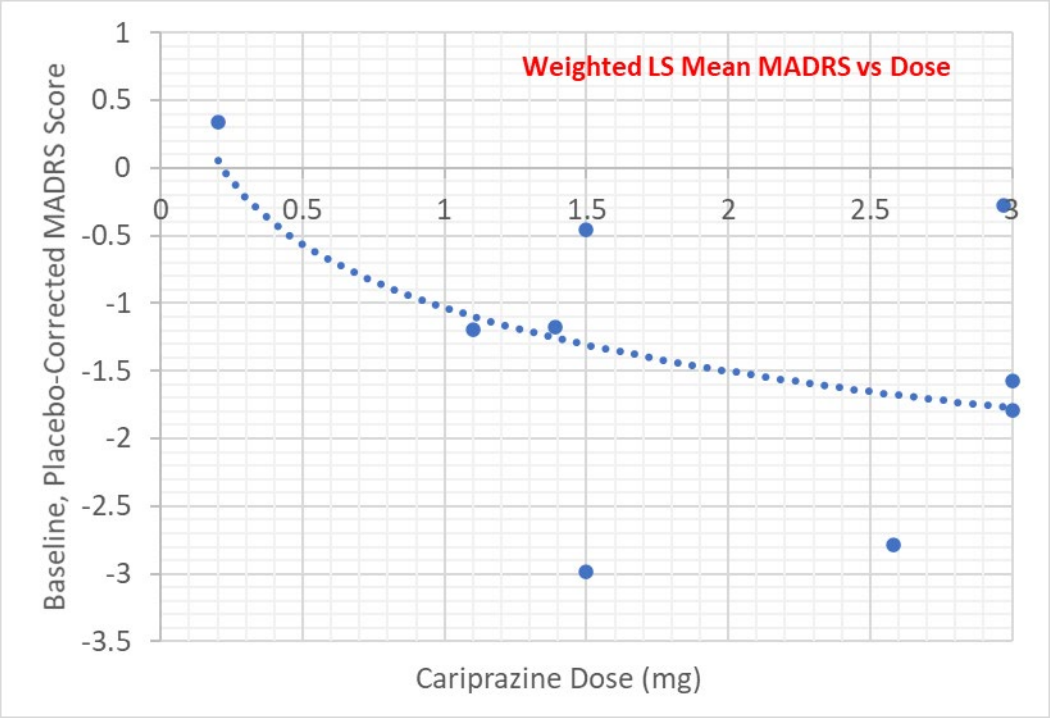
The clinical development program for cariprazine as an adjunctive treatment for MDD comprised five placebo-controlled studies with either 6- or 8-week double-blind treatment periods. The primary efficacy endpoint for each of the placebo-controlled studies was the change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at the end of the double-blind treatment period.

The investigation of cariprazine for the adjunctive treatment of MDD was initiated with Study RGH-MD-71, an 8-week, exploratory, flexible-dose-range study, followed by two additional 8-week studies (Studies RGH-MD-72 [flexible-dose] and RGH-MD-75 [flexible-dose-range]). Flexible doses were utilized because the efficacious and safe doses of cariprazine had not yet been established and approved by the FDA when these studies were initiated. Study RGH-MD-71 assessed cariprazine in doses of either 0.1 to 0.3 mg/day + ADT (antidepressant therapy) or 1 to 2 mg/day + ADT. Study RGH-MD-72 assessed cariprazine doses of 1.5 to 4.5 mg/day, with a target dose of 3 mg/day (mean dose was 2.97 ± 0.81 mg/day) + ADT. Study RGH-MD-75 evaluated cariprazine 1 to 2 mg/day and cariprazine 2 to 4.5 mg/day versus placebo as an adjunctive treatment to ongoing ADT. Studies 3111-301-001 and 3111-302-001 were two identically designed studies comparing 6 weeks of double-blind treatment with fixed doses of cariprazine 1.5 mg/day and cariprazine 3 mg/day with placebo as an adjunctive treatment to ongoing ADT. These fixed doses were selected after the efficacy and safety of cariprazine doses of 1.5 mg/day and 3 mg/day were established in bipolar depression studies.

The clinical development program for cariprazine in subjects with MDD showed heterogeneity in treatment response across clinical trials. The presence of a relationship between dose and

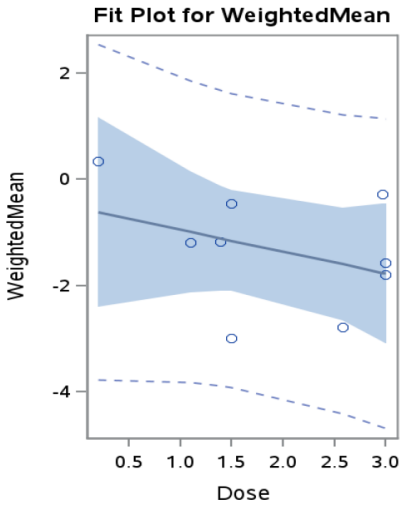
baseline, placebo-corrected total MADRS score across the five clinical studies was explored (Figure 1). The estimate of dose-response slope using a linear model (Figure 2), is -0.41 (95%CI (-1.15, 0.33), p=0.32), suggesting a 0.4 unit decrease in total MADRS score for every 1 mg cariprazine dose.

Figure 1 Relationship between Cariprazine Dose and Weighted LSMean (Baseline-, Placebo-Corrected) Change in Total MADRS Score for Studies RGH-MD-71, RGH-MD-72, RGH-MD-75, 3111-301-001, and 3111-302-001



Source: Reviewer's analysis. Reported LSMEANS from each study were weighted using standard error to derive weighted LSMean.

Figure 2 Dose-response Analysis for Weighted LSMean Change in Total MADRS Score (Baseline, Placebo-Corrected) versus Dose in Studies RGH-MD-71, RGH-MD-72, RGH-MD-75, 3111-301-001, and 3111-302-001



Source: Reviewer's analysis

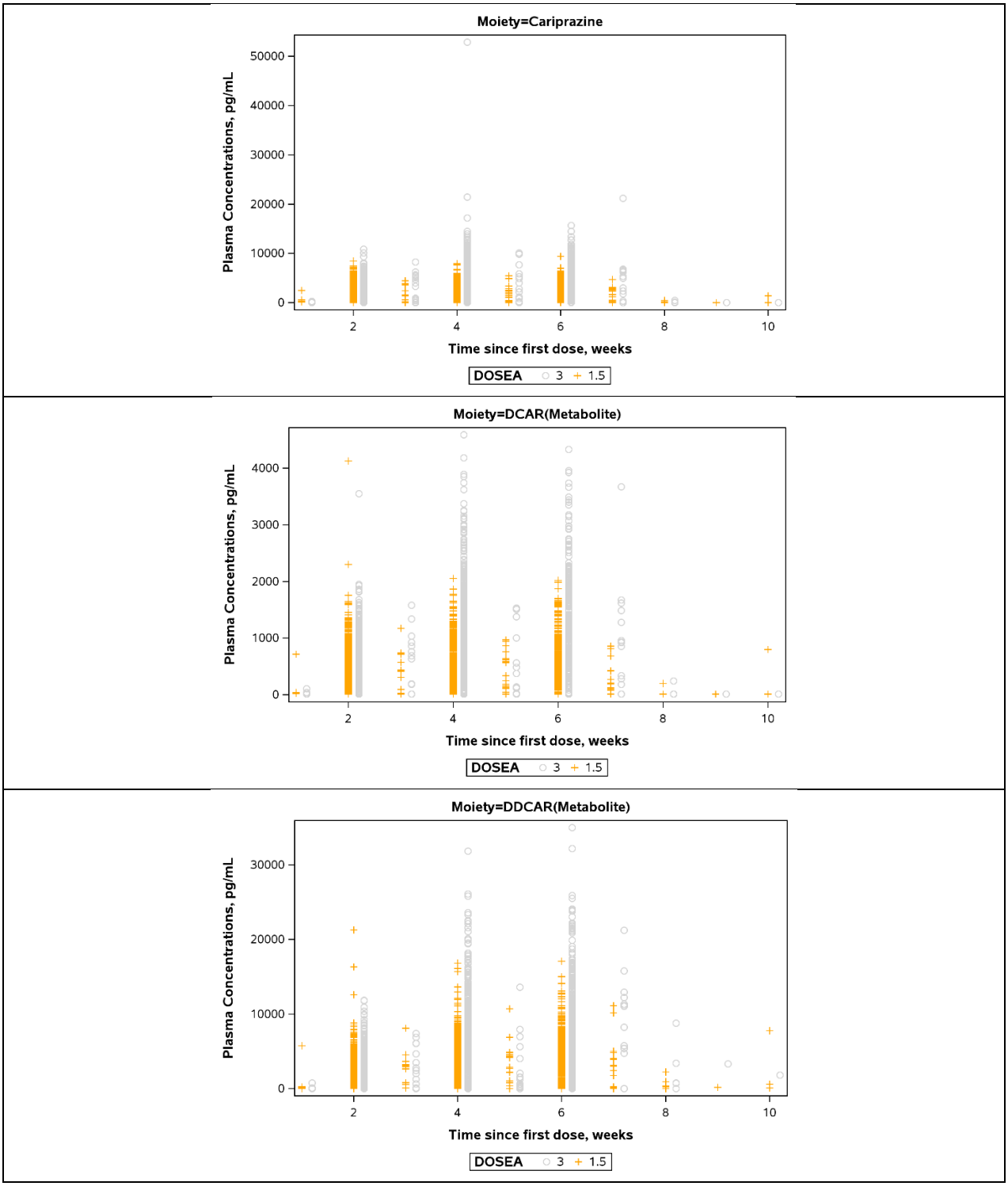
As noted in Figure 3, there is considerable heterogeneity in treatment response across doses and clinical trials, and doses of 1.5 and 3 mg show similar efficacy. One potential reason for lack of clear dose-response between 1.5 and 3 mg is the variability in PK of cariprazine and its metabolites, in addition to the possibility of saturation of clinical response.

The Applicant provided information on plasma concentrations of cariprazine (CAR) and its metabolites desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR) from Studies 3111-301-001 and 3111-302-001. When applying the legacy CAR population PK model to data from studies 3111-301-001 and 3111-302-001, it was apparent that some subjects had unexpectedly low CAR exposures, and consequently low DCAR and DDCAR exposures. The number of subjects in the low exposure population was estimated to be 25.2%, and cariprazine bioavailability was estimated to be 0.129 (coefficient of variation (CV) 283%) in those subjects. The reasons for the low cariprazine bioavailability in 25.2% of subjects is not clear.

Figure 3 shows the distribution of CAR, DCAR, and DDCAR plasma levels by dose and study week in Studies 3111-301-001 and 3111-302-001. The data suggest an overlap in plasma concentrations of CAR, DCAR, and DDCAR after 1.5 mg or 3 mg dose. The presence of overlap in plasma concentrations of CAR, DCAR, and DDCAR likely resulted in lack of dose-efficacy response between 1.5 mg and 3 mg, as noted in Studies 3111-301-001 and 3111-302-001.

Overall, there is a trend of improvement in total MADRS scores with cariprazine with a likely plateau between 1.5 and 3 mg doses.

Figure 3 Plasma Concentrations of Cariprazine (CAR) and Metabolites (DCAR, DDCAR) by Study Week in Studies 3111-301-001 and 3111-302-001



Source: Reviewer's analysis. Data from 1.5 mg and 3 mg are shown. The dose level data are jittered for display purposes.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant's supplemental NDA application contains one phase 2 and four phase 3 safety and efficacy studies for the treatment of MDD with cariprazine (CAR) or placebo (PBO) plus antidepressant therapy (ADT) and one open-label safety extension study, as presented in chronological order in Table 2.

Table 2: Table of Clinical Studies in NDA 204370/ S-009

Study ID	Study Design	Regimen	Primary Endpoint	Treatment Duration	Subjects Enrolled	Number of Clinical sites
RGH-MD-71	Randomized, double-blind, placebo-controlled, flexible-dose; (8-week ADT lead-in period)	CAR 0.1-0.3 mg/day + ADT; CAR 1-2 mg/day + ADT; PBO + ADT	Change from baseline on MADRS	8 weeks	230	41
RGH-MD-72	Randomized, double-blind, placebo-controlled, flexible-dose; (8-week ADT lead-in period)	CAR 1.5-4.5 mg/day +ADT; PBO + ADT	Change from baseline on MADRS	8 weeks	527	66
RGH-MD-76	Open-label, flexible-dose, long-term	CAR 1.5-4.5 mg/day	Change from baseline on MADRS	26 weeks	345; Rolled over from RGH-MD-72 or *de novo*	59
RGH-MD-75	Randomized, double-blind, placebo-	CAR 1-2 mg/day + ADT; CAR 2-4.5	Change from baseline on MADRS	8 weeks	812	76

Study ID	Study Design	Regimen	Primary Endpoint	Treatment Duration	Subjects Enrolled	Number of Clinical sites
	controlled, flexible-dose	mg/day + ADT; PBO + ADT				
3111-301-001	Randomized, double-blind, placebo-controlled, fixed-dose	CAR 1.5 mg/day +ADT; CAR 3 mg/day +ADT; PBO +ADT	Change from baseline on MADRS	6 weeks	757	116
3111-302-001	Randomized double-blind, placebo-controlled, fixed-dose	CAR 1.5 mg/day + ADT; CAR 3 mg/day +ADT; PBO +ADT	Change from baseline on MADRS	6 weeks	751	107

Source: Clinical Reviewer modified from Module 5.2 submitted 2/18/2022

7.2. Review Strategy

Allergan submitted five phase 2 and 3 safety and efficacy studies, dating from 2009 to 2021, conducted in subjects diagnosed with MDD who had an inadequate response to antidepressants. The Applicant listed two registration trials, RGH-MD-75 and 3111-301-001. The efficacy review focuses primarily on the following phase 3 studies:

- RGH-MD-75- randomized, placebo-controlled, double-blind, flexible-dose, 8 weeks
- 3111-301-001- randomized, placebo-controlled, double-blind, fixed-dose, 6 weeks
- 3111-302-001- randomized, placebo-controlled, double-blind, fixed-dose, 6 weeks

The efficacy data from studies RGH-MD-71 and RGH-MD-72 were also analyzed for supportive evidence of efficacy or dosing regimen. However, because their efficacy results were negative, and their dosing and design was quite different than the other registration studies, the review for these studies only focuses on assessing the potential rationale for study failure. Refer to 8.1.78.1.7, Assessment of Efficacy Across Trials.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study RGH-MD-75

A Double-Blind, Placebo-Controlled Study of Cariprazine as Adjunctive Therapy in Major Depressive Disorder

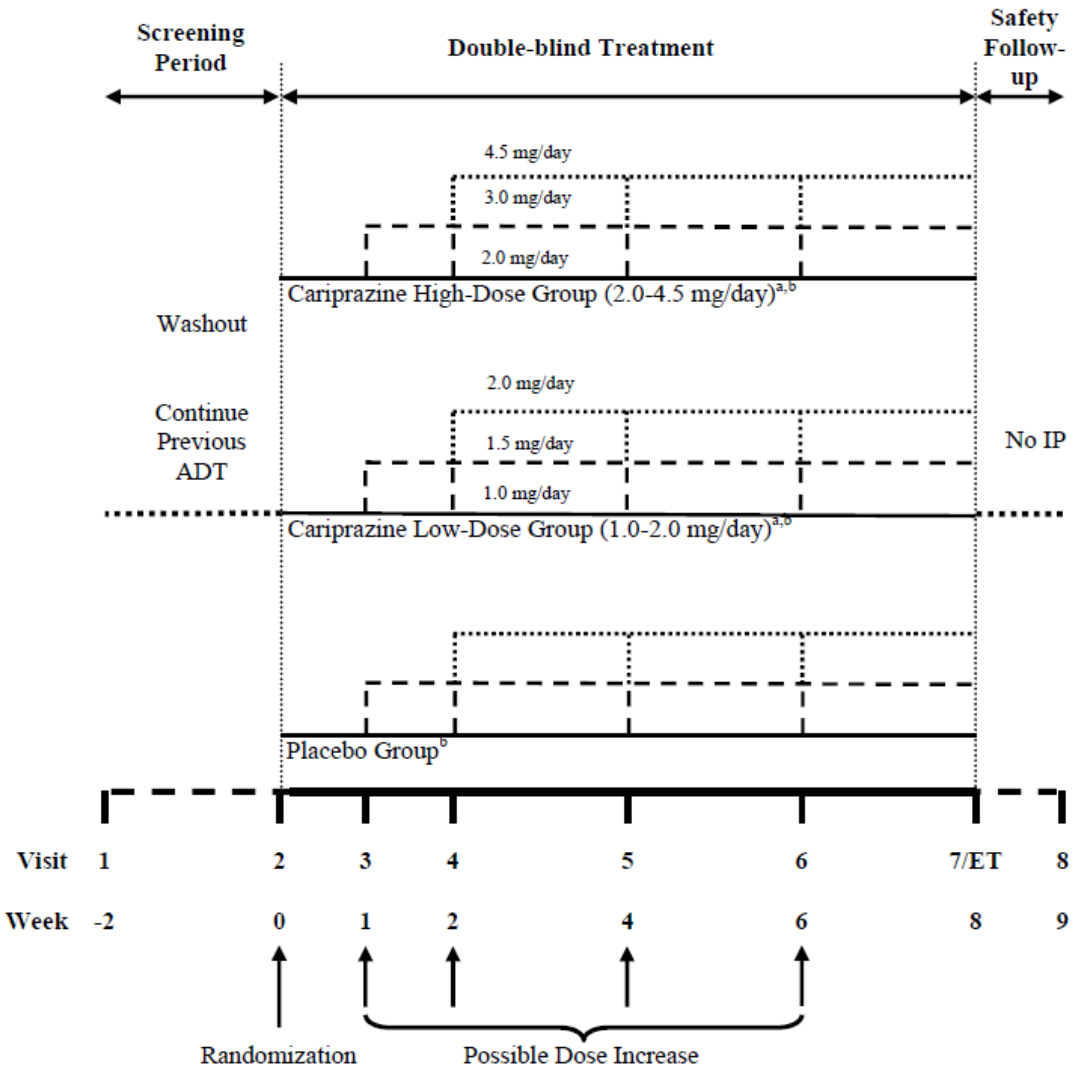
Trial Design

Allergan conducted Study RGH-MD-75 as a phase 3, multicenter, randomized, placebo-controlled, double-blind, flexible-dose, 8-week study of two dosage arms of cariprazine plus antidepressant therapy (ADT) compared to a placebo plus ADT arm in subjects who had an inadequate response to ADT during the current MDD episode.

There was a 7- to 14-day screening and washout period, followed by 8 weeks of double-blind treatment, followed by 1 week of a safety follow-up period. At randomization, the subjects were randomized to one of three treatment arms: cariprazine 1 to 2 mg/day (low flexible dose) + ADT, cariprazine 2 to 4.5 mg/day (high flexible dose) + ADT, or placebo + ADT. Dose increases were allowed at Weeks 1, 2, 4, and 6. The study schematic is in Figure 4.

This multicenter trial took place in 76 clinical sites: eight in Estonia, eight in Finland, seven in Slovakia, four in Sweden, eight in Ukraine, and 41 in the United States.

Figure 4: Schematic of RGH-MD-75



Source: Applicant's CSR for Study RGH-MD-75

Key Inclusion Criteria

A total of 812 (safety population) males and females aged 18 to 65 years and medically healthy were enrolled. The subject's current episode of depression and inadequate treatment were defined from:

- DSM-IV-TR criteria for MDD without psychotic features based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID-IV), with a current major depressive episode of at least 8 weeks and not exceeding 24 months in duration at Visit 1

- Ongoing inadequate response to protocol-allowed ADT (bupropion, citalopram,

desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) administered at an adequate dose and duration in accordance with the respective package insert, documented in the Antidepressant Treatment History Form (ATHF) with a resistance rating of ≥ 3 and a global confidence score of ≥ 3

- Montgomery Åsberg Depression Rating Scale (MADRS) total score ≥ 22 at both Screening (Visit 1) and Baseline (Visit 2).

Key Exclusion Criteria

The study excluded subjects if they had a history of depression with psychotic or catatonic features or any other psychiatric disorder. Subjects with a suicide attempt within the past year or who were deemed at significant risk based on scoring on the Columbia-Suicide Severity Rating Scale (C-SSRS) were excluded. Females who were pregnant or lactating were excluded.

The study also excluded subjects with treatment refractory depression. The Applicant defined treatment refractory status as:

- Failure to respond (< 50% reduction in depressive symptoms) to ≥ 3 ADTs given at an adequate dose (as defined by the ADT package insert) and duration of > 6 weeks during the present episode

- History of inadequate response to electroconvulsive therapy (ECT), a monoamine oxidase inhibitor, or adjunctive treatment with an antipsychotic.

Reviewer's Comment: The diagnostic and severity inclusion criteria for Study RGH-MD-75 are acceptable. At the time of this trial, the DSM-IV was the standard diagnostic tool for MDD. Use of the ATHF creates a uniform method of obtaining subjects' treatment history; the score of three or more for resistance is appropriate because scores of one or two on the form for resistance indicate an inadequate medication trial. Also, a score of three on the global confidence means that adequate information is available and based largely on one source (like the subject or medical records) that appears reliable.

The inclusion and exclusion criteria for the number of antidepressants that the subject either responded inadequately to after 8 weeks of at least minimum dose, or failed to respond to, was at least one but not more than three drugs. These criteria were similar to the enrollment criteria from the adjunct treatment of depression trials of aripiprazole and brexpiprazole, and therefore acceptable. Quetiapine extended-release also has an indication of adjunct treatment of depression; however, the analogous inclusion criterion (i.e., an inadequate response after 6 weeks to at least one antidepressant) was less strict.

In Study RGH-MD-75, the inclusion criterion of a score of 22 on the MADRS means moderate depressive symptoms. Likewise, the severity of depressive symptoms based on enrollment scores on a screening depression scale from the aripiprazole trials was mild to moderate depression

and from the quetiapine trials, moderate depression. It appears that 17% of the subjects in the quetiapine trials had severe depression at enrollment. The brexpiprazole package insert (PI) does not describe subjects' severity at enrollment so there is no available comparison to the cariprazine study, RGH-MD-75.

Concomitant Medication

The study prohibited the use of additional psychotropic medication except for the ADT. This prohibition included benzodiazepines for as-needed usage. Strong inducers or inhibitors of cytochrome P4503A4 were prohibited due to potential drug interactions with cariprazine. Certain sleep drugs from the z-drug class were allowed at specified doses for insomnia. For treatment of extrapyramidal symptoms (EPS) or akathisia, benztropine or diphenhydramine were allowed.

Dose Changes

Subjects continued taking background antidepressant if they were having an ongoing inadequate response to bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone given at an adequate dose and duration (minimum effective dose in accordance with the respective package insert) at study entry. Upon entry into the study at Visit 1, the dosage of the ADT was held stable through Visit 7 or End of Trial. If a subject experienced an AE, intercurrent illness, or intolerance, investigator discretion permitted the subject to stop taking the ADT for a maximum of 3 consecutive days. No other alterations in the ADT dose regimen were allowed. In the event of an ADT dose change, the study team recorded the change, but they could also have discontinued the subject from the trial.

For those subjects assigned to either cariprazine group, dose titration occurred during the first week. During the second week, the Investigator could increase the dose (within the flexible low- or high-dose arm ranges) or at any visit if there were no AEs. Similar to the ADT dosing, if a subject could not tolerate cariprazine after a dose increase, they could stop the medication for up to 3 days. The Investigator could elect to decrease the dose. If lowering the dose remained intolerable, the subject was withdrawn from the study.

Reviewer's Comment: For some antidepressants, particularly paroxetine or venlafaxine, abrupt cessation may cause withdrawal symptoms when the drugs are already at steady state. The protocol for Study RGH-MD-75 did not describe all of the case scenarios or preventing withdrawal by lowering the ADT dose; instead, the protocol relied on investigator discretion. The CSR for Study RGH-MD-75 did not describe reports of subjects having withdrawal symptoms from abruptly stopping their ADT for 3 days.

For those subjects assigned to cariprazine, abruptly stopping the drug for 3 days is less likely to result in withdrawal symptoms becausecariprazine and DCAR (one major metabolite) do not reach steady state until 1 to 2 weeks of dosing. (The second metabolite may not reach steady

state for 4 to 8 weeks.)

The 3-week dose titration plan for the cariprazine low- and high-dose arms could lead to intolerability, especially in the high-dose group. The doses were titrated to the initial dose level of 1 mg/day for the low-dose group and 2 mg/day for the high-dose group at Week 1. At the beginning of Week 2, the Investigator could increase the cariprazine to 1 (stayed the same) or 1.5 mg/day for the low-dose group and 2 (stayed the same) or 3 mg/day for the high-dose group. At the beginning of Week 3, a second increase could take place and then remain stable until the end of double-blind period of the trial (Week 8). The doses at Week 3 and beyond were 1, 1.5, or 2 mg/day for the low-dose group and 2, 3, or 4.5 mg/day for the high-dose group. The Applicant's CSR does not list intolerability events for subjects who stopped cariprazine for the 3 allowed days. However, the most AEs leading to discontinuation occurred in the high-dose cariprazine arm. (Refer to Table 3 in Section 8.1.2 for more information about patient disposition.)

Blinding

Study RGH-MD-75 was double-blinded. The investigational products (placebo, cariprazine) were identical in appearance (size, shape, and color), taste, and blister card packaging. The randomization and treatment assignment procedure included a list of subject randomization codes generated by Statistical Programming at Forest Research Institute (former Sponsor) and implemented by a vendor. This list identified each subject by a randomization number and included the subject's corresponding treatment assignment. Unblinding at the clinical site level was only to take place in an emergency. Breaking the code at the clinical site level immediately disqualified the subject from further participation in the study. Any such emergency unblinding was to be recorded in the case report form (CRF).

Study Endpoints

Efficacy Endpoints

The primary efficacy endpoint for Study RGH-MD-75 was the change from baseline in the MADRS total score at Week 8. The MADRS is a 10-item, clinician-rated scale that evaluates the subject's depressive symptomatology during the past week. Subjects are rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidal ideation, reduced sleep or appetite, difficulty in concentration, and lack of interest. Each item is scored on a 7-point scale with a score of 0 reflecting no symptoms and a score of 6 reflecting symptoms of maximum severity.

The secondary endpoint was the change from baseline in the Sheehan Disability Scale (SDS) at Week 8. The SDS is a five item, patient-rated, measure of disability and impairment. The subject rates areas such as work or school, social life, family life, and home responsibilities.

Additional efficacy parameters were:

- Change from baseline in the Clinical Global Impression-Severity (CGI-S) score

- Clinical Global Impression-Improvement (CGI-I) score
- CGI-I response (CGI-I score ≤ 2)
- MADRS response (≥ 50% reduction from baseline in MADRS total score)
- MADRS remission (MADRS total score ≤ 10)
- Change from baseline in each of the SDS item scores (work, social life, family life).

Safety Assessment Endpoints

The safety assessments during Study RGH-MD-75 were AE recording, clinical laboratory evaluations, vital signs, electrocardiograms (ECGs), physical examinations, EPS symptom scales (Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale, Simpson-Angus Scale), and the C-SSRS.

Reviewer's Comment: The blinding plan for Study RGH-MD-75 is acceptable. The chosen primary endpoint of change from baseline on the MADRS is also acceptable because many approved drugs for treatment of MDD also used this endpoint. The secondary endpoint of the SDS is unusual because it is a functional impairment scale and is self-reported and not typically used for MDD studies. (Notably, the Applicant did not choose this scale for any other studies.) The safety assessments were acceptable, and it was important to monitor EPS with various scales because the label for cariprazine lists both EPS and akathisia.

Statistical Analysis Plan

Study MD-75 is an eight week, randomized, double-blind, phase 2 study comparing two dose bands 1 mg – 2 mg and 2 mg – 4.5 mg cariprazine to placebo with the primary analysis planned at 8 weeks. Key statistical analysis feature:

- Primary endpoint of change from baseline (CFB) to Week 8 in MADRS total score. MADRS total score was measured at baseline and weeks 1, 2, 4, 6, and 8.

- Secondary efficacy endpoint of change from baseline to Week 8 in the SDS. SDS was measured at baseline and weeks 2, 4, 6, and 8.

- Planned to enroll 270 patients per arm to provide approximately 90% power to show a statistically significant effect in at least one cariprazine dose controlling alpha at a family-wise error rate of 5% using two-stage matched parallel gatekeeping procedure. The effect size was assumed to be 0.285 (treatment difference relative to standard deviation) with 30% of patients dropping out by week 8. Patients were randomized at 1:1:1.

- Both CFB MADRS total score and CFB SDS were analyzed using a mixed model for repeated measures (MMRM) with fixed effects of treatment group, study center, visit, baseline value, treatment by visit interaction terms, and baseline value by visit

interaction terms with an unstructured covariance matrix. Treatment effects and standards errors were estimated with least square means (LS mean).

- Overall type I error rated was controlled for multiple comparisons of two active doses with placebo for primary and secondary endpoints using the matched parallel gatekeeping procedure. The primary hypotheses family (F1) consisted of two null hypotheses for comparisons of the two active doses with placebo on the primary endpoint. Similarly, the secondary hypotheses family (F2) consisted of two null hypotheses for comparisons of the two active doses with placebo on the secondary endpoint. The F1 family served as a gatekeeper for the F2 family: F2 was examined only when the gatekeeper F1 has been successfully passed (i.e., at least one of the hypotheses in the F1 family is rejected). The matched gatekeeping procedure utilized the special logical relationship between the primary and the secondary parameters to enhance the power of statistical testing. The hypothesis for the lower dose comparison on the secondary endpoint was tested only if the hypothesis for the lower dose comparison on the primary endpoint is rejected. Similarly, the hypothesis for the higher dose comparison on the secondary endpoint was tested only if the hypothesis for the higher dose comparison on the primary endpoint is rejected. Local p-values for the intersection hypotheses were calculated based on the Simes test using the matched parallel gatekeeping weighting scheme. Adjusted p-values for the four elementary hypotheses were calculated based on the closed testing principle. Statistical significance was determined by comparing the adjusted p-values to $\alpha = 0.050$.

Statistical Reviewer's Comment: The statistical analysis plan was reasonable.

Protocol Amendments

The Applicant submitted two protocol amendments on May 18, 2012, and July 11, 2012, respectively.

Amendment #1 added the Antidepressant Treatment History Form at Screening and expanded the population pool by increasing the allowed current episode of depression to 24 months, allowing the ADT of fluoxetine, excluding for hospitalization, expanding the allowed baseline vital signs, and removing the inclusion criterion of a certain SDS total score.

Amendment #2 removed the required washout period for fluoxetine because fluoxetine was added to the allowed ADTs in Amendment #1. The amendment modified the ATHF protocol rater-qualification language to ensure consistency with the Forest (Sponsor) rater-qualification methodology. Finally, Amendment #2 removed the requirement for reflex collection of hemoglobin A1c in subjects with elevated glucose because detectable changes occur over a duration of time that is longer than the study duration; the amendment also modified the collection of folate and B12 to be based on the Investigator's clinical judgment.

There were no major concerns about the potential impact of these amendments on the study

results.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant conducted Study RGH-MD-75 in conformance with the ICH E8 Guidance on General Considerations for Clinical Trials, ICH E6 guideline for GCP, and the principles of the Declaration of Helsinki, and 21 CFR §312.120.

Financial Disclosure

The Applicant did not enter into any financial arrangement with the listed clinical investigators from Study RGH-MD-75. Refer to Section 15.1 Financial Disclosurefor more details.

Patient Disposition

Study RGH-MD-75 started with 1248 subjects screened for eligibility; 819 subjects were randomized to receive double-blind treatment; 812 subjects received at least one dose of double-blind treatment (Safety Population); and 808 subjects had at least one postbaseline MADRS assessment (Efficacy Population). Seven subjects were discontinued from the study after randomization but did not receive investigational product and were excluded from the Safety Population.

The disposition of the safety population is displayed in Table 3. The number of subjects (n=36 (13%)) in the cariprazine 2- to 4.5- mg/day (high dose) group + ADT who discontinued because of an AE was greater than the placebo + ADT group (8 (3.0%)). Discontinuations from AEs are discussed in Section 8.2.4 Safety Results. “Other” reasons for discontinuation were as follows: one subject was discontinued by Investigator decision for moderate gastroenteritis, a second one moved out of the country. Both subjects were randomized to placebo + ADT. Tables 4 and 5 list the disposition of the efficacy population.

Table 3: Subject Disposition of Safety Population (RGH-MD-75)

	Placebo (N = 266) n (%)	*Cariprazine 1-2 mg/day (N = 273) n (%)*	*Cariprazine 2-4.5 mg/day (N = 273) n (%)*	*Total (N = 812) n (%)*
Completed study	234 (88)	226 (83)	210 (77)	670 (83)
Prematurely discontinued	32 (12)	47 (17)	63 (23)	142 (18)

	Placebo (N = 266) n (%)	*Cariprazine 1-2 mg/day (N = 273) n (%)*	*Cariprazine 2-4.5 mg/day (N = 273) n (%)*	*Total (N = 812) n (%)*
Reason for discontinuation				
Adverse event	8 (3)	18 (6.6)	36 (13)	62 (7.6)
Insufficient therapeutic response	3 (1.1)	4 (1.5)	0	7 (0.9)
Protocol deviation	6 (2.3)	10 (3.7)	9 (3.3)	25 (3.1)
Withdrawal of consent	11 (4.1)	13 (4.8)	14 (5.1)	38 (4.7)
Lost to follow-up	2 (0.8)	2 (0.7)	4 (1.5)	8 (1)
Other	2 (0.8)	0	0	2 (0.2)
Entered safety follow-up period	253 (95)	256 (94)	254 (93)	763 (94)

Source: Clinical Reviewer modified from CSR Table 10.1-1

Table 4: Number of Patients by Dropout Reason in Efficacy Population (RGH-MD-75)

	Number of Patients	Percent of Patients
Dropout AE	61	7.6
Dropout LOE	7	0.9
Dropout Else	70	8.7
Completer	670	82.9
N	808	100

LOE- Lack of Efficacy
Source: Statistical Analyst

Table 5: Number and Percentages of Patients by Dropout Reason and Treatment Arm in Efficacy Population (RGH-MD-75)

	Dropout AE	Dropout LOE	Dropout Else	Completer	N
Placebo	7 (2.7)	3 (1.1)	20 (7.6)	234 (88.6)	264
Cariprazine 1-2 mg/d	18 (6.6)	4 (1.5)	25 (9.2)	226 (82.8)	273
Cariprazine 2-4.5 mg/d	36 (13.3)	0 (0)	25 (9.2)	210 (77.5)	271

Source: Statistical Analyst

Reviewer's Comment: At 7.6%, AEs were the primary reason for trial discontinuation.

Discontinuations for the other reasons were similar among treatment groups. Subjects in both cariprazine groups discontinued Study RGH-MD-75 due to AEs at a greater rate than those assigned to placebo. In the high-dose cariprazine + ADT group, 13% of subjects dropped out due to an AE. Section 8.2.4 Safety Results notes that the AEs leading to dropouts are the same as the most frequently reported AEs from Study RGH-MD-75. Subsequently, the 13% of subjects in the cariprazine 2 to 4.5 mg/day + ADT arm who withdrew due to AEs led to the lowest percentage of completers (77%). In the cariprazine 1 to 2 mg/day + ADT arm, 83% completed. In the placebo + ADT arm, 88% of subjects completed the study. Overall, the number of subjects that did not complete Study RGH-MD-75 did not affect the study outcomes. Also, there is minimal difference in patient dispositions between the safety population and the intent to treat population.

Protocol Violations/Deviations

Protocol deviations occurred at similar rates by treatment group (i.e., 14% in the placebo + ADT arm, 19% in the cariprazine 1- to 2- mg/day ADT arm, and 15% in the cariprazine 2- to 4.5-mg/day arm.) The most frequent reasons for protocol deviations were compliance issues, positive urine drug screens, and use of prohibited medications as seen in Table 6.

Table 6: Protocol Deviations during Study RGH-MD-75 (All Randomized Patients)

	Placebo (N = 269) n (%)	*Cariprazine 1-2 mg/day (N = 274) n (%)*	*Cariprazine 2-4.5 mg/day (N = 276) n (%)*
Any protocol deviation	37 (14)	51 (19)	41 (15)
Failed to meet eligibility criteria	2 (0.7)	1 (0.4)	3 (1.1)
< 80% compliance with investigational product	0	2 (0.7)	1 (0.4)
< 80% compliance with ADT	0	0	0
Missed ≥ 4 doses of investigational product	0	2 (0.7)	1 (0.4)
Missed ≥ 4 doses of ADT	0	1 (0.4)	1 (0.4)
Took investigational product other than the assigned treatment	0	1 (0.4)	2 (0.7)
Took > 1 dose of investigational product per day	6 (2.2)	6 (2.2)	3 (1.1)

	Placebo (N = 269) n (%)	*Cariprazine 1-2 mg/day (N = 274) n (%)*	*Cariprazine 2-4.5 mg/day (N = 276) n (%)*
Changed the dose of ADT	0	1 (0.4)	0
Had postbaseline positive urine drug screen results	19 (7.1)	31 (11)	18 (6.5)
Took prohibited concomitant medication	17 (6.3)	18 (6.6)	23 (8.3)

Source: Clinical Reviewer modified from CSR Table 10.2-1

Reviewer's Comment: The quantity of protocol violations from Study RGH-MD-75 is unlikely to affect efficacy. Subjects appeared compliant with their assigned treatment. The protocol deviation of taking prohibited concomitant medications was highest in the cariprazine 2 to 4.5 mg/day + ADT arm. Because benzodiazepine usage was prohibited in the protocol, I analyzed how many were taken as concomitant medications by each treatment group. In the high-dose cariprazine group, nine subjects received a benzodiazepine; there were three subjects in the low-dose cariprazine group and one in the placebo group. Prohibited benzodiazepine use does not explain all of the protocol deviations from prohibited medications, but there was more benzodiazepine use in the high-dose cariprazine group, which could be an indicator of trying to treat agitation from akathisia or restlessness. Adverse events are discussed in Section 8.2.4 Safety Results.

Table of Demographic Characteristics

In Study RGH-MD-75, the subject demographics for the Efficacy Population (N=808) were similar among the treatment groups by age, sex, race, and ethnicity as shown in Table 7. The subjects' mean age was approximately 46 years, and most subjects were white (87%) and female (71%).

Table 7: RGH-MD-75: Baseline Demographics (Efficacy Population)

	Placebo N=264	**Cariprazine 1-2 mg/d N=273**	**Cariprazine 2-4.5 mg/d N=271**	**Total N=808**
Age (years)				
Mean (SD)	46.6 (11.41)	45.5 (11.90)	45.1 (11.46)	45.7 (11.60)
Median	48	47	47	47
Min, Max	18, 65	19, 65	19, 65	18, 65
Age, n (%)				
< 20 years	3 (1.1)	2 (<1)	2 (<1)	7 (<1)
20 - 29 years	22 (8.3)	29 (10.6)	34 (12.5)	85 (10.5)
30 - 39 years	45 (17)	58 (21.2)	47 (17.3)	150 (18.6)
40 - 49 years	72 (27.3)	64 (23.4)	80 (29.5)	216 (26.7)
50 - 59 years	87 (33)	93 (34.1)	77 (28.4)	257 (31.8)

	Placebo N=264	Cariprazine 1-2 mg/d N=273	Cariprazine 2-4.5 mg/d N=271	Total N=808
≥ 60 years	35 (13.3)	27 (9.9)	31 (11.4)	93 (11.5)
Sex, n (%)				
Male	76 (28.8)	86 (31.5)	71 (26.2)	233 (28.8)
Female	188 (71.2)	187 (68.5)	200 (73.8)	575 (71.2)
Race, n (%)				
White	228 (86.4)	234 (85.7)	241 (88.9)	703 (87.0)
Black or African American	32 (12.1)	31 (11.4)	23 (8.5)	86 (10.6)
Asian	1 (<1)	4 (1.5)	4 (1.5)	9 (1.1)
American Indian or Alaska Native	2 (<1)	1 (<1)	1 (<1)	4 (<1)
Other	1 (<1)	3 (1.1)	2 (<1)	6 (<1)
Ethnicity, n (%)				
Hispanic or Latino	13 (4.9)	17 (6.2)	22 (8.1)	52 (6.4)
Not Hispanic or Latino	251 (95.1)	256 (93.8)	249 (91.9)	756 (93.6)
Country, n (%)				
USA	148 (56.1)	157 (57.5)	153 (56.5)	458 (56.7)
EST	36 (13.6)	36 (13.2)	36 (13.3)	108 (13.4)
FIN	25 (9.5)	23 (8.4)	28 (10.3)	76 (9.4)
SVK	28 (10.6)	27 (9.9)	26 (9.6)	81 (10.0)
UKR	18 (6.8)	22 (8.1)	20 (7.4)	60 (7.4)
SWE	9 (3.4)	8 (2.9)	8 (3.0)	25 (3.1)
Weight (kg)				
Mean (SD)	81.5 (16.2)	79.7 (16.3)	82.2 (17.4)	81.1 (16.7)
Median	80.7	79.6	82.0	80.6
Min, Max	44.8, 124.6	45.9, 127.9	45.4, 134.2	44.8, 134.2
Height (cm)				
Mean (SD)	167.8 (8.9)	168.1 (8.8)	168.1 (9.1)	168.0 (8.9)
Median	166.6	167.6	167.0	167.0
Min, Max	149.2, 200.7	146.5, 193.0	148.0, 196.0	146.5, 200.7
BMI ($kg/m^{2)}$				
Mean (SD)	28.9 (5.1)	28.2 (5.5)	29.1 (5.6)	28.7 (5.4)
Median	28.8	27.3	28.6	28.2
Min, Max	18.2, 39.8	18.0, 40.7	17.8, 41.5	17.8, 41.5

Abbreviations: SD = standard deviation
Source: adsl.xpt; Statistical Analyst

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline characteristics for major depression in Study RGH-MD-75 were similar among treatment groups. Over 86% of subjects (i.e., 86 to 89%) had recurrent major depression with a mean of four depressive episodes per subject, ranging from one to 61 episodes. Previous suicide attempts were reported for 11%, 8%, and 10% of subjects in the placebo, low-dose, and high-dose cariprazine groups, respectively.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In Study RGH-MD-75, compliance was not concerning, as judged by only having three subjects with <80% compliance in the protocol deviation Table 6, above.

Table 8, below, displays the concomitant antidepressants or rescue medications taken by ≥2% of the Efficacy Population (N=808) in addition to the study treatments; (ITT flag and Concomitant Medication during DB flag in dataset ADCM.xpt). Around 17 to 20% of the subjects in all three study treatment groups took ibuprofen, compared to 24% of the whole Efficacy Population. After ibuprofen, the three most common concomitant medications were a multivitamin 9%, paracetamol (acetaminophen) 9.2%, and levothyroxine 5.8%.

The rescue medications taken by at least 2% of subjects were benztropine for EPS and various treatments for insomnia. The usage of z-drugs for insomnia was similar among the three treatment groups.

Table 8: Concomitant and Rescue Medications (Study RGH-MD-75)

Concomitant Medication		n (%) of Efficacy Population (N=808)
Antidepressant (ADT)		
	Bupropion	55 (6.8)
	Citalopram	146 (18)
	Desvenlafaxine	15 (1.9)
	Duloxetine	86 (11)
	Escitalopram	149 (18)
	Fluoxetine	76 (9.4)
	Sertraline	162 (20)
	Venlafaxine	96 (12)
Rescue Medication		
	Benztropine	32 (4.0)
	Zolpidem	143 (18)
	Zopiclone	33 (4.1)

Source: Clinical Reviewer created using JMP from dataset ADCM.xpt in Study RGH-MD-75

Reviewer's Comment: The use of concomitant medication during Study RGH-MD-75 was relatively similar across the three treatment groups. Efficacy should not be affected by rescue medications; however, it is notable that the high-dose cariprazine group received the most benztropine for EPS or akathisia given that akathisia is a dose-related AE. Refer to Safety Results for more discussion of AEs. Other concomitant medications included analgesics, antihistamines, antihypertensives, proton pump inhibitors, and vitamins which are not known to cause changes in mood.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the change from baseline to Week 8 in the MADRS total score. The MADRS scores at the baseline visit appear comparable across treatment groups with a mean around 29 (Table 9). The primary analysis showed that high dose cariprazine (2 to 4.5 mg/day) resulted in statistically significantly greater improvement verus placebo, but low dose cariprazine (1 to 2 mg/day) did not (Table 10). The mean response trajectories by treatment group suggest a consistent trend over time in favor of the high-dose group (Figure 5).

The Applicant conducted sensitivity analyses based on a pattern-mixture model at various shift parameters to explore the impact of the missing data. Their results largely supported the primary analysis findings.

Table 9: MADRS Total Score at Baseline (RGH-MD-75: Efficacy Population)

			Cariprazine	
Scale	Statistics	Placebo (N=264)	1-2 mg (N=273)	2-4.5 mg (N=271)
MADRS	Mean	28.89	28.99	29.30
	SD	4.24	4.26	4.07
	Median	28	29	29
	Min, Max	22, 43	22, 42	22, 43

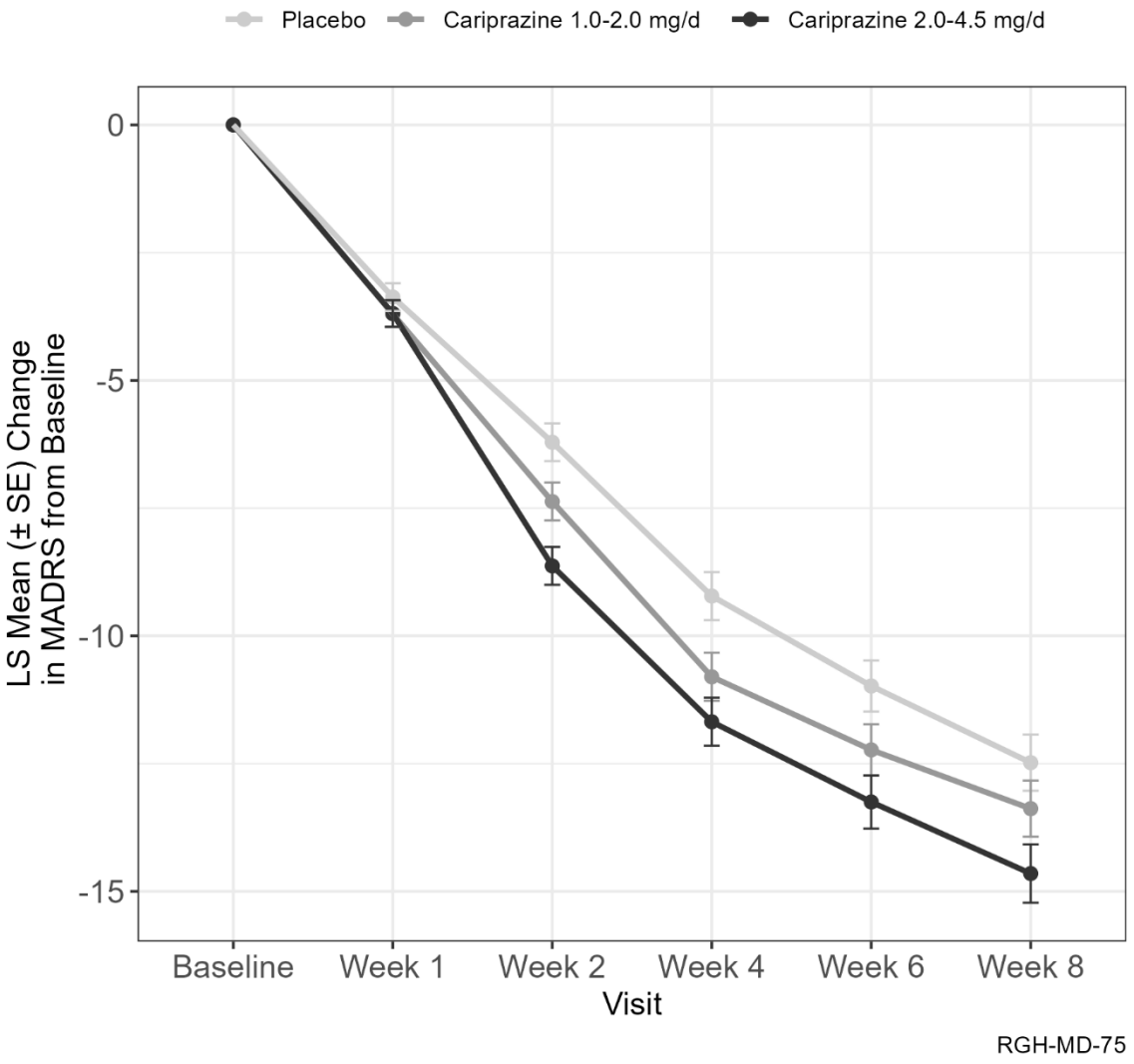
N: sample size; SD: standard deviation
Source: created by Statistical Analyst

Table 10 : MADRS Total Score at Week 8 (RGH-MD-75: Efficacy Population)

Endpoint	Treatment Group	N	LS Mean Change from Baseline (SE)	Difference from Placebo (95% CI)	Raw p-value	Adjusted p-value
MADRS	Placebo	264	-12.48 (0.55)	--	--	--
	Cariprazine 1-2 mg	273	-13.38 (0.55)	-0.91 (-2.42, 0.61)	0.2403	0.2403
	Cariprazine 2-4.5 mg*	271	-14.65 (0.57)	-2.17 (-3.71, -0.64)	0.0057	0.0114

N: sample size; LS mean: least-squares mean, SE: standard error; CI: unadjusted confidence interval
*Dose that was statistically significantly different from placebo after adjusting for multiplicity.
Source: Statistical Analyst; consistent with Applicant's results (CSR Table 11.4.1.1--1)

Figure 5: MADRS Total Score - LS Mean (± SE) Change from Baseline over Time - Mixed Model for Repeated Measures (RGH-MD-75: Efficacy Population)



Treatment	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8
Placebo	264	262	257	253	245	237
Cariprazine 1.0-2.0 mg/d	273	270	259	251	236	232
Cariprazine 2.0-4.5 mg/d	271	270	258	242	219	211
N	808	802	774	746	700	680

LS mean: least-squares mean; SE: standard error; the numbers in the table denote numbers of patients who stayed.
Source: Statistical Analyst

Data Quality and Integrity

The Applicant submitted all necessary analysis datasets and SAS programs. Reviewers found the datasets acceptable.

Efficacy Results – Secondary and Other Relevant Endpoints

Secondary

In Study RGH-MD-75, the secondary endpoint was change from baseline to Week 8 on the SDS. The cariprazine 1- to 2- mg/day (low dose) and the 2- to 4.5- mg/day (high dose) arms decreased scores on the SDS (indicating improvement) numerically more than the mean score from the placebo arm. However, the difference in SDS scores among treatment groups did not reach statistical significance for either dose arm; see Table 11.

Table 11 SDS Change from Baseline at Week 6 (RGH-MD-75: Efficacy Population)

Endpoint	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Difference from Placebo (95% CI)	Raw p-value
SDS	Placebo	264	18.4 (4.8)	–6.6 (0.5)	--	--
	Cariprazine 1-2 mg	273	18.6 (4.8)	–7.7 (0.5)	–1.1 (–2.5, 0.3)	0.2404
	Cariprazine 2-4.5 mg	271	18.9 (4.8)	–8.0 (0.5)	–1.4 (–2.8, 0.0)	0.1140

N: sample size; LS mean: least-squares mean, SE: standard error; CI: unadjusted confidence interval
Source: CSR Table 11.4.1.2-1

Additional Efficacy Parameters

The additional efficacy endpoints such as the global impression scales, CGI-S and CGI-I, had differing results between the cariprazine + ADT arms and the placebo + ADT arm. Baseline scores on the CGI-S per treatment arm are in Table 12. As displayed in Table 13, the observed treatment effects for both cariprazine groups do not appear to be clinically meaningful. Although the raw p-value for CGI-S in the high-dose cariprazine group compared with placebo at Week 8 was less than 0.05, it could not be considered statistically significant given that it was not part of the prespecified statistical hierarchy. Further, because the SDS failed to demonstrate statistical significance, all subsequent testing should be considered exploratory. The low-dose cariprazine arm was not also not significant given that its raw p-value was > 0.05. The results for CGI-I at Week 8 were similar to those for CGI-S.

Table 12: CGI-S Score at Baseline (RGH-MD-75: Efficacy Population)

			Cariprazine	
Scale	Statistics	Placebo (N=264)	1-2 mg (N=273)	2-4.5 mg (N=271)
CGI-S	Mean	4.39	4.37	4.42
	SD	0.52	0.52	0.56
	Median	4	4	4
	Min, Max	4, 6	3, 6	4, 6

Source: Statistical Analyst

Table 13: CGI-S Change from Baseline at Week 8 (RGH-MD-75: Efficacy Population)

Endpoint	Treatment Group	N	LS Mean Change from Baseline (SE)	Difference from Placebo (95% CI)	Raw p-value
CGI-S	Placebo	264	-1.4 (0.1)	--	--
	Cariprazine 1-2 mg	273	-1.5 (0.1)	-0.1 (-0.3, 0.1)	0.1964
	Cariprazine 2-4.5 mg	271	-1.6 (0.1)	-0.2 (-0.4, -0.0)	0.0233

N: sample size; LS mean: least-squares mean; SE: standard error; 95% CI: unadjusted 95% confidence interval
Source: Statistical Analyst

Further discussion of the additional efficacy parameters is limited because the cariprazine low-dose treatment arm was not positive on the primary endpoint. The response and remission rates based on the percentage improvement on the MADRS scale for either cariprazine group were not reviewed in depth because those efficacy measures are considered to be exploratory (and redundant with the primary).

Reviewer's Comment: For Study RGH-MD-75, there is a lack of clinically meaningful efficacy trends for both cariprazine arms over the placebo group on secondary and exploratory endpoints.

Dose/Dose Response

For adjunctive treatment of MDD, the Applicant proposes a starting dose of cariprazine 1.5 mg/day and recommends increasing to 3 mg/day if there is a lack of response. These dosages were not specifically tested in Study RGH-MD-75. The mean dose for the low-dose arm was 1.39 mg/day with a modal dose of 2 mg/day and the mean dose in the high-dose arm was 2.58 mg/day with the modal dose also of 2 mg/day (see Table 14). Although the modal doses of both cariprazine groups were 2 mg/day, only the high-dose dose arm was positive on the primary efficacy endpoint. A dose response for cariprazine as adjunctive treatment for MDD was not evident in Study RGH-MD-75.

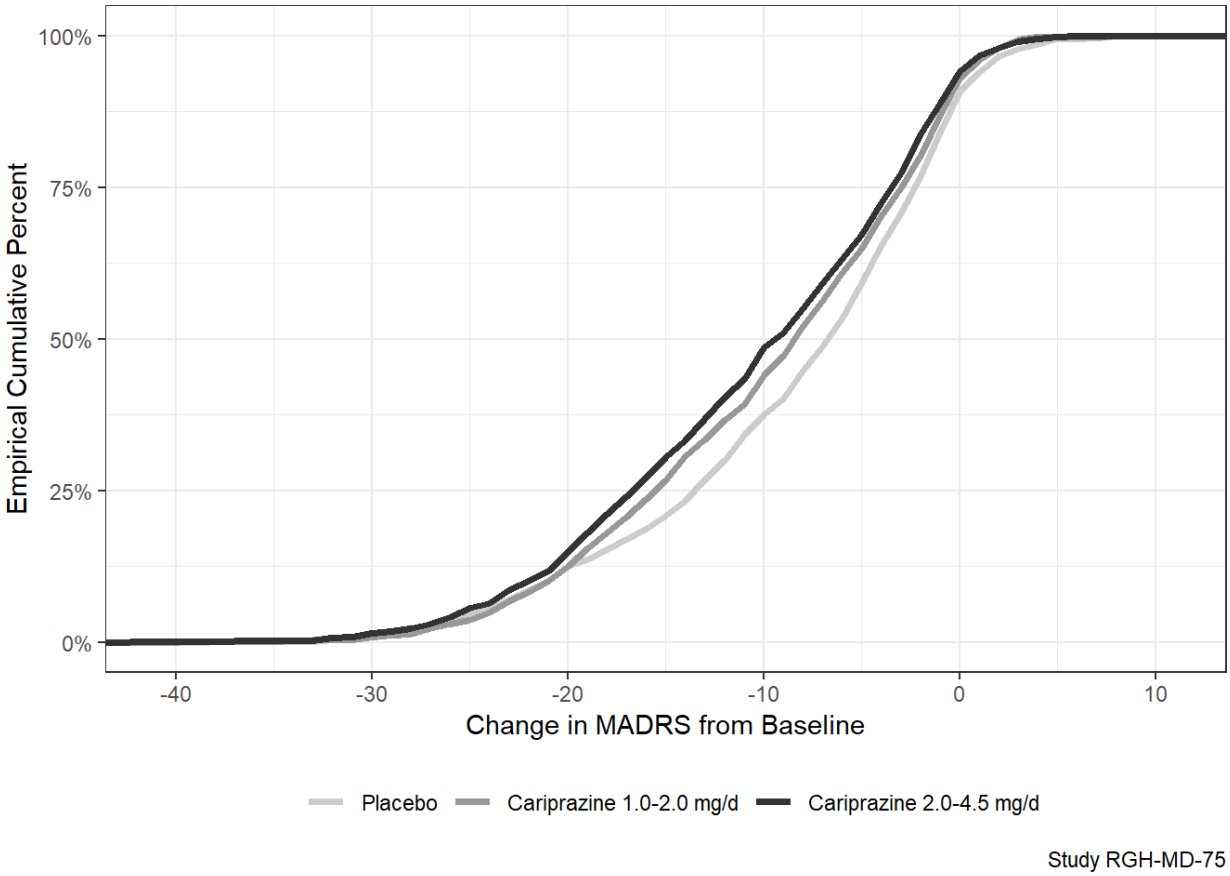
Table 14: Modal and Mean Doses from Cariprazine Arms (Study RGH-MD-75)

Cariprazine dose, n (%) Safety Population= 812			
mg/day	Placebo (N=266)	CAR 1-2 mg/day (N=273)	CAR 2-4.5 mg/day (N=273)
0.5	—	3 (1.1)	4 (1.5)
1	—	87 (31.9)	0
1.5	—	68 (24.9)	1 (0.4)
2 (modal dose)	—	**115 (42.1)**	**120 (44.0)**
3	—	0	72 (26.4)
4.5	—	0	76 (27.8)
Mean dose	—	1.39mg/day	2.58mg/day

Source: Clinical Reviewer modified Table 12.1-1 from CSR of Study RGH-MD-75

The empirical cumulative distribution function plot in Figure 6 shows the cumulative percentage of subjects with changes in MADRS scores smaller than any given threshold for the Efficacy Population. A notable separation between the high dose and placebo is seen between -20 and -10 score changes. Overall, this figure supports the primary analysis finding.

Figure 6: Empirical CDF Plot of Change in MADRS Total Score (Study RGH-MD-75, Completers on Efficacy population)



Source: Statistical Analyst

Durability of Response

In Study RGH-MD-75, the primary efficacy timepoint was at Week 8. Only the high-dose (2 to 4.5 mg/day) cariprazine + ADT treatment group demonstrated efficacy at Week 8 on the primary endpoint. As illustrated in Figure 5 at Week 6, the MADRS score tragectory of the cariprazine low-dose (1 to 2 mg/day) arm slightly turns upward, thus making it harder to reach statistical significance by Week 8. Study RGH-MD-75 does not present definitive data in terms of durability of response for recommending approval of either proposed cariprazine doses of 1.5 and 3 mg/day. See Section 8.1.8 Integrated Assessment of Effectiveness for a broader discussion of durability of response including other trials.

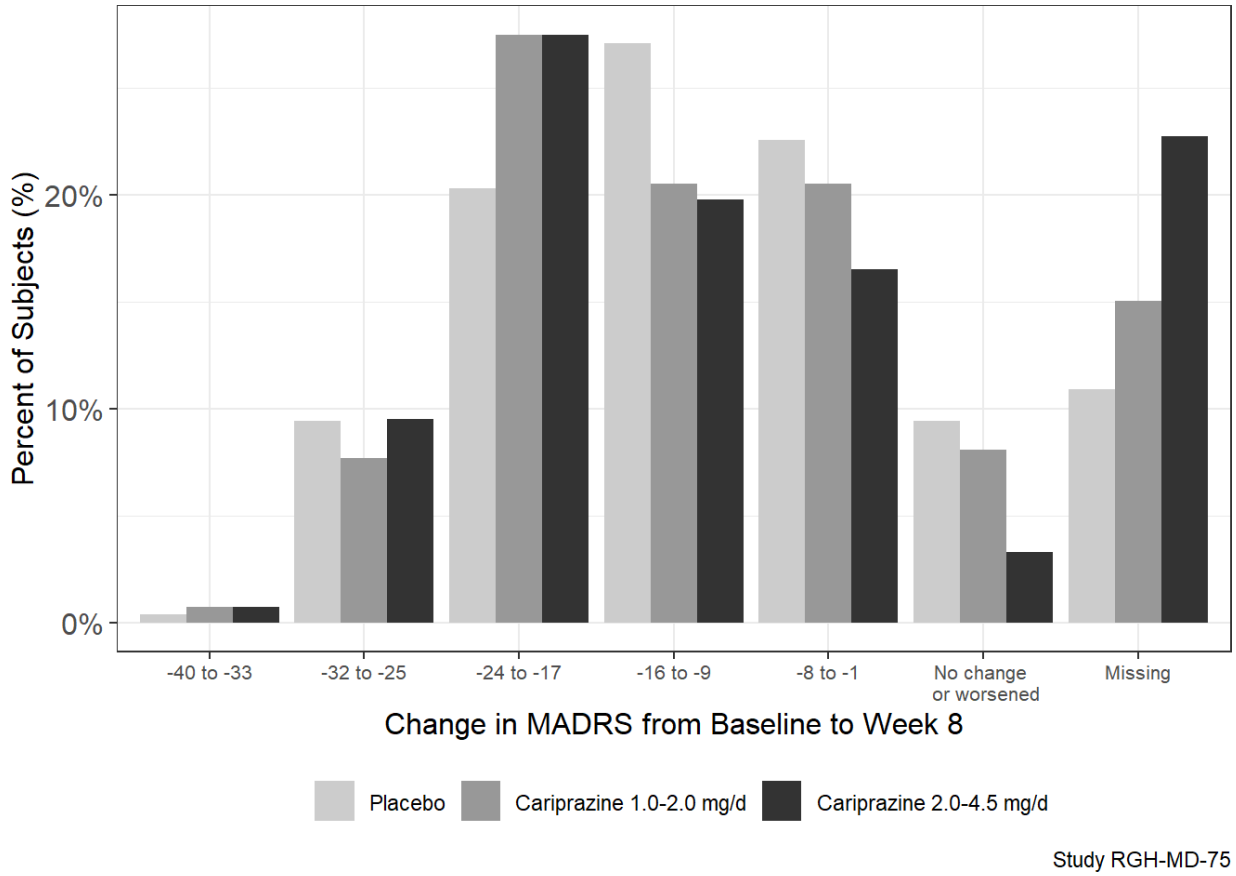
Persistence of Effect

Study RGH-MD-75 was not designed to assess persistence of effect, which is the effect of the drug over time after treatment is stopped or withheld. No assessments of efficacy were performed after Week 8.

Additional Analyses Conducted on the Individual Trial

The histogram in Figure 7 includes categories for patients who showed no improvement or worsening MDD. Patients who dropped out before the 8th week are included in the "Missing" category. Within the total score range of improvement (<-40 to -9-point change from baseline in MADRS total score), both cariprazine doses had a greater percentage of patients who showed some improvement when compared to placebo only in the range of -24 to -7. Outside of this range, there are no clear patterns of improvement compared to placebo. Dropout rates increased with increasing dosage.

Figure 7: Percentage of Subjects with Specified Change in MADRS Total Score (RGH-MD-75: Efficacy Population)



Source: Statistical Analyst

8.1.3. Study 3111-301-001

A Double-Blind, Placebo-Controlled Study of Cariprazine as an Adjunct to Antidepressants in the Treatment of Patients with Major Depressive Disorder Who Have Had an Inadequate Response to Antidepressants Alone

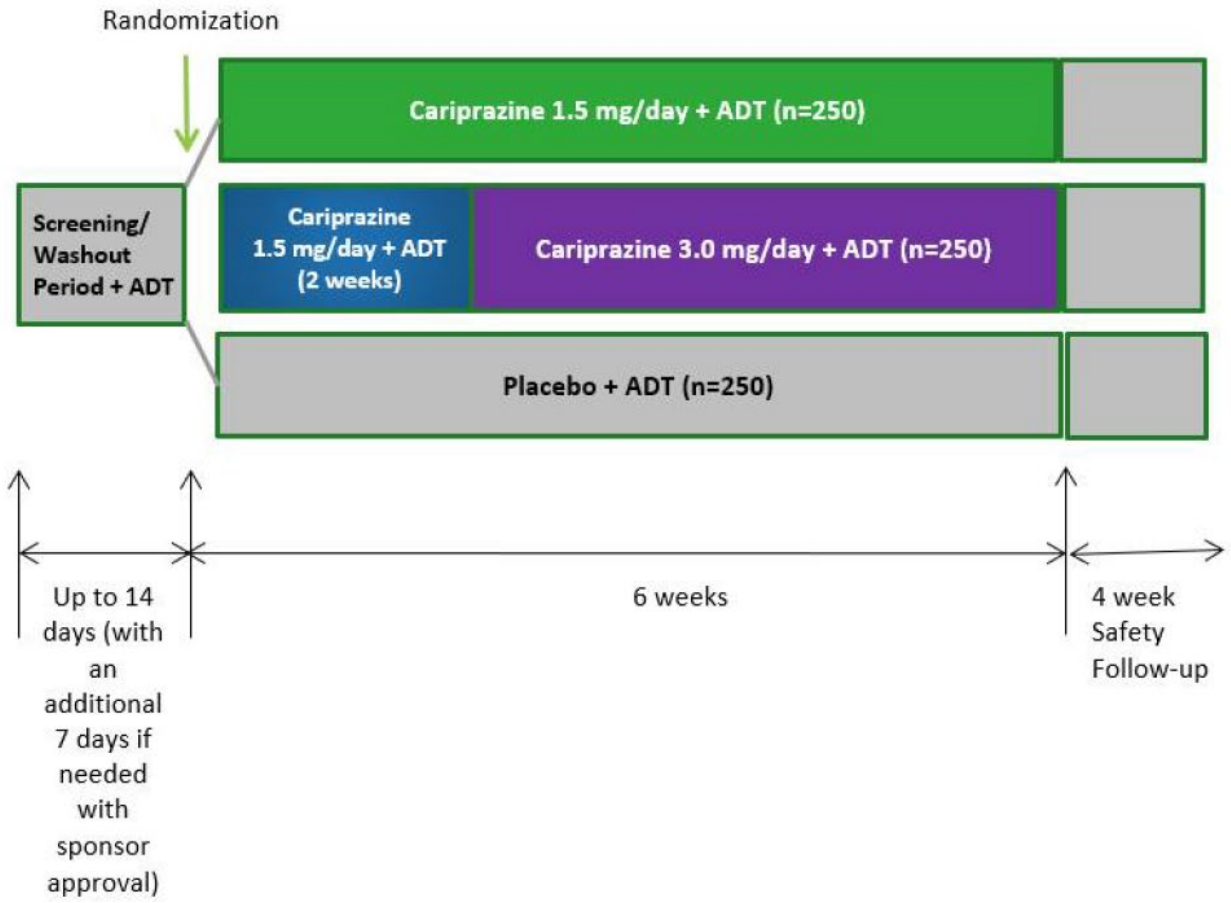
Trial Design

Allergan conducted Study 3111-301-001 as a phase 3, multicenter, randomized, placebo-controlled, double-blind, fixed-dose, 6-week study of two dose arms of cariprazine plus antidepressant therapy (ADT) compared to a placebo plus ADT arm in subjects who had an inadequate response to ADT during the current MDD episode.

The study consisted of a 14-day screening period to allow washout of prohibited medications (with up to an additional 7 days if needed), followed by a 6-week double-blind treatment period and a 4-week safety follow-up period. At randomization, the subjects were randomized to one of three treatment arms: cariprazine 1.5 mg/day (low dose) + ADT, cariprazine 3 mg/day (high dose) + ADT, or placebo + ADT. The study schematic diagram is in Figure 8.

This multicenter trial took place in 116 clinical sites: 15 in Bulgaria, six in Germany, four in Estonia, seven in the United Kingdom, eight in Hungary, 16 in Ukraine, and 60 in the United States.

Figure 8: Schematic Diagram of Study 3111-301-001



Source: Applicant's CSR for Study 3111-301-001

Reviewer's Comment: Unlike Study RGH-MD-75, Study 3111-301-001 set the primary endpoint and duration of the study at 6 weeks instead of 8 weeks. There is precedent for a 6-week trial for the adjunctive treatment of MDD using an antipsychotic; the two registration trials from the quetiapine XR development program for adjunctive treatment of MDD were each 6 weeks. It is possible that the Applicant chose the 6-week endpoint for efficacy reasons based on results from Study RGH-MD-75.

By shortening the duration of the cariprazine efficacy trial, 3111-301-001 to 6 weeks, there will be less time for the major metabolites of cariprazine to be at steady state. The DCAR and DDCAR metabolites are known to contribute to late-occurring AEs due to their long half-lives, so a shorter trial may capture fewer AEs.

Key Inclusion Criteria

A total of 759 (randomized population) male and female subjects 18 to 65 years of age were enrolled in Study 3111-301-001.

Eligible subjects were required to have:

- An MDD diagnosis defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, as interviewed by a structured clinical interview (Structured Clinical Interview for DSM-5)

- The current major depressive episode of at least 8 weeks, up to 24 months in duration

- An inadequate response (< 50% improvement) to one to three ADTs of adequate dose (defined by the minimum labeled dose) and adequate duration of 6 weeks with 3 of 6 weeks above the minimal dose. This history was recorded on the ATHQ. The protocol did not limit any class of ADTs; however, subjects currently being treated with monoamine oxidase inhibitors were excluded.

- A minimum score of 22 on the Hamilton Depression Rating Scale–17 items (HAMD-17) and a score of ≥ 2 on Item 1 of the HAMD-17 was required at both Screening and Baseline (Visit 2).

- Subject has normal physical examination findings, clinical laboratory test results, and ECG results at Screening, or abnormal results that are judged to be clinically insignificant by the investigator.

Key Exclusion Criteria

Subjects were excluded from Study 3111-301-001 if they had any current psychiatric diagnosis other than MDD, including intellectual development disability or a substance-related disorder, with the exception of specific phobias. Subjects with a suicide attempt within the past year or who were deemed at significant risk from scoring on the item 10 on the MADRS, item 3 on the HAMD-17, or on the C-SSRS were excluded.

Additional exclusion criteria were:

- Per ATRQ, subject failed to respond to > 3 trials of ADTs given at an adequate dose and duration of ≥ 6 weeks during the present episode

- Subject was treated with clozapine > 50 mg/day or any depot antipsychotic

- Subject has history of treatment with esketamine, electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental central nervous system treatment during the current episode or in the 6 months before Visit 1. If the subject has a history of non-response to the aforementioned treatments, they were excluded

- Females who were pregnant or lactating

- Any medical condition that may endanger the subject or confound the study results or any significant cardiovascular disease.

Reviewer's Comment: The diagnostic and severity inclusion criteria for Study 3111-301-001 is acceptable. At the time of this trial, the DSM-5 was the standard diagnostic tool for MDD. Like Study RGH-MD-75, the subjects' treatment history is documented on the ATHF which creates a uniform record. The duration of the current depressive episode is to be between 8 weeks and 24 months; Study RGH-MD-75 also enrolled subjects whose episode was at least 8 weeks in duration. The Applicant defined inadequate response as <50% improvement from one to three ADTs taken for 6 weeks. These inadequate response and duration of depression criteria were similar to the enrollment criteria from the adjunctive treatment of depression trials for aripiprazole and brexpiprazole and therefore are acceptable. Quetiapine XR also has an indication of adjunctive treatment of depression; however, the inclusion criterion for subjects (i.e., an inadequate response after 6 weeks to at least one antidepressant), was less strict.

Instead of listing acceptable ADTs as in Study RGH-MD-75, Study 3111-301-001 allows any baseline ADT except for MAOIs. Subjects taking MAOIs were excluded.

The inclusion criterion of a minimum score of 22 on the HAMD-17 indicates moderate to severe depression (score of >17). This severity is worse than the "moderate" depression criterion in Study RGH-MD-75 and the quetiapine XR trials, and "mild to moderate" in the aripiprazole trials for the same indication. The brexpiprazole package insert (PI) does not describe subjects' severity at enrollment, so there is no available comparison.

Dose Changes

Those subjects assigned to the cariprazine 3 mg/day arm started at 1.5 mg/day for 2 weeks, then increased to 3 mg/day at the end of Week 2 until Week 6. All subjects were to continue taking the same antidepressant at the same dose that they were taking at baseline.

Concomitant Medication

Use of any psychotropic medications in addition to the study treatments was prohibited with the exception of benzodiazepine use at a stable dose that started at least 1 month prior to Screening. Drugs that inhibit or induce cytochrome P450 were prohibited because cariprazine is metabolized via that pathway.

Rescue medications may be opioid analgesics for up to 3 days for acute medical treatment. For insomnia, the z-drugs, chloral hydrate, or suvorexant were allowed on a periodic basis. For as needed treatment of EPS or akathisia, subjects were allowed to take benztropine, biperiden, diphenhydramine, trihexyphenidyl, or propranolol.

Blinding

During the double-blind period of Study 3111-301-001, all treatment medications (cariprazine

or placebo) were provided in identical blister cards to maintain masking throughout the study. Enrolled subjects were assigned a subject number via an automated interactive web response system that served as the subject identification number on all study documents.

Reviewer's Comment: Study 3111-301-001 is a fixed-dose study, whereas Study RGH-MD-75 was flexibly dosed. In Study 3111-301-001, subjects assigned to the cariprazine 1.5 mg/day + ADT arm are started at that dose and remain at a stable dose for the entire trial. Subjects assigned to the 3 mg/day + ADT arm are titrated from 1.5 mg/day after 2 weeks to 3 mg/day. Although the cariprazine titration doubles the dose after 2 weeks, I believe that this planned titration would be more tolerable than the dose changing schedule from Study RGH-MD-75 because the initial dose is taken for 2 weeks and not 3 days prior to increasing the cariprazine dose. Also, in Study 3111-301-001, the maximum dose is 3 and not 4.5 mg/day. Cariprazine has dose-dependent AEs, and therefore subjects enrolled in Study 3111-301-001 could tolerate the high-dose cariprazine arm better than subjects in Study RGH-MD-75. Refer to the Section on Safety Results.

The Applicant's plan for blinding is acceptable.

Study Endpoints

Efficacy Endpoints

The primary efficacy endpoint of Study 3111-301-001 was the change from baseline to Week 6 in the MADRS total score. The MADRS is a 10-item, clinician-rated scale that evaluates the subject's depressive symptomatology during the past week. Subjects are rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest.

The secondary efficacy endpoint was the change from baseline to Week 6 in the Clinical Global Impressions–Severity (CGI-S) score. The CGI-S is a clinician-rated scale that measures the overall severity of a subject's illness in comparison with the severity in other subjects the physician observed.

Additional Efficacy Measures were:

- Change from baseline in the MADRS total score at Weeks 1, 2, and 4
- MADRS response (≥ 50% reduction from baseline in MADRS total score)
- MADRS remission (MADRS total score ≤ 10)
- Change from baseline in CGI-S score at Weeks 1, 2, and 4
- Clinical Global Impressions–Improvement (CGI-I) score
- CGI-I response (CGI-I score ≤ 2)
- Change from baseline in the HAMD-17 total score
- Change from baseline in the Hamilton Anxiety Rating Scale (HAM-A) total score
- HAM-A response (≥ 50% reduction from baseline in HAM-A total score)

- HAM-A remission (HAM-A total score ≤ 7)
- Change from baseline in the individual item scores for MADRS and HAM-A.

Safety Assessment Endpoints

The safety assessments for Study 3111-301-001 were: recording AEs, ocular events of special interest, clinical laboratory evaluations, vital signs, ECGs, physical examinations, EPS symptom scales, the Columbia-Suicide Severity Rating Scale (C-SSRS), and the Young Mania Rating Scale (YMRS).

Pharmacokinetic Measures

Plasma concentrations of cariprazine, DCAR, and DDCAR were collected. The pharmacokinetic data was not part of the sNDA submission. The COVID-19 pandemic decreased the amount of planned plasma collections.

Reviewer's Comment: The primary and secondary endpoints for Study 3111-301-001 are acceptable. Change from baseline on the MADRS and CGI-S were primary endpoints on many MDD trials for approved drugs. Unlike the earlier trial, RGH-MD-75, the endpoint is at Week 6 instead of Week 8. Although there is precedent for 6-week trials of adjunctive treatment of MDD with an antipsychotic (quetiapine XR), the Applicant may have chosen the 6-week endpoint based on the efficacy results from the low-dose arm of Study RGH-MD-75.

The safety-related assessments are acceptable.

Statistical Analysis Plan

Studies 301 and 302 are identical, six-week, randomized, double-blind, phase 3 studies comparing 1.5 mg and 3 mg cariprazine to placebo. For both studies:

- Primary efficacy endpoint is change from baseline (CFB) to week 6 in MADRS total score for studies 301 and 302. MADRS total score is measured at baseline and weeks 1, 2, 4, and 6.

- Secondary efficacy endpoint for potential inclusion in labeling is change from baseline to week 6 in CGI-S. CGI-S is measured at baseline and weeks 1, 2, 4, and 6.

- In 301 and 302, the Applicant planned to enroll 250 patients per arm to provide approximately 90% power to show a statistically significant effect in at least one cariprazine dose controlling alpha at a family-wise error rate of 5% using Hochberg's procedure. The effect size was assumed to be 0.286 (treatment difference relative to standard deviation) with 15% of patients dropping out by week 6. Patients are randomized at 1:1:1.

- Both CFB MADRS total score and CFB CGI-S are analyzed using a mixed model for repeated measures (MMRM) with fixed effects of treatment group, country, ADT failure category (one ADT failure, more than one ADT failure), visit, baseline value, treatment by visit interaction terms, and baseline value by visit interaction terms with an unstructured covariance matrix. Treatment effects and standard errors are estimated with least square means (LS mean).

- The Applicant adjusts p-values for multiple comparisons using a two-stage gatekeeping procedure with a truncated Hochberg's procedure in the first stage (truncation parameter $\gamma = 0.9$) and regular Hochberg's procedure in the second stage, as described below.

  Step 1 (primary endpoint MADRS):
  - If the larger p-value from the two comparisons (high dose vs placebo, low dose vs placebo) $< \alpha (1+\gamma)/2$, then conclude statistical significance for both doses.
  - Otherwise, if the smaller p-value from the two comparisons $< \alpha/2$, then conclude statistical significance for the corresponding dose.

  Step 2 (secondary endpoint CGI-S):
  - If statistical significance is found for both comparisons in Step 1 above, then use regular Hochberg procedure at full α level for CGI-S. That is,
    - if the larger p-value from the two comparisons on CGI-S $< \alpha$; then conclude statistical significance for both doses;
    - otherwise, if the smaller p-value $< \alpha/2$, then conclude statistical significance for the corresponding dose.
  - If statistical significance is found for only one of the two doses in Stage 1, then test CGI-S for that dose only. If the CGI-S p-value for that dose $< \alpha (1-\gamma)/2$, then conclude statistical significance on CGI-S for that dose.

  Step 3 (recycling alpha):
  - If only one dose shows statistical significance for both MADRS and CGI-S in the two steps above, the other dose is re-tested for the MADRS endpoint at full α level. If statistically significant, then it is re-tested for the CGI-S endpoint at full α level again.

Statistical Reviewer's Comment: The proposed SAP for both studies 301 and 302 is reasonable.

Protocol Amendments

The Applicant amended Study 3111-301-001 globally three times on December 19, 2018, March 11, 2020, and July 27, 2020. Amendment #2 from March 2020 was not implemented. There were also country-specific amendments to Bulgaria and the United Kingdom (two each

respectively).

Amendment #1 and #3 protocol changes were as follows:

- To account for greater than expected screening failures, the screening period was extended for 7 days, and the potential pool was increased from 1125 subjects to 1700
- Excluded treatment with esketamine
- Text changes to improve clarity, readability, and completeness
- Added modifications during study visits for COVID-19
- Changed exclusion criterion for hemoglobin A1c to be >8% instead of 7%.

There are no concerns that these amendments would have significantly impacted study results.

8.1.4. Study Results

Compliance with Good Clinical Practices

The Applicant conducted Study 3111-301-001 in conformance with the ICH E6 guideline for GCP, ICH guidelines of Technical Requirements for Pharmaceuticals for Human Use, and the principles of the Declaration of Helsinki, and 21 CFR §312.120.

Financial Disclosure

The Applicant did not enter into any financial arrangement with the listed clinical investigators from Study 3111-301-001. Refer to Section 15.1 Financial Disclosure for more details.

Patient Disposition

The subject disposition for Study 3111-301-001 started with 1575 subjects screened for eligibility, but 816 did not meet the inclusion criteria. Therefore, 759 subjects were randomized to receive double-blind treatment, 757 subjects received at least one dose of double-blind treatment (Safety Population), and 751 subjects had at least one postbaseline MADRS assessment (Efficacy Population). Two subjects were discontinued from the study after randomization but did not receive investigational product and were excluded from the Safety Population.

The disposition of the efficacy population is displayed in Table 15. Adverse events (27) and withdrawal by subject (33) were the most frequently reported reasons for premature discontinuation. The greatest percentage of premature discontinuations (13%) and AEs (7.1%) as the reason for discontinuation occurred in the cariprazine 3 mg/day + ADT group. Discontinuations from AEs are discussed in Section 8.2.4 Safety Results.

Tables 16 and 17 also display the disposition of the efficacy population.

Table 15: Subject Disposition of Efficacy Population (3111-301-001)

	Placebo (N=249) n (%)	*Cariprazine 1.5 mg/day (N=250) n (%)*	*Cariprazine 3 mg/day (N=252) n (%)*	*Total (N=751) n (%)*
Completed Study	229 (92)	231 (92)	219 (87)	679 (90)
Prematurely Discontinued	24 (9.6)	21 (8.4)	33 (13)	78 (10)
Reason for Discontinuation				
Adverse Event	6 (2.4)	3 (1.2)	18 (7.1)	27 (3.6)
Lack of efficacy	2 (0.8)	2 (0.8)	0	4 (0.5)
Lost to Follow-Up	3 (1.2)	3 (1.2)	5 (2.0)	11 (1.5)
Withdrawal by subject	13 (5.2)	11 (4.4)	9 (3.6)	33 (4.4)
Protocol Deviation	0	1 (0.4)	0	1 (0.1)
Non-compliance with study drug	0	1 (0.4)	1 (0.4)	2 (0.3)
Entered into the Safety Follow-up Period	240 (96)	239 (96)	238 (94)	717 (95)

Source: Clinical Reviewer modified Table 4 in CSR to Efficacy Population for Study 3111-301-001

Table 16: Number of Patients by Dropout Reason in Efficacy Population (3111-301-001)

	Number of Patients	Percent of Patients
Dropout AE	27	3.6
Dropout LOE	4	0.5
Dropout Else	41	5.5
Completer	679	90.4
N	751	100

Source: Statistical Analyst

Table 17: Number and Percentage of Patients by Dropout Reason and Treatment Arm of Efficacy Population (311-301-001)

	Dropout AE	Dropout LOE	Dropout Else	Completer	N
Placebo + ADT	6 (2.4)	2 (0.8)	12 (4.8)	229 (92.0)	249
Cariprazine 1.5 mg/day + ADT	3 (1.2)	2 (0.8)	14 (5.6)	231 (92.4)	250
Cariprazine 3 mg/day + ADT	18 (7.1)	0 (0)	15 (6.0)	219 (86.9)	252

Source: Statistical Analyst

Reviewer's Comment: Around 10 percent of subjects prematurely discontinued Study 3111-301-001. The most frequent reasons for discontinuation were experiencing an AE (3.6%) or withdrawal by subject (4.4%). Subjects assigned to the cariprazine 3 mg/day + ADT arm discontinued at a higher rate (13%) than those in the cariprazine 1.5 mg/day + ADT (1.2%) or placebo + ADT arms (2.4%); the premature discontinuations in the 3 mg/day group (again, 13%) was primarily driven by 7.1% dropouts due to AEs. The total AE-related dropouts in Study 3111-301-001 (3.6%) were less than those from Study RGH-MD-75 (7.6%). The difference is likely from a greater rate of AEs leading to withdrawal in the high-dose arm in Study RGH-MD-75 and a 2-week longer study duration. The Section on Safety Results discusses the AEs leading to dropouts. Discontinuations for reasons other than AEs were similar among treatment groups. The percentage of study completers was lowest for subjects in the cariprazine 3 mg/day group (87%). Overall, the number of subjects that did not complete Study 3111-301-001 did not affect the study outcomes.

Protocol Violations/Deviations

Protocol deviations occurred at similar rates by treatment group (i.e., 8% in the placebo + ADT arm, 8% in the cariprazine 1.5 mg/day + ADT arm, and 11% in the cariprazine 3 mg/day + ADT arm.) The reasons for protocol deviations in the randomized population (N=759) included: inclusion/exclusion criteria violations (related to lab data), receipt of wrong treatment or incorrect dose of investigational product, and use of prohibited concomitant medications as displayed in Table 18. The most prohibited medications were taken by subjects in the cariprazine 3 mg/day + ADT group. In the placebo + ADT group, one deviation occurred, where an unqualified rater conducted a subject's efficacy assessment.

Table 18: Protocol Deviations during Study 3111-301-001 (Randomized Population)

	Placebo (N=254) n (%)	*Cariprazine 1.5 mg/day (N=252) n (%)*	*Cariprazine 3 mg/day (N=253) n (%)*	*Total (N=759) n (%)*
Number of Participants with at Least One Protocol Deviation	21 (8.3)	19 (7.5)	28 (11)	68 (9.0)

	Placebo (N=254) n (%)	*Cariprazine 1.5 mg/day (N=252) n (%)*	*Cariprazine 3 mg/day (N=253) n (%)*	*Total (N=759) n (%)*
ADT Compliance <80% and >120%	1 (0.4)	1 (0.4)	0	2 (0.3)
AESI not reported to Sponsor by Site	0	0	1 (0.4)	1 (0.1)
Efficacy scale performed by a non-certified rater	1 (0.4)	0	0	1 (0.1)
Randomized despite exclusion criteria are met	1 (0.4)	2 (0.8)	2 (0.8)	5 (0.7)
Randomized despite inclusion criteria not met	2 (0.8)	2 (0.8)	3 (1.2)	7 (0.9)
Mis-stratification	13 (5.1)	11 (4.4)	12 (4.7)	36 (4.7)
Prohibited Concomitant Medication	3 (1.2)	5 (2.0)	10 (4.0)	18 (2.4)
SAE not reported	0	0	1 (0.4)	1 (0.1)
Wrong drug treatment administered	1 (0.4)	0	0	1 (0.1)

Source: Clinical Reviewer modified Table 5 in CSR for Study 3111-301-001

Reviewer's Comment: The quantity of protocol violations from Study 3111-301-001 is unlikely to have affected efficacy results. Subjects appeared compliant with their assigned treatment. Across treatment groups, the rate of most types of protocol deviations are comparable. The protocol deviation of taking prohibited concomitant medications was highest in the cariprazine 3 mg/day + ADT group, as in Study RGH-MD-75. While a greater percentage of subjects took prohibited medications in the cariprazine 2 to 4.5 mg/day arm (8.3%) of Study RGH-MD-75, compared to the cariprazine 3 mg/day arm (4%) in Study 3111-301-001, the rates in both studies were only two percentage points above the rate for subjects assigned to the lower dose cariprazine + ADT arms of each study.

Table of Demographic Characteristics

In Study 3111-301-001, the subject demographics of the Efficacy Population (N=751) were similar among the treatment groups by age, sex, race, and ethnicity as shown in Table 19. Mean

age was 45 years. A majority of the participants were female (74%), and a majority of participants were white (82%) and non-Hispanic (91%).

Table 19: 3111-301-001: Baseline Demographics (Efficacy Population)

	Placebo + ADT N=249	Cariprazine 1.5 mg/day + ADT N=250	Cariprazine 3 mg/day + ADT N=252	Total N=751
Age (years)				
Mean (SD)	46.5 (11.9)	43.2 (13.6)	44.8 (13.3)	44.8 (13.0)
Median	49	45	48	47
Min, Max	20, 65	18, 65	18, 65	18, 65
Age, n (%)				
< 20 years	0	9 (3.6)	7 (2.8)	16 (2.1)
≥ 20 to < 30 years	29 (11.6)	44 (17.6)	41 (16.3)	114 (15.2)
≥ 30 to < 40 years	41 (16.5)	48 (19.2)	39 (15.5)	128 (17.0)
≥ 40 to < 50 years	63 (25.3)	53 (21.2)	50 (19.8)	166 (22.1)
≥ 50 to < 60 years	81 (32.5)	62 (24.8)	81 (32.1)	224 (29.8)
≥ 60 years	35 (14.1)	34 (13.6)	34 (13.5)	103 (13.7)
Sex, n (%)				
Male	68 (27.3)	60 (24.0)	72 (28.6)	200 (26.6)
Female	181 (72.7)	190 (76.0)	180 (71.4)	551 (73.4)
Race, n (%)				
White	200 (80.3)	203 (81.2)	215 (85.3)	618 (82.3)
Black or African American	42 (16.9)	37 (14.8)	30 (11.9)	109 (14.5)
Asian	5 (2.0)	4 (1.6)	7 (2.8)	16 (2.1)
American Indian or Alaska Native	1 (<1)	1 (<1)	0	2 (<1)
Native Hawaiian or Other Pacific Islander	1 (<1)	3 (1.2)	0	4 (<1)
Multiple	0	2 (<1)	0	2 (<1)
Ethnicity, n (%)				
Hispanic or Latino	25 (10.0)	24 (9.6)	19 (7.5)	68 (9.1)
Not Hispanic or Latino	224 (90.0)	226 (90.4)	233 (92.5)	683 (90.9)
Country, n (%)				
USA	148 (59.4)	151 (60.4)	153 (60.7)	452 (60.2)
BGR	35 (14.1)	34 (13.6)	34 (13.5)	103 (13.7)
EST	10 (4.0)	10 (4.0)	9 (3.6)	29 (3.9)
DEU	13 (5.2)	12 (4.8)	12 (4.8)	37 (4.9)
HUN	7 (2.8)	7 (2.8)	7 (2.8)	21 (2.8)
UKR	33 (13.3)	33 (13.2)	34 (13.5)	100 (13.3)
GBR	3 (1.2)	3 (1.2)	3 (1.2)	9 (1.2)
Weight (kg)				
Mean (SD)	86.4 (24.1)	85.3 (22.7)	82.0 (21.1)	84.6 (22.7)
Median	83.0	81.3	79.5	81.4
Min, Max	40.0, 174.9	40.5, 156.7	37.2, 172.8	37.2, 174.9
BMI ($kg/m^{2)}$				
Mean (SD)	30.4 (7.9)	30.1 (7.6)	29.0 (7.0)	29.9 (7.5)
Median	29.6	28.8	27.9	28.6
Min, Max	15.2, 66.3	18.0, 58.3	13.8, 53.8	13.8, 66.3
ADT Therapy Category (by CRF)				
One ADT failure	215 (86.3)	218 (87.2)	219 (86.9)	652 (86.8)

More than one ADT failure	34 (13.7)	32 (12.8)	33 (13.1)	99 (13.2)
ADT Therapy Category (by IRWS)				
One ADT failure	210 (84.3)	213 (85.2)	213 (84.5)	636 (84.7)
More than one ADT failure	39 (15.7)	37 (14.8)	39 (15.5)	115 (15.3)

Abbreviations: SD = standard deviation
Source: adsl.xpt; Statistical Analyst

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Approximately 85% (IWRS data) of participants had failed one ADT, and there was little difference in the treatment arms, as seen in Table 19, above. Participants were categorized by ADT failure (one ADT failure, more than one ADT failure) based on the randomization system called the interactive web response system (IWRS) data and based on eCRF data, also in the demographic Table 19. The Applicant explained that the small difference in the number of participants categorized based on IWRS versus the eCRF is attributed to the ability to update the eCRF if additional information on prior ADT failure was provided. The mean number of depressive episodes at baseline for each treatment arm was approximately six. Previous suicide attempts were reported for 10%, 12%, and 13% of subjects in the placebo, cariprazine 1.5 mg/day, and cariprazine 3 mg/day groups, respectively.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was not an issue during Study 3111-301-001 based on the two subjects (0.3%) with compliance protocol deviations from Table 18, above.

Concomitant medications were taken by 87% of the placebo, 89% of the cariprazine 1.5 mg/day, and 84% of the cariprazine 3 mg/day treatment arms. The list of concomitant antidepressants and rescue medications taken at a rate of ≥2% in the safety population (N=757) is displayed in Table 20.

Use of rescue medication was more frequent in the cariprazine + ADT treatment groups (11% in the 1.5-, 12% in the 3- mg/day) than in the placebo + ADT treatment group (6%). Subjects in the cariprazine groups received more rescue medications for insomnia, EPS or akathisia, or as needed benzodiazepines.

Table 20: Concomitant Medications ≥2% in Safety Population (Study 3111-301-001)

Concomitant Medication		n (%) of Safety Set (N=757)
Antidepressant (ADT)		
	Amitriptyline	15 (2.0)
	Buproprion	42 (5.5)
	Citalopram	44 (4.8)
	Duloxetine	66 (8.7)
	Escitalopram	133 (18)
	Fluoxetine	72 (9.5)

Concomitant Medication		n (%) of Safety Set (N=757)
	Mirtazapine	25 (3.3)
	Paroxetine	45 (5.9)
	Sertraline	120 (16)
	Venlafaxine	98 (13)
	Vortioxetine	21 (2.8)
Rescue Medication		
	Alprazolam	23 (3.0)
	Clonazepam	18 (2.4)
	Eszopiclone	22 (2.9)
	Lorazepam	20 (2.6)
	Zaleplon	23 (3.0)
	Zolpidem	115 (15)
	Zopiclone	51 (6.0)

Source: Clinical Reviewer created using JMP from dataset ADCM.xpt in Study 3111-301-001

Reviewer's Comment: The percentage use of concomitant medications during Study 3111-301-001 was comparable among treatment groups. Efficacy results of this study should not be affected by rescue medications, but safety results could be affected. The cariprazine 1.5 and 3 mg/day + ADT groups (11 to 12%) took twice as many rescue medications as those in the placebo group (6%). Unlike the previous study, RGH-MD-75, benzodiazepines were allowed as necessary for anxiety during Study 3111-301-001, indicating that the cariprazine treatment caused anxiety and/or was associated with akathisia which caused anxiety. Specific rescue medications such as propranolol or benztropine were not taken at a rate >2% (to treat akathisia or movement disorders), but alprazolam (3%), clonazepam (2.4%), and lorazepam (2.6%) were used over 2% in the safety population (includes placebo arm). Concomitant treatment of insomnia was also greater in the cariprazine 1.5 and 3 mg/day + ADT than in placebo-treated subjects. Refer to Safety Results for more discussion of AEs.

As with Study RGH-MD-75, the additional concomitant medications such as analgesics, antihistamines, antihypertensives, HMG-CoA reductase inhibitors, proton pump inhibitors, and vitamins are not known to cause changes in mood and should not confound efficacy results. The levothyroxine concomitant use is reasonable and also should not affect mood as long as the subject receives the right dosage to correct thyroid hormone levels.

Efficacy Results – Primary Endpoint

At baseline, all arms had a similar MADRS total score, see Table 21.

Table 21: MADRS Total Score at Baseline (3111-301-001: Efficacy Population)

			Cariprazine	
Scale	Statistics	Placebo (N=249)	1.5 mg (N=250)	3 mg (N=252)
MADRS	Mean	31.89	32.82	32.72
	SD	5.64	4.95	4.92
	Median	32	32	33
	Min, Max	12, 48	18, 45	17, 46

N: sample size; SD: standard deviation
Source: Statistical Analyst

In the primary efficacy endpoint family (change from baseline to week 6 (CFB6) in MADRS total score), the 1.5-mg dose arm showed evidence of efficacy with adjusted p = 0.0050, and the 3-mg dose arm did not have evidence of efficacy with adjusted p = 0.0727. The 1.5-mg dose had a placebo subtracted treatment difference (ΔΔMADRS) of -2.53 points and the 3-mg dose's ΔΔMADRS = -1.52. Detailed results are found in Table 22. For this study, adjusted p-values were compared to threshold of 0.05. Throughout this Section, negative change indicates improvement.

Table 22: MADRS Total Score at Week 6 (3111-301-001: Efficacy Population)

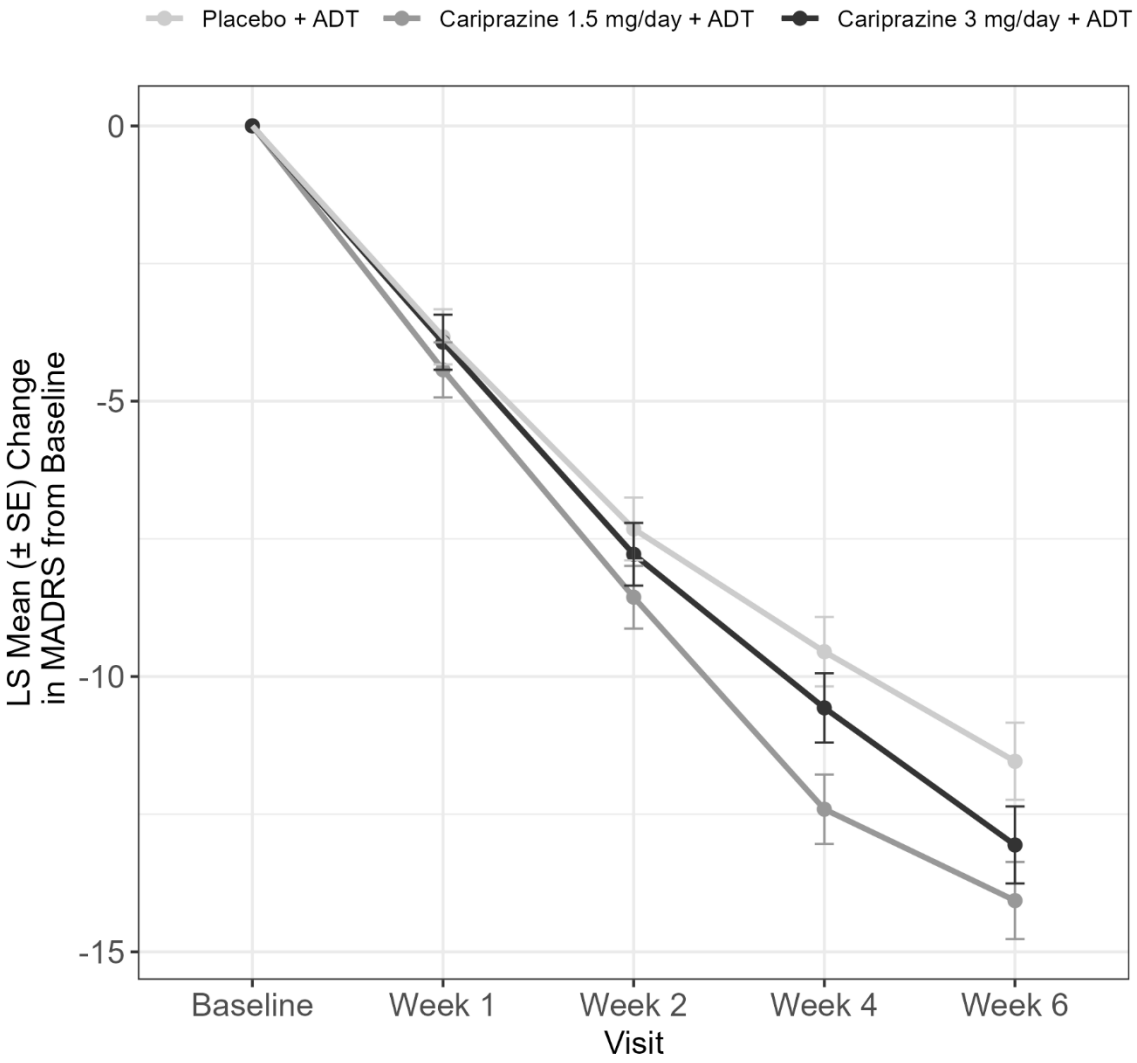
Endpoint	Treatment Group	N	LS Mean Change from Baseline (SE)	Difference from Placebo (95% CI)	Raw p-value	Adjusted p-value
MADRS	Placebo	249	-11.54 (0.70)	--	--	--
	Cariprazine 1.5 mg*	250	-14.07 (0.70)	-2.53 (-4.17, -0.89)	0.0025	0.0050
	Cariprazine 3 mg	252	-13.06 (0.70)	-1.52 (-3.16, 0.12)	0.0690	0.0727

N: sample size; LS mean: least-squares mean, SE: standard error; CI: unadjusted confidence interval
*Dose that was statistically significantly different from placebo after adjusting for multiplicity.
Source: Statistical Analyst; consistent with Applicant's results (CSR Table 14)

Over the 6-week study period, the mean MADRS total score declined in all dose arms in Study 301, see Figure 9. Both cariprazine doses separate from placebo by week 2 and continue to decline through week 6. Throughout the entire 6-week double-blind period, the 1.5-mg dose appears to have a greater decline in MADRS total score compared to both the 3-mg dose arm and placebo.

The Applicant conducted sensitivity analyses using a pattern mixture model with various shift parameters and a copy-reference method to explore the impact of missing data. The results supported the primary analysis findings.

Figure 9: MADRS Total Score - LS Mean (± SE) Change from Baseline over Time - Mixed Model for Repeated Measures (3111-301-001: Efficacy Population)



Treatment	Baseline	Week 1	Week 2	Week 4	Week 6
Placebo + ADT	249	246	246	238	231
Cariprazine 1.5 mg/day + ADT	250	250	242	237	231
Cariprazine 3 mg/day + ADT	252	252	245	235	223
N	751	748	733	710	685

LS mean: least-squares mean; SE: standard error; the numbers in the table denote numbers of patients who stayed.
Source: Statistical Analyst

Data Quality and Integrity

The Applicant submitted all necessary analysis datasets and SAS programs. Reviewers found the datasets acceptable.

Efficacy Results – Secondary and Other Relevant Endpoints

Secondary

In Study 3111-301-001, the secondary endpoint was the change from baseline to Week 6 on the CGI-S. For the CGI-S, only the 1.5-mg dose was tested because only the 1.5-mg MADRS endpoint in the primary family showed statistical evidence. Baseline scores on the CGI-S per treatment arm are in Table 23. As displayed in Table 24, after adjusting for multiplicity, neither cariprazine + ADT groups had statistically significant improvement over the placebo + ADT group on the CGI-S at Week 6. The CGI-S results do not warrant a labeling claim for either cariprazine dose.

Table 23: CGI-S Score at Baseline (3111-301-001: Efficacy Population)

			Cariprazine	
Scale	Statistics	Placebo (N=249)	1.5 mg (N=250)	3 mg (N=252)
CGI-S	Mean	4.56	4.62	4.64
	SD	0.63	0.60	0.63
	Median	4	5	5
	Min, Max	4, 6	3, 6	4, 6

Source: Statistical Analyst

Table 24: CGI-S Change from Baseline at Week 6 (3111-301-001: Efficacy Population)

Endpoint	Treatment Group	N	LS Mean Change from Baseline (SE)	Difference from Placebo (95% CI)	Raw p-value	Adjusted p-value
CGI-S	Placebo	249	-1.13 (0.09)	--	--	--
	Cariprazine 1.5 mg	250	-1.40 (0.09)	-0.28 (-0.49, -0.07)	0.0091	0.0727
	Cariprazine 3 mg	252	-1.32 (0.09)	-0.18 (-0.39, 0.03)	0.0944	0.0944

N: sample size; LS mean: least-squares mean, SE: standard error; CI: unadjusted confidence interval
Source: Statistical Analyst; consistent with Applicant's results (Table 14.2-3.3 of Applicant's CSR)

Additional efficacy measures were change from baseline on the CGI-I, HAMD-17, and the Hamiton Anxiety Scale (HAM-A) at Week 6. The results of these secondary endpoints trend towards positivity of the cariprazine 1.5 mg/day group over the placebo group; however, the trend is small and remains uncertain.

Because the cariprazine 1.5 mg/day + ADT arm was nominally significant on the HAM-A, the Applicant requested that the "key" secondary endpoint be changed to the HAM-A instead of the CGI-S. This request occurred in 2021, during discussion of the statistical analysis plan (SAP) with the Applicant; the Division denied the request because anxiety is a separate indication

requiring its own study population with designated primary endpoints. (Also, benzodiazepines were allowed as rescue medications in the study.)

The response and remission rates based on the percentage improvement on the MADRS, CGI-I, and HAM-A scales were not reviewed in depth because those efficacy measures are considered to be exploratory (and redundant) in this registration trial, 3111-301-001.

For Study 3111-301-001, the conclusion about efficacy of the secondary parameters is that there is lack of clinically meaningful efficacy trends for both cariprazine arms over the placebo group.

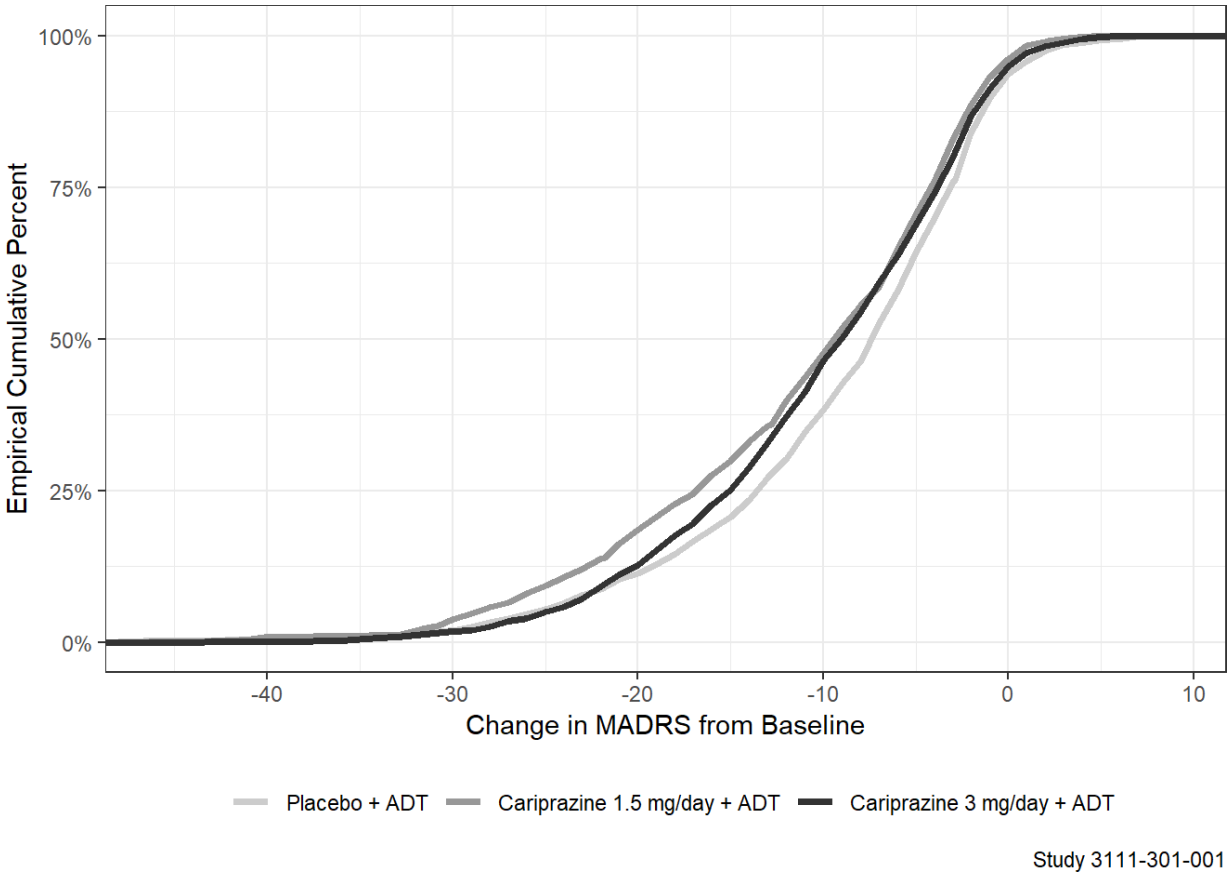
Dose/Dose Response

In the Applicant's sNDA 204370/ S-009 application, they propose a starting dose of cariprazine 1.5 mg/day and recommend increasing to 3 mg/day if there is lack of response. Study 3111-301-001 was a fixed-dose evaluation of both cariprazine 1.5 and 3 mg/day. The 1.5 mg/day cariprazine + ADT treatment arm demonstrated improvement over the placebo + ADT arm on the change from baseline at Week 6 using the MADRS. Because the treatment groups were similar in all baseline aspects (e.g., history of MDD, demographics, sex, and race), there appears to be no clear separate reason that the cariprazine 3 mg/day group failed to reach statistical significance. Also, although there were more subjects who prematurely discontinued in the cariprazine 3 mg/day arm (13% versus 8% in the 1.5-mg arm and 8% in the placebo arm), this difference did not affect the overall statistical results.

Figure 10 is an empirical cumulative distribution function plot that shows the cumulative percentage of subjects with changes in MADRS smaller than any given magnitude. The line for the cariprazine 1.5 mg + ADT arm separates from the placebo arm at -30 to -5 points of change. The line for the 3 mg/day arm has a slight separation from the placebo arm at -20 to -5. Also, in Figure 910, the difference between the 1.5 and 3 mg/day lines is minimal, indicating that there is no dose response.

Overall, the efficacy results of study 3111-301-001 indicate that a significant dose response for cariprazine as adjunctive treatment for MDD is absent, with the cariprazine 1.5 mg/day + ADT treatment group (the lower dose arm) being positive on the primary endpoint.

Figure 10: Empirical CDF Plot of Change in MADRS Total Score (Study 3111-301-001, Completers in Efficacy Population)



Source: Statistical Analyst

Durability of Response

In Study 3111-301-001, the primary efficacy timepoint was at Week 6. Only the low-dose, 1.5-mg/day cariprazine + ADT treatment group demonstrated efficacy at Week 6 on the primary endpoint. Based on the trajectories of each treatment arm at the end of the trial, Week 6, it appears likely that if the trial continued for a few weeks further, the cariprazine 1.5 mg/day arm would maintain response over the placebo arm, see Figure 9. See Section 8.1.8 Integrated Assessment of Effectiveness for a broader discussion of durability of response including other trials.

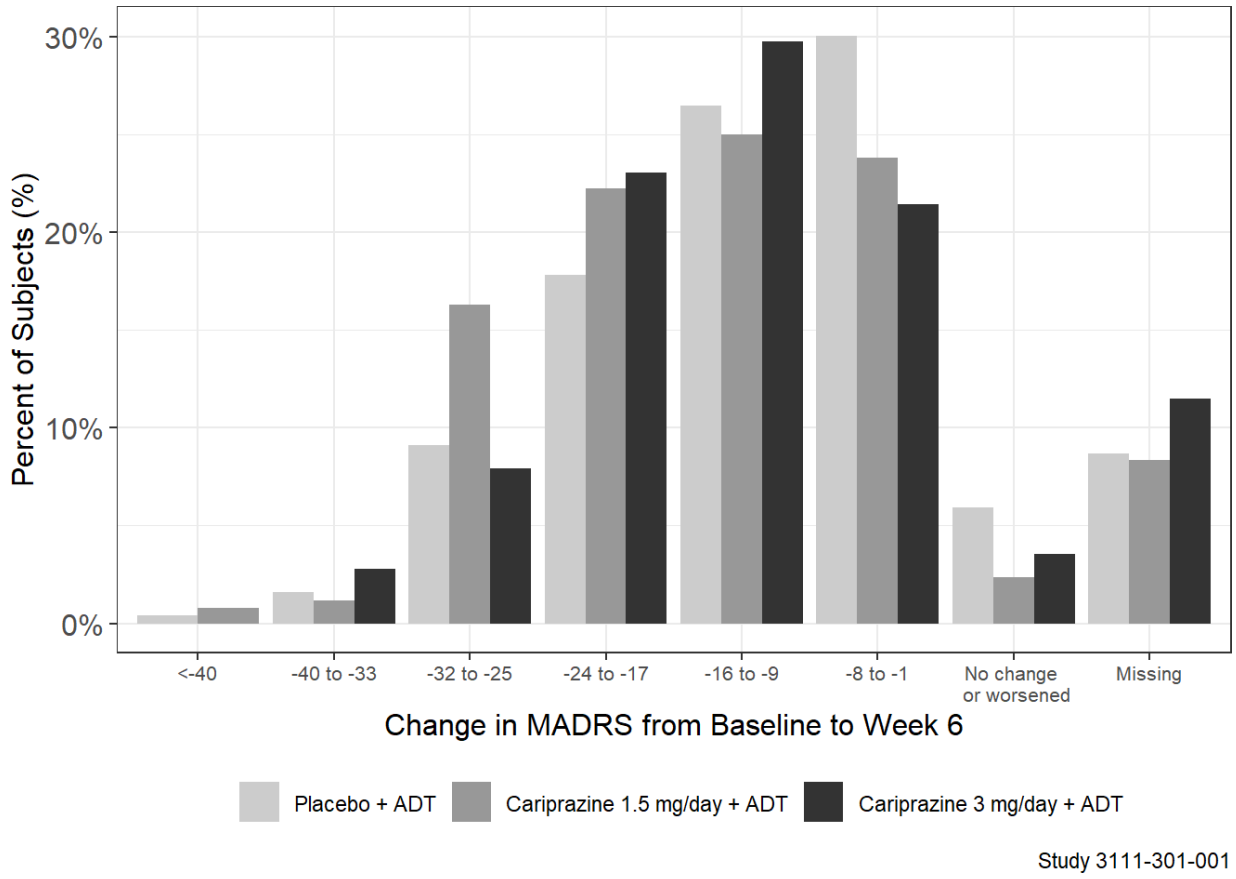
Persistence of Effect

Study 3111-301-001 was not designed to assess persistence of effect, which is the effect of the drug over time after treatment is stopped or withheld. No assessments of efficacy were performed after Week 6.

Additional Analyses Conducted on the Individual Trial

Using Figure **10**11, the Biostatistics Reviewer analyzed the usefulness of cariprazine for the adjunctive treatment of major depressive disorder (MDD). The histogram includes categories for patients who showed no improvement or worsening MDD. In addition, patients who dropped out before the 6th week are included in the "Missing" category. In the total score range of improvement (<-40 to -9-point change from baseline in MADRS total score), at least one dose of cariprazine shows a greater percentage of patients than placebo with the amount of improvement. Dropout rates are similar across all doses. Therefore, cariprazine may be more effective than placebo in the adjunctive treatment of MDD considering the results of Study 301.

Figure 10: Percentage of Subjects with Specified Change in MADRS Total Score (3111-301-001: Efficacy Population)



Source: Statistical Analyst

Also, the Applicant submitted an analysis of the impact of the COVID-19 pandemic on Study 3111-301-001. They believe that the COVID-19 pandemic had no significant impact on the analysis and interpretation of the primary efficacy endpoint.

8.1.5. Study 3111-302-001

A Double-Blind, Placebo-Controlled Study of Cariprazine as an Adjunct to Antidepressants in the Treatment of Patients with Major Depressive Disorder Who Have Had an Inadequate Response to Antidepressants Alone

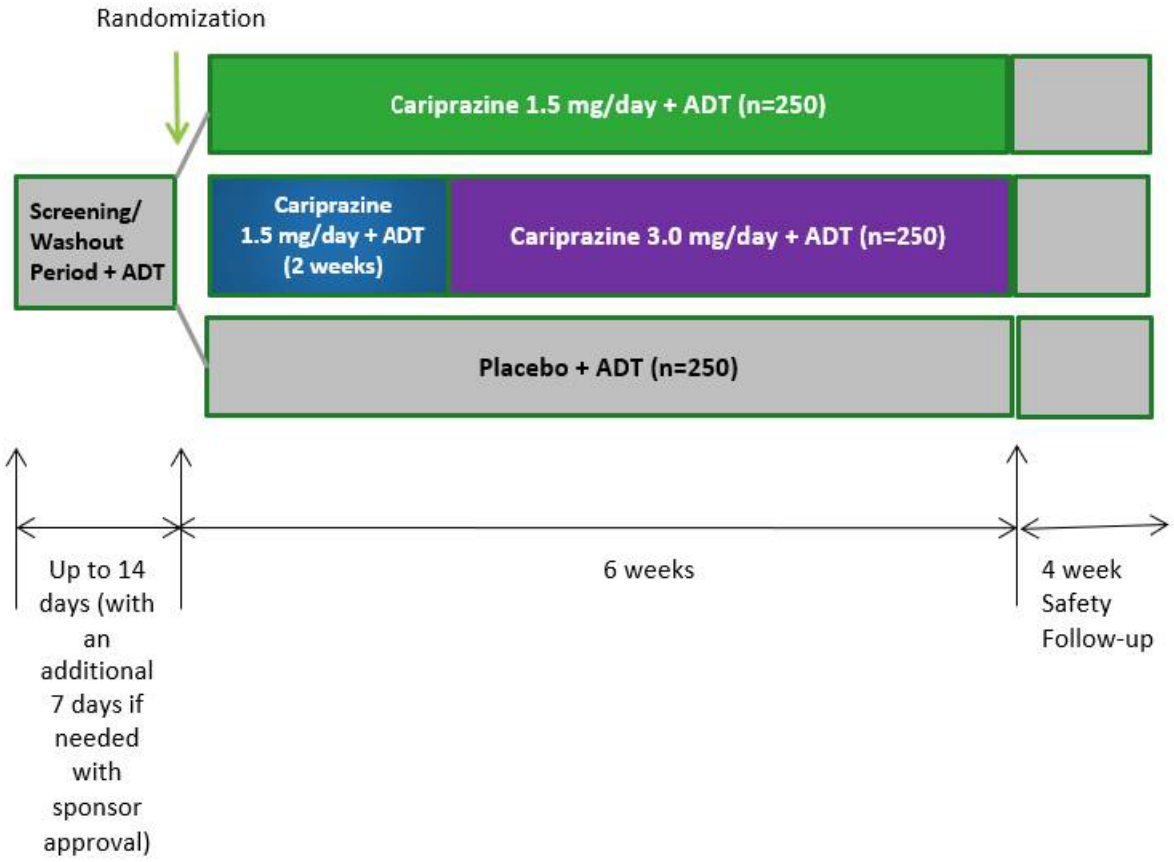
Trial Design

The trial design of Study 3111-302-001 is identical to Study 3111-301-001. Allergan conducted Study 3111-302-001 as a phase 3, multicenter, randomized, placebo-controlled, double-blind, fixed-dose, 6-week study of two dose arms of cariprazine plus antidepressant therapy (ADT) compared to a placebo plus ADT arm in subjects who had an inadequate response to ADT during the current MDD episode.

The study consisted of up to a 14-day screening period to allow washout of prohibited medications (with up to an additional 7 days if needed), followed by a 6-week double-blind treatment period and a 4-week safety follow-up period. At randomization, the subjects were randomized to one of three treatment arms: cariprazine 1.5 mg/day (low dose) + ADT, cariprazine 3 mg/day (high dose) + ADT, or placebo + ADT. The study schematic diagram is in Figure 12.

This multicenter trial took place in 107 clinical sites: three in Canada, seven in Czech Republic, five in Finland, 14 in Poland, 12 in Serbia, eight in Slovakia, and 58 in the United States.

Figure 11: Schematic Diagram of Study 3111-302-001



Source: Applicant's CSR for Study 3111-302-001

Reviewer's Comment: The trial design of Study 3111-302-001 is identical to Study 3111-301-001. The primary efficacy endpoint is at 6 weeks, instead of 8 weeks like Study RGH-MD-75. There will be less time for the major metabolites of cariprazine to be at steady state. The DCAR and DDCAR metabolites are known to cause late-occurring AEs due to extensive half-lives, so a shorter trial may artificially appear to be safer because fewer AEs are reported.

Key Inclusion Criteria

A total of 752 (randomized population) male and female subjects who were 18 to 65 years-old were enrolled in Study 3111-302-001.

Eligible subjects were required to have:

- An MDD diagnosis defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, as interviewed by a structured clinical interview (Structured Clinical Interview for DSM-5)

- Current major depressive episode of at least 8 weeks and up to 24 months in duration

- An inadequate response (< 50% improvement) to one to three ADTs of adequate dose (defined by the minimum labeled dose) and adequate duration of 6 weeks with 3 of 6 weeks above the minimal dose. This history was recorded on the ATHQ. The protocol did not limit any class of ADTs; however, subjects currently being treated with monoamine oxidase inhibitors were excluded

- A minimum score of 22 on the 17-item Hamilton Depression Rating Scale (HAMD-17) and a score of ≥ 2 on Item 1 of the HAMD-17 was required at both Screening and Baseline (Visit 2)

- Normal physical examination findings, clinical laboratory test results, and electrocardiogram (ECG) results at Screening, or abnormal results that were judged to be clinically insignificant by the investigator.

Key Exclusion Criteria

Subjects were excluded from Study 3111-302-001 if they had any current psychiatric diagnosis other than MDD, including intellectual development disability or a substance-related disorder, with the exception of specific phobias. Subjects with a suicide attempt within the past year or who were deemed at significant risk based on their scores on the item 10 on the MADRS, item 3 on the HAMD-17, or on the Columbia-Suicide Severity Rating Scale (C-SSRS) were excluded.

Additional exclusion criteria were:

- Per ATHQ, subject failed to respond to > 3 trials of ADTs given at an adequate dose and duration of ≥ 6 weeks during the present episode

- Treatment with clozapine > 50 mg/day or any depot antipsychotic

- History of treatment with esketamine, electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental central nervous system treatment during the current episode or in the 6 months before Visit 1. If the subject had a history of non-response to the aforementioned treatments, they were excluded

- Females who were pregnant or lactating

- Any medical condition that may endanger the subject or confound the study results or any significant cardiovascular disease.

Reviewer's Comment: The inclusion and exclusion criteria are the same as Study 3111-301-001. It is worth reiterating that the inclusion criterion of a minimum score of 22 on the HAMD-17 indicates moderate to severe depression (score of >17). This severity is worse than the "moderate" depression criterion in Study RGH-MD-75 and the quetiapine extended-release trials, and "mild to moderate" in the aripiprazole trials for the (b) (4)

(b) (4)

Dose Changes

Those subjects assigned to the cariprazine 3 mg/day arm were started at 1.5 mg/day for 2 weeks, then increased to 3 mg/day at Week 2 until Week 6. Subjects were to continue taking the same antidepressant at the same dose that they were taking at baseline.

Concomitant Medication

Use of any psychotropic medications in addition to the study treatments was prohibited with the exception of benzodiazepine use at a stable dose that started at least 1 month prior to Screening. Drugs that inhibit or induce cytochrome P450 were prohibited because cariprazine is metabolized via that pathway.

Rescue medications could include opioid analgesics for up to 3 days for acute medical treatment. For insomnia, the z-drugs, chloral hydrate, or suvorexant were allowed on a periodic basis. For as-needed treatment of EPS or akathisia, subjects were allowed to take benztropine, biperiden, diphenhydramine, trihexyphenidyl, or propranolol.

Blinding

During the double-blind period of Study 3111-302-001, subjects received all treatment medications (cariprazine or placebo) as identical blister cards to maintain masking throughout the study. Enrolled subjects were assigned a subject number via an automated interactive web response system that would serve as the subject identification number on all study documents.

Study Endpoints

Efficacy Endpoints

The primary efficacy endpoint of Study 3111-301-001 was the change from baseline to Week 6 in the MADRS total score. The MADRS is a 10-item, clinician-rated scale that evaluates the subject's depressive symptomatology during the past week. Subjects are rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest.

The secondary efficacy endpoint was the change from baseline to Week 6 in the Clinical Global Impressions–Severity (CGI-S) score. The CGI-S is a clinician-rated scale that measures the overall severity of a subject's illness in comparison with the severity in other subjects the physician has observed.

Additional Efficacy Measures were:

- Change from baseline in the MADRS total score at Weeks 1, 2, and 4

- MADRS response (≥ 50% reduction from baseline in MADRS total score)
- MADRS remission (MADRS total score ≤ 10)
- Change from baseline in CGI-S score at Weeks 1, 2, and 4
- Clinical Global Impressions-Improvement (CGI-I) score
- CGI-I response (CGI-I score ≤ 2)
- Change from baseline in the HAMD-17 total score
- Change from baseline in the Hamilton Anxiety Rating Scale (HAM-A) total score
- HAM-A response (≥ 50% reduction from baseline in HAM-A total score)
- HAM-A remission (HAM-A total score ≤ 7)
- The change from baseline in the individual item scores for MADRS and HAM-A.

Safety Assessment Endpoints

The safety assessments for Study 3111-302-001 were: recording AEs, ocular events of special interest, clinical laboratory evaluations, vital signs, electrocardiograms (ECGs), physical examinations, EPS symptom scales, the Columbia-Suicide Severity Rating Scale (C-SSRS), and the Young Mania Rating Scale (YMRS).

Pharmacokinetic Measures

Plasma concentrations of cariprazine, DCAR, and DDCAR were collected. The pharmacokinetic data was not part of the sNDA submission.

Statistical Analysis Plan

See discussion of statistical analysis plan (SAP) under Study 301; the two studies had identical SAPs.

Protocol Amendments

The Applicant amended Study 3111-302-001 globally three times on December 19, 2018, March 11, 2020, and July 27, 2020. Amendment 2 from March 2020 was not implemented. There were also country-specific amendments to Finland and the Czech Republic (two each respectively).

Amendment #1 and #3 protocol changes were as follows:

- To account for greater than expected screening failures, the screening period was extended for 7 days, and the potential pool was increased from 1125 subjects to 1700
- Excluded treatment with esketamine
- Text changes to improve clarity, readability, and completeness
- Added modifications during study visits for COVID-19

- Changed exclusion criterion for hemoglobin A1c to be >8% instead of 7%.

There are no concerns that these amendments would have significantly impacted study results.

8.1.6. Study Results

Compliance with Good Clinical Practices

The Applicant conducted Study 3111-302-001 in conformance with the ICH E6 guideline for GCP, ICH guidelines of Technical Requirements for Pharmaceuticals for Human Use, and the principles of the Declaration of Helsinki, and 21 CFR §312.120.

Financial Disclosure

The Applicant did not submit a Financial Disclosure for Study 3111-302-001 because it was not considered a registration trial by the Applicant. The registration trials in this sNDA are Studies RGH-MD-75 and 3111-301-001.

Patient Disposition

The subject disposition for Study 3111-302-001 started with 1382 subjects screened for eligibility, but 630 did not meet the inclusion criteria. Therefore, 752 subjects were randomized to receive double-blind treatment, 751 subjects received at least one dose of double-blind treatment (Safety Population), and 750 subjects had at least one postbaseline MADRS assessment (Efficacy Population). One subject was discontinued from the study after randomization but did not receive investigational product and were excluded from the Safety Population.

The disposition of the Efficacy Population is displayed in Table 25. Adverse events (28) and withdrawal by subject (14) were the most frequently reported reasons for premature discontinuation. The greatest percentage of premature discontinuations (10%) and AEs (5.2%) as the reason for discontinuation occurred in the cariprazine 3 mg/day + ADT group. Discontinuations from AEs are discussed in Section 8.2.4 Safety Results.

Tables 26 and 27 also display the disposition of the efficacy population.

Table 25: Subject Disposition of Efficacy Population (3111-302-001)

	Placebo (N=249) n (%)	*Cariprazine 1.5 mg/day (N=250) n (%)*	*Cariprazine 3 mg/day (N=251) n (%)*	*Total (N=750) n (%)*
Completed Study	235 (94)	233 (93)	226 (90)	694 (93)

	Placebo (N=249) n (%)	*Cariprazine 1.5 mg/day (N=250) n (%)*	*Cariprazine 3 mg/day (N=251) n (%)*	*Total (N=750) n (%)*
Prematurely Discontinued	15 (6.0)	17 (6.8)	25 (10)	57 (7.6)
Reason for Discontinuation				
Adverse Event	6 (2.4)	9 (3.6)	13 (5.2)	28 (3.7)
Lack of efficacy	1 (0.4)	0	1 (0.4)	2 (0.3)
Lost to Follow-Up	1 (0.4)	1 (0.4)	2 (0.8)	4 (0.5)
Withdrawal by subject	4 (1.6)	4 (1.6)	6 (2.4)	14 (1.9)
Protocol Deviation	1 (0.4)	0	1 (0.4)	2 (0.3)
Non-compliance with study drug	1 (0.4)	3 (1.2)	1 (0.4)	5 (0.7)
Other	1 (0.4)	0	1 (0.4)	2 (0.3)

Source: Clinical Reviewer modified Table 4 in CSR to Efficacy Population for Study 3111-302-001

Table 26: Number of Patients by Dropout Reason in Efficacy Population (3111-302-001)

	Number of Patients	Percent of Patients
Dropout AE	28	3.7
Dropout LOE	2	0.3
Dropout Else	26	3.5
Completer	694	92.5
N	750	100

Source: Statistical Analyst

Table 27: Number of Patients and Percentage by Dropout Reason and Treatment Arm of Efficacy Population (3111-302-001)

	Dropout AE	Dropout LOE	Dropout Else	Completer	N
Placebo + ADT	6 (2.4)	1 (0.4)	7 (2.8)	235 (94.4)	249
Cariprazine 1.5 mg/day + ADT	9 (3.6)	0 (0)	8 (3.2)	233 (93.2)	250
Cariprazine 3 mg/day + ADT	13 (5.2)	1 (0.4)	11 (4.4)	226 (90.0)	251

Source: Statistical Analyst

Reviewer's Comment: The cariprazine 3 mg/day + ADT group had the highest rate of study discontinuations, mostly due to 5.2% subjects listing AEs as the reason for dropping out of the study. Study 3111-302-001 was negative for efficacy, and it is unclear if the quantity of dropouts affected results.

Protocol Violations/Deviations

The reasons for protocol deviations in the randomized population (N=752) were inclusion/ exclusion criteria violations, informed consent deviation, receipt of wrong treatment or incorrect dose of investigational product, and use of prohibited concomitant medications as displayed in Table 28. The most protocol violations and prohibited medications taken by subjects occurred in the cariprazine 1.5 mg/day + ADT group.

Table 28: Protocol Deviations during Study 3111-302-001 (Randomized Population)

	Placebo (N=251) n (%)	*Cariprazine 1.5 mg/day (N=250) n (%)*	*Cariprazine 3 mg/day (N=251) n (%)*	*Total (N=752) n (%)*
Number of Participants with at Least One Protocol Deviation	27 (11)	45 (18)	37 (15)	109 (15)
AESI (AE of Special Interest) not reported to Sponsor by Site	0	0	1 (0.4)	1 (0.1)
Randomized despite exclusion criteria are met	2 (0.8)	4 (1.6)	6 (2.4)	12 (1.6)
Randomized despite inclusion criteria not met	2 (0.8)	3 (1.2)	3 (1.2)	8 (1.1)
Mis-stratification	14 (5.6)	17 (6.8)	17 (6.8)	48 (6.4)
Prohibited Concomitant Medication	11 (4.4)	18 (7.2)	8 (3.2)	37 (4.9)
Positive urine drug screen	0	0	1 (0.4)	1 (0.1)
Wrong drug treatment administered	0	1 (0.4)	0	1 (0.1)

Source: Clinical Reviewer modified Table 5 in CSR for Study 3111-302-001

Table of Demographic Characteristics

In Study 3111-302-001, the subject demographics of the Efficacy Population (N=750) were similar among the treatment groups by age, sex, race, and ethnicity as shown in Table 29. Mean age was approximately 46 years. A majority of the participants were female (76%), and a

majority of participants were white (87%) and non-Hispanic (86%).

Table 29: 3111-302-001: Baseline Demographics (Efficacy Population)

	Placebo + ADT N=249	Cariprazine 1.5 mg/day + ADT N=250	Cariprazine 3 mg/day + ADT N=251	Total N=750
Age (years)				
Mean (SD)	46.1 (12.12)	45.0 (12.95)	45.8 (12.45)	45.7 (12.50)
Median	48	47	47	47
Min, Max	18, 64	18, 65	20, 65	18, 65
Age, n (%)				
< 20 years	3 (1.2)	3 (1.2)	0	6 (<1)
≥ 20 to < 30 years	31 (12.4)	42 (16.8)	38 (15.1)	111 (14.8)
≥ 30 to < 40 years	38 (15.3)	36 (14.4)	37 (14.7)	111 (14.8)
≥ 40 to < 50 years	67 (26.9)	60 (24.0)	70 (27.9)	197 (26.3)
≥ 50 to < 60 years	81 (32.5)	78 (31.2)	68 (27.1)	227 (30.3)
≥ 60 years	29 (11.6)	31 (12.4)	38 (15.1)	98 (13.1)
Sex, n (%)				
Male	59 (23.7)	65 (26.0)	54 (21.5)	178 (23.7)
Female	190 (76.3)	185 (74.0)	197 (78.5)	572 (76.3)
Race, n (%)				
White	216 (86.7)	216 (86.4)	221 (88.0)	653 (87.1)
Black or African American	29 (11.6)	32 (12.8)	22 (8.8)	83 (11.1)
Asian	4 (1.6)	0	5 (2.0)	9 (1.2)
American Indian or Alaska Native	0	0	2 (<1)	2 (<1)
Native Hawaiian or Other Pacific Islander	0	1 (<1)	0	1 (<1)
Multiple	0	1 (<1)	1 (<1)	2 (<1)
Ethnicity, n (%)				
Hispanic or Latino	30 (12.0)	38 (15.2)	34 (13.5)	102 (13.6)
Not Hispanic or Latino	219 (88.0)	212 (84.8)	217 (86.5)	648 (86.4)
Country, n (%)				
USA	126 (50.6)	127 (50.8)	128 (51.0)	381 (50.8)
CAN	3 (1.2)	3 (1.2)	3 (1.2)	9 (1.2)
CZE	21 (8.4)	21 (8.4)	21 (8.4)	63 (8.4)
FIN	6 (2.4)	7 (2.8)	6 (2.4)	19 (2.5)
POL	42 (16.9)	41 (16.4)	42 (16.7)	125 (16.7)
SRB	29 (11.6)	30 (12.0)	29 (11.6)	88 (11.7)
SVK	22 (8.8)	21 (8.4)	22 (8.8)	65 (8.7)
Weight (kg)				
Mean (SD)	82.9 (19.4)	85.0 (21.8)	82.9 (20.1)	83.6 (20.5)
Median	82.0	80.3	80.1	80.7
Min, Max	44.5, 164.7	49.9, 159.0	45.7, 154.8	44.5, 164.7
BMI ($kg/m^{2)}$				
Mean (SD)	29.4 (6.8)	30.3 (7.4)	29.7 (6.9)	29.8 (7.0)
Median	29.2	28.9	28.8	28.9
Min, Max	17.7, 58.1	17.3, 56.5	17.1, 62.4	17.1, 62.4
ADT Therapy Category (by CRF)				
One ADT failure	201 (80.7)	195 (78.0)	203 (80.9)	599 (79.9)
More than one ADT failure	48 (19.3)	55 (22.0)	48 (19.1)	151 (20.1)
ADT Therapy Category (by				

	Placebo + ADT N=249	Cariprazine 1.5 mg/day + ADT N=250	Cariprazine 3 mg/day + ADT N=251	Total N=750
IRWS)				
One ADT failure	193 (77.5)	196 (78.4)	196 (78.1)	585 (78.0)
More than one ADT failure	56 (22.5)	54 (21.6)	55 (21.9)	165 (22.0)

Abbreviations: SD = standard deviation
Source: adsl.xpt; Statistical Analyst

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Approximately 78% (IWRS data) of participants had failed one ADT, and there was little difference in the treatment arms, as in Table 29, above. Participants were categorized by ADT failure (one ADT failure, more than one ADT failure) based on the IWRS randomization system and based on eCRF data, also in the demographic Table 29. The Applicant explained that the small difference in the number of participants categorized based on IWRS versus the eCRF is attributable to the ability to update the eCRF if additional information on prior ADT failure was provided. The mean number of depressive episodes at baseline for each treatment arm was approximately five. Previous suicide attempts were reported for 10%, 9%, and 6% of subjects in the placebo, cariprazine 1.5 mg/day, and cariprazine 3 mg/day groups, respectively.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

During Study 3111-302-001, there were no protocol deviations based on treatment compliance.

Concomitant medications were taken by 82% of the placebo, 87% of the cariprazine 1.5 mg/day, and 87% of the cariprazine 3 mg/day treatment arms. The list of concomitant antidepressants and rescue medications taken at a rate of ≥2% in the safety population (N=751) is displayed in Table 30.

Use of rescue medication was more frequent in the cariprazine + ADT treatment groups (10% in the 1.5 mg/day group, 10% in the 3 mg/day) than in the placebo + ADT treatment group (4%). Subjects in both cariprazine groups received more rescue medications for insomnia, EPS or akathisia, or as needed benzodiazepines than subjects assigned to placebo.

Table 30: Concomitant Medication ≥2% in Safety Population (Study 3111-302-001)

Concomitant Medication		n (%) of Safety Set (N=751)
Antidepressants		
	Buproprion	31 (4.1)
	Citalopram	36 (4.8)
	Duloxetine	70 (9.3)
	Escitalopram	98 (13)
	Fluoxetine	61 (8.1)
	Mirtazapine	17 (2.3)
	Paroxetine	47 (6.3)
	Sertraline	110 (15)

	Trazodone	16 (2.1)
	Venlafaxine	91 (12)
	Vortioxetine	31 (4.1)
Rescue Medications		
	Alprazolam	30 (4.0)
	Clonazepam	27 (3.4)
	Lorazepam	38 (5.1)
	Propranolol	18 (2.4)
	Zolpidem	39 (5.2)

Source: Clinical Reviewer created using JMP from dataset ADCM.xpt in Study 3111-302-001

Reviewer's Comment: The use of concomitant medications (non-rescue) during Study 3111-302-001 was comparable among treatment groups. Like the other studies, concomitant medications included analgesics, antihistamines, antihypertensives, HMG-CoA reductase inhibitors, proton pump inhibitors, levothyroxine, and vitamins. Both cariprazine dosage groups took 10% rescue medication compared to only 4% of the placebo-treated subjects. Study 3111-302-001 was negative and it is unclear if concomitant medications, including rescue medications affected results.

Efficacy Results – Primary Endpoint

At baseline, all arms had a similar MADRS total score, see Table **31**.

Table 31: MADRS Total Score at Baseline (3111-302-001: Efficacy Population)

			Cariprazine	
Scale	**Statistics**	**Placebo (N=249)**	**1.5 mg (N=250)**	**3 mg (N=251)**
MADRS	Mean	32.98	32.00	32.25
	SD	4.78	4.25	4.69
	Median	33	32	32
	Min, Max	22, 46	21, 44	20, 44

N: sample size; SD: standard deviation
Source: Statistical Analyst

In the primary efficacy endpoint family (change from baseline to week 6 (CFB6) in MADRS total score), 1.5 mg dose arm did not show evidence of efficacy with p = 0.6798, and 3 mg dose arm did not have evidence of efficacy with p = 0.1245. In the secondary endpoint family (CFB6 in CGI-S), no endpoints were tested because both endpoints in the primary family failed to reject. The 1.5 mg dose had a placebo subtracted treatment difference (ΔΔMADRS) of -0.37 points and the 3 mg dose's ΔΔMADRS = -1.36. Detailed results are found in Table 32. For this study, only unadjusted p-values were reported and compared to threshold of 0.05. Throughout this Section, negative change indicates improvement.

Table 32: MADRS Total Score at Week 6 (3111-302-001: Efficacy Population)

Endpoint	Treatment Group	N	LS Mean Change from Baseline (SE)	Difference from Placebo (95% CI)	Raw p-value
MADRS	Placebo	249	-13.39 (0.70)	--	--
	Cariprazine 1.5 mg	250	-13.75 (0.69)	-0.37 (-2.10, 1.37)	0.6798
	Cariprazine 3 mg	251	-14.75 (0.70)	-1.36 (-3.11, 0.38)	0.1245

N: sample size; LS mean: least-squares mean, SE: standard error; CI: unadjusted confidence interval
*Dose that was statistically significantly different from placebo after adjusting for multiplicity.
Source: Statistical Analyst; consistent with Applicant's results (CSR Table 14)

Over the 6-week study period, the mean MADRS total score declined in all dose arms in Study 302, see Figure 12. Both cariprazine doses separate from placebo by week 2 and continue to decline through week 6. By Week 6, the difference between placebo and the cariprazine arms narrowed. Throughout the entire 6 week double-blind period, the 3-mg dose appears to have a greater decline in MADRS total score compared to both the 1.5-mg dose arm and placebo.

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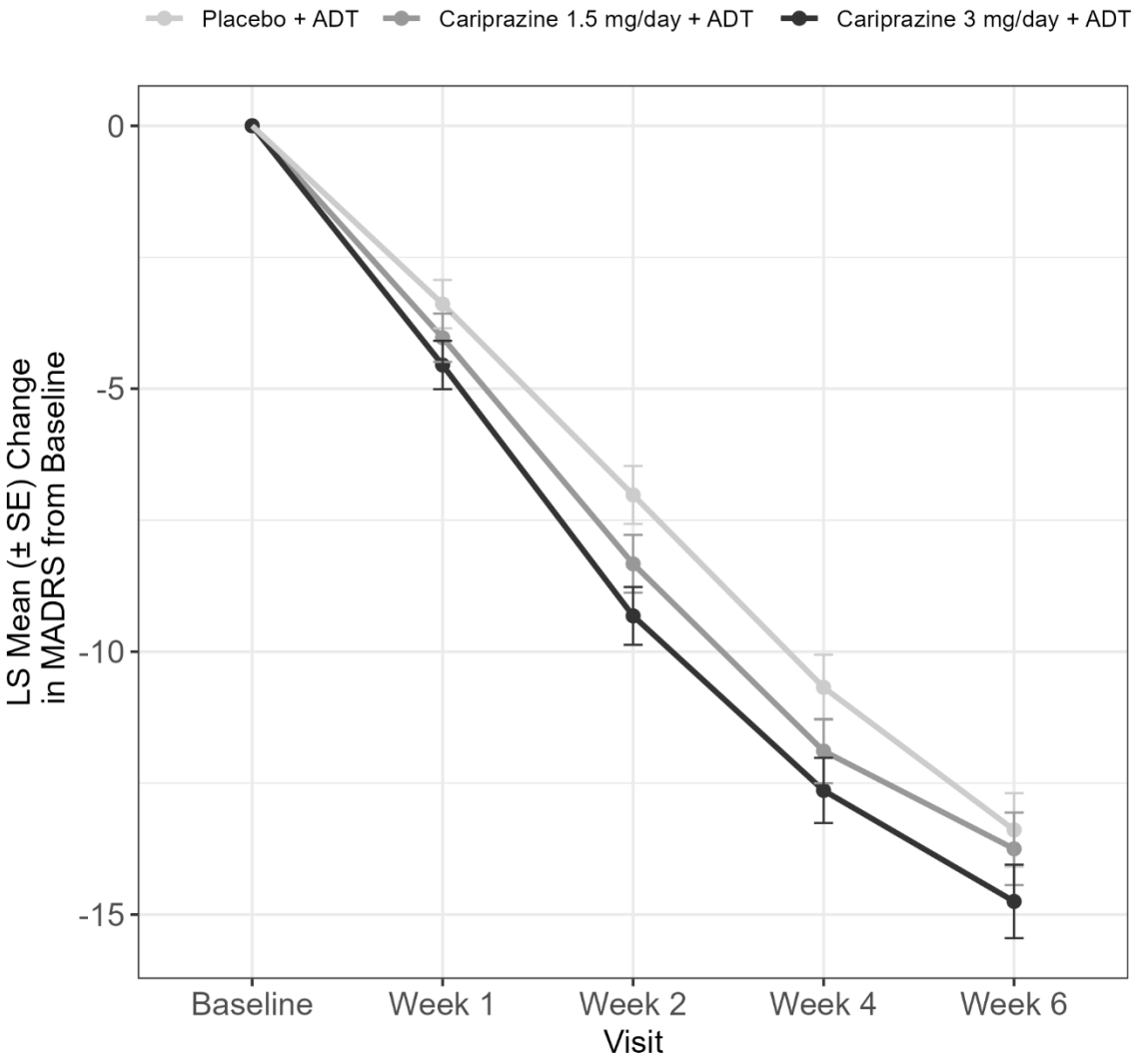
Figure 12: MADRS Total Score - LS Mean (± SE) Change from Baseline over Time - Mixed Model for Repeated Measures (3111-302-001: Efficacy Population)



Treatment	Baseline	Week 1	Week 2	Week 4	Week 6
Placebo + ADT	249	248	244	237	236
Cariprazine 1.5 mg/day + ADT	250	247	246	244	237
Cariprazine 3 mg/day + ADT	251	250	243	234	231
N	750	745	733	715	704

LS mean: least-squares mean; SE: standard error; the numbers in the table denote numbers of patients who stayed.
Source: Statistical Analyst

Data Quality and Integrity

The Applicant submitted all necessary analysis datasets and SAS programs. Reviewers found the datasets acceptable.

Efficacy Results – Secondary and Other Relevant Endpoints

Secondary

In Study 3111-302-001, the secondary endpoint was the change from baseline to Week 6 on the CGI-S. Baseline scores on the CGI-S per treatment arm are in Table 33. Because neither dose of cariprazine + ADT was statistically significantly better than placebo + ADT on the primary endpoint, the results of CGI-S scores are considered exploratory. As displayed in Table 34, neither the cariprazine + ADT treatment arms were statistically significant over the placebo group at Week 6 with raw p-values greater than 0.05.

Table 33: CGI-S at Baseline (3111-302-001: Efficacy Population)

			Cariprazine	
Scale	Statistics	Placebo (N=249)	1.5 mg (N=250)	3 mg (N=251)
CGI-S	Mean	4.67	4.61	4.65
	SD	0.60	0.59	0.65
	Median	5	5	5
	Min, Max	3, 6	3, 6	3, 6

Source: Statistical Analyst

Table 34: CGI-S Score at Week 6 (3111-302-001: Efficacy Population)

Endpoint	Treatment Group	N	LS Mean Change from Baseline (SE)	Difference from Placebo (95% CI)	Raw p-value
CGI-S	Placebo	249	-1.36 (0.09)	--	--
	Cariprazine 1.5 mg	250	-1.43 (0.09)	-0.07 (-0.29, 0.15)	0.5152
	Cariprazine 3 mg	251	-1.58 (0.09)	-0.21 (-0.43, 0.01)	0.0573

N: sample size; LS mean: least-squares mean, SE: standard error; CI: unadjusted confidence interval
Source: Statistical Analyst; consistent with Applicant results (CSR Table 16)

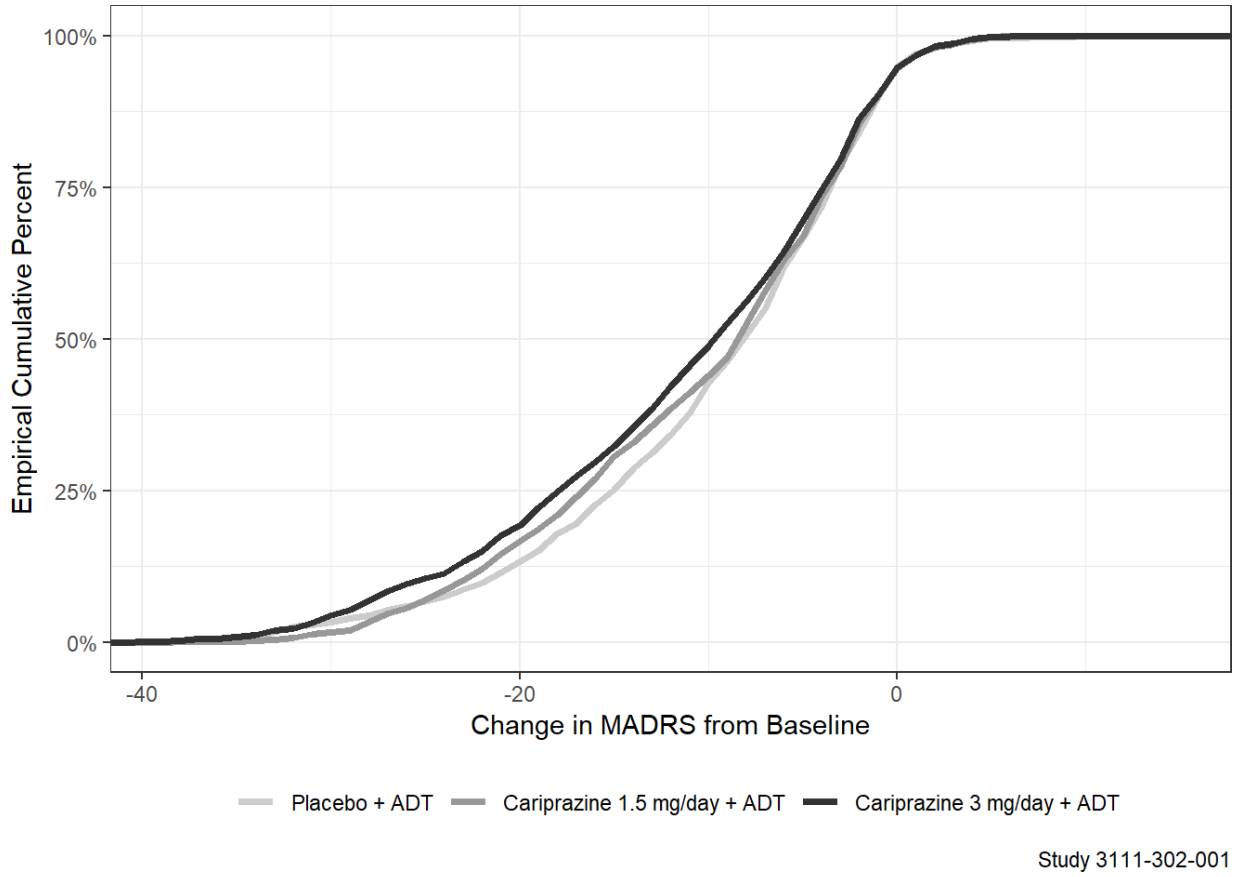
Additional efficacy measures were change from baseline on the CGI-I, HAMD-17, and the Hamiton Anxiety Scale (HAM-A) at Week 6, as well as the response and remission rates based on the percentage improvement on the MADRS, CGI-I, and HAM-A scales. Rates of response and remission are considered exploratory and redundant with the earlier endpoints. These aforementioned additional efficacy measures are only viewed as exploratory. Also, the results of the primary efficacy endpoint were negative, and none of the measurements of efficacy demonstrated improvement over the placebo + ADT treatment arm at the specified timepoint.

For Study 3111-302-001, the conclusion about efficacy of the secondary parameters is that there is lack of statistically significant efficacy trends for both cariprazine arms over the placebo group.

Dose/Dose Response

Because neither cariprazine dose (1.5 nor 3 mg/day) + ADT demonstrated greater efficacy than the placebo + ADT group, there is no clear dose response. Furthermore, Figure 14 (empirical cumulative distribution function) shows an inconsistent dose response trend with Study 3111-301-001; these results are also indicative of no dose response.

Figure 14 : Empirical CDF Plot of Change in MADRS Total Score (Study 3111-302-001, Completers on Efficacy population)



Source: Statistical Analyst

Durability of Response

Study 3111-302-001 did not show efficacy of cariprazine as an adjunctive to antidepressant therapy compared to placebo. Differences between cariprazine arms and placebo in the CFB in MADRS total score and CGI-S appear to indicate a small improvement of the 1.5- and 3- mg/day

doses of cariprazine between Weeks 2 and 4 but the separation is lost at the primary endpoint of Week 6. Figure 123 displays the treatment arms over time, and the widest separation can be seen between Weeks 2 and 4. Study 3111-302-001 provides no clear information about the durability of response.

Persistence of Effect

Study 3111-302-001 was not designed to assess persistence of effect, which is the effect of the drug over time after treatment is stopped or withheld. No assessments of efficacy were performed after Week 6.

Additional Analyses Conducted on the Individual Trial

Using Figure 13, the Biostatistics Reviewer analyzed the usefulness of cariprazine for the adjunctive treatment of major depressive disorder (MDD). In the range of improvement (-40 to -9-point change from baseline in MADRS total score), no dose of cariprazine consistently shows a greater percentage of patients than placebo with the amount of improvement. Dropout rates are similar across all doses. Therefore, Study 302 provides no clear evidence of cariprazine's efficacy in the adjunctive treatment of MDD.

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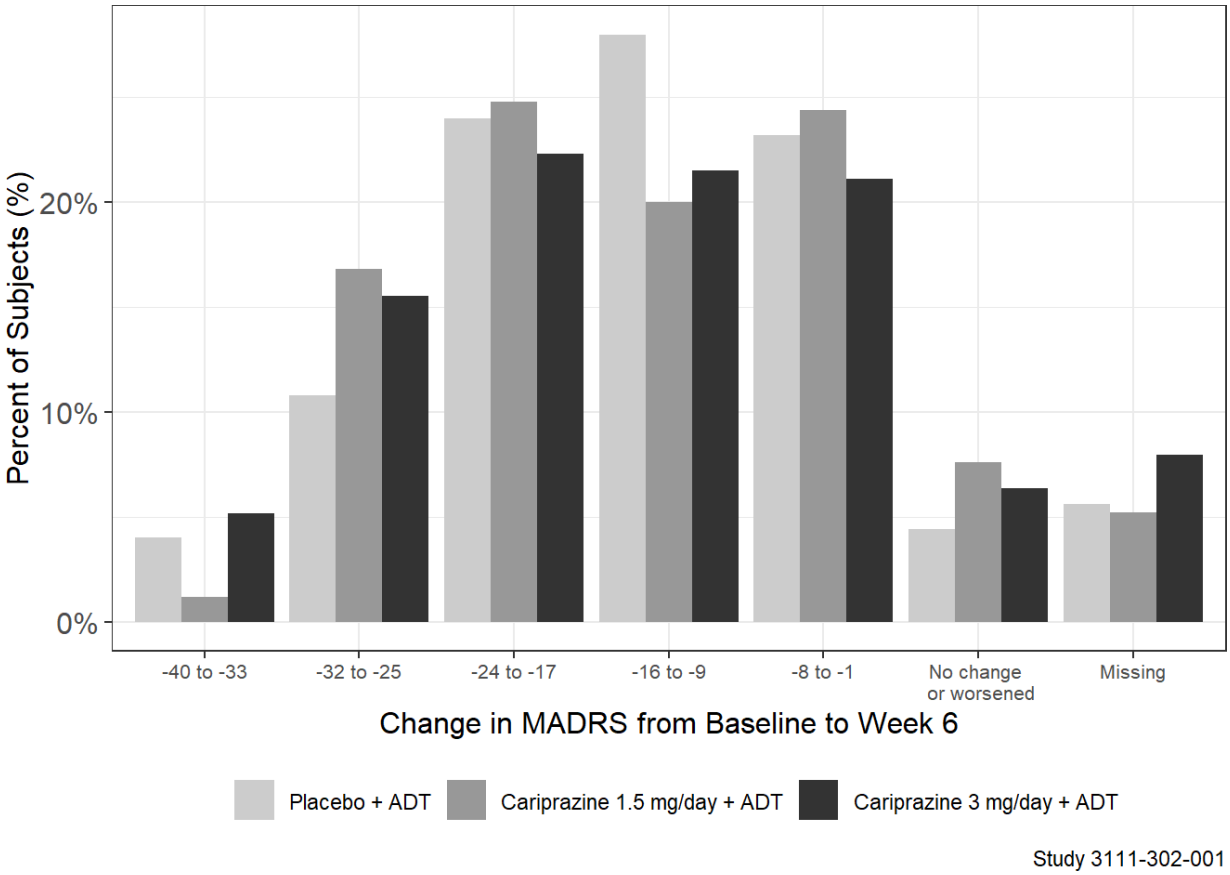
Figure 13: Percentage of Subjects with Specified Change in MADRS Total Score (3111-302-001: Efficacy Population)



Source: Statistical Analyst

Again, the Applicant submitted an analysis of the impact of the COVID-19 pandemic on Study 3111-302-001. They believe that the COVID-19 pandemic had no significant impact on the analysis and interpretation of the primary efficacy endpoint.

8.1.7. Assessment of Efficacy Across Trials

The efficacy of studies RGH-MD-75, 3111-301-001, and 3111-302-001 is discussed in this section. The three studies were designed as adequate and well-controlled trials.

The Applicant's early trials of cariprazine in MDD were RGH-MD-71 and RGH-MD-72. There are marked differences in the study designs of Studies RGH-MD-71 and RGH-MD-72 which led to exclusion from in-depth Clinical and Statistical reviews for this sNDA. They are:

- Study RGH-MD-71 was a dose-finding study and therefore one of the arms was too low for efficacy (cariprazine 0.1 to 0.3 mg/day + ADT) and to be compared to the other trials. The second cariprazine arm was 1 to 2 mg/day + ADT

- Study RGH-MD-71 enrolled the least number of subjects (N=230) of the other trials where enrollment numbers were similar
- Study RGH-MD-72 assessed a broad range of cariprazine doses of 1.5 to 4.5 mg/day (mean 2.97 mg/day + ADT in one treatment arm vs. a placebo + ADT arm)
- Both studies established subjects' inadequate response to their ADT by an 8-week prospective ADT treatment period prior to randomization to the cariprazine + ADT or placebo + ADT groups
- Both studies were negative on the primary and secondary endpoints
- Both studies enrolled only U.S. subjects but the other trials enrolled approximately 50% U.S. subjects, therefore regional differences could affect efficacy results (i.e., placebo effect from U.S. subjects with MDD).

Primary Endpoints

The primary efficacy endpoint of the three studies reviewed was the change from baseline on the MADRS at a prespecified timepoint. For the flexible-dose study, RGH-MD-75, the endpoint was Week 8; for the identical fixed-dose studies, 3111-301-001 and 3111-302-001, the endpoint was at Week 6.

Table 35 displays the LS Means and 95% confidence intervals across all three studies. Study RGH-MD-75 demonstrated efficacy of the high-dose cariprazine (2 to 4.5 mg/day) + ADT at Week 8 (LSMD (95% CI) -2.2 (-3.7; -0.6) over placebo + ADT. Study 3111-301-001 demonstrated efficacy of the lower dose cariprazine (1.5 mg/day) + ADT at Week 6 (LSMD (95% CI) -2.5 (-4.2; -0.9) over placebo + ADT. Study 3111-302-001 was negative with a nearly neutral effect for the lower dose and a trend in favor of the higher dose.

In each of the three cariprazine studies for adjunctive treatment of MDD, the subjects assigned to cariprazine show numerical improvement (based on the mean change from baseline on the MADRS placebo score difference from the MADRS scores for the cariprazine arms) during the 1 or 2 weeks prior to the primary timepoint, regardless of whether the study demonstrated efficacy at the primary timepoint (Weeks 6 or Week 8). However, the degree of difference (in change from baseline on MADRS) between the cariprazine arms and the placebo arm diminishes from the next to last study visit and the primary endpoint at either Week 8 or 6. Per our Statistics Review Staff, dropouts near the end of the trials do not account for this trend of higher mid-trial improvement in efficacy.

Evaluation of the LS Means indicates no clear dose response and that efficacy of either the low- or high-dose cariprazine arm is not replicated for each specific dose (Table 34). However, the PK analysis indicates that there may not be a major difference in exposure between the 1.5-mg and 3-mg doses. Therefore, it is plausible that the clinical studies did not show a clear dose response (i.e., they may be essentially overlapping doses in terms of efficacy). In addition, the pre-specified statistical testing plan allowed for declaring a study positive if there was a positive result for either dose arm (i.e., there was no preset dose testing sequence). Therefore, the two

positive studies still provide replication of efficacy for cariprazine, despite each specific dose not being replicated.

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Table 35: Change from Baseline in MADRS Total Score by Visit in Studies RGH-MD-75, 3111-301-001, and 3111-302-001 (MMRM) (Efficacy Population)

	Study RGH-MD-75: LS Mean Change from Baseline			Comparison vs. Placebo + ADT	
	Placebo + ADT N=264	Cariprazine 1-2 mg/d + ADT N=273	Cariprazine 2-4.5 mg/d + ADT N=271	Cariprazine 1-2 mg/d + ADT LSMD (95% CI); raw p-value	Cariprazine 2-4.5 mg/d + ADT LSMD (95% CI); raw p-value
Week 1	-3.4 (0.27)	-3.7 (0.26)	-3.7 (0.26)	-0.3 (-1.04; 0.38); p = 0.3604	-0.3 (-1.04; 0.39); p = 0.3681
Week 2	-6.2 (0.37)	-7.4 (0.37)	-8.6 (0.37)	-1.2 (-2.18; -0.15); p = 0.0247	-2.4 (-3.44; -1.41); p = <.0001
Week 4	-9.2 (0.47)	-10.8 (0.47)	-11.7 (0.47)	-1.6 (-2.86; -0.30); p = 0.0160	-2.5 (-3.76; -1.17); p = 0.0002
Week 6	-11.0 (0.50)	-12.2 (0.50)	-13.3 (0.52)	-1.3 (-2.64; 0.14); p = 0.0774	-2.3 (-3.68; -0.87); p = 0.0016
Week 8	-12.5 (0.55)	-13.4 (0.55)	-14.6 (0.57)	-0.9 (-2.42; 0.61); p = 0.2403	-2.2 (-3.71; -0.64); p = 0.0057
	Study 3111-301-001: LS Mean Change from Baseline			**Comparison vs. Placebo + ADT**	
	Placebo + ADT N=249	Cariprazine 1.5 mg/day + ADT N=250	Cariprazine 3 mg/day + ADT N=252	Cariprazine 1.5 mg/day + ADT LSMD (95% CI); raw p-value	Cariprazine 3 mg/day + ADT LSMD (95% CI); raw p-value
Week 1	-3.8 (0.50)	-4.4 (0.50)	-3.9 (0.50)	-0.6 (-1.53; 0.34); p = 0.2123	-0.1 (-1.03; 0.83); p = 0.8301
Week 2	-7.3 (0.57)	-8.6 (0.57)	-7.8 (0.57)	-1.2 (-2.45; -0.03); p = 0.0453	-0.5 (-1.67; 0.74); p = 0.4512
Week 4	-9.5 (0.63)	-12.4 (0.63)	-10.6 (0.63)	-2.9 (-4.26; -1.47); p = <.0001	-1.0 (-2.41; 0.38); p = 0.1529
Week 6	-11.5 (0.70)	-14.1 (0.70)	-13.1 (0.70)	-2.5 (-4.17; -0.90); p = 0.0025	-1.5 (-3.16; 0.12); p = 0.0690
	Study 3111-302-001: LS Mean Change from Baseline			**Comparison vs. Placebo + ADT**	
	Placebo + ADT N=249	Cariprazine 1.5 mg/day + ADT N=250	Cariprazine 3 mg/day + ADT N=251	Cariprazine 1.5 mg/day + ADT LSMD (95% CI); raw p-value	Cariprazine 3 mg/day + ADT LSMD (95% CI); raw p-value
Week 1	-3.4 (0.46)	-4.0 (0.46)	-4.5 (0.46)	-0.6 (-1.58; 0.30); p = 0.1821	-1.2 (-2.09; -0.22); p = 0.0152
Week 2	-7.0 (0.55)	-8.3 (0.55)	-9.3 (0.55)	-1.3 (-2.57; -0.05); p = 0.0411	-2.3 (-3.56; -1.04); p = 0.0004
Week 4	-10.7 (0.62)	-11.9 (0.61)	-12.6 (0.62)	-1.2 (-2.68; 0.26); p = 0.1057	-2.0 (-3.44; -0.49); p = 0.0092
Week 6	-13.4 (0.70)	-13.8 (0.69)	-14.8 (0.70)	-0.4 (-2.10; 1.37); p = 0.6796	-1.4 (-3.10; 0.37); p = 0.1244

ADT = antidepressant therapy; LS = least squares; LSMD = least squares mean difference; 95% CI: unadjusted 95% confidence interval; MADRS = Montgomery-Esberg Depression Rating Scale; MMRM = mixed-effects model for repeated measures.
Source: Statistical Analyst; Applicant's Summary of Clinical Efficacy

Secondary and Other Endpoints

The prespecified secondary endpoints were negative for efficacy in both cariprazine dose arms across the three studies, RGH-MD-75, 3111-301-001, and 3111-302-001, reiterated in Table 36. Refer to the Section 8.1 Review of Relevant Individual Trials Used to Support Efficacy for more secondary endpoint details from each trial. The secondary endpoint data do not offer trends to support the primary efficacy results.

Table 36: Prespecified Secondary Endpoint Efficacy Results (RGH-MD-75, 3111-301-001, 3111-302-001)

Study	Prespecified Secondary Endpoint	Efficacy Result	Unadjusted 95% CI
RGH-MD-75	Sheehan Disability Scale	Negative for both CAR doses	(–2.5, 0.3) for 1-2 mg; (-2.8, 0) for 2-4.5 mg
3111-301-001	Clinical Global Impression-Severity	Negative for both CAR doses (1.5 mg/day arm negative after adjusting for multiplicity, 1.5 mg arm was the only arm tested)	(-0.49, -0.07) for 1.5 mg; (-0.39, 0.03) for 3 mg
3111-302-001	Clinical Global Impression-Severity	Negative for both CAR doses (neither dose was tested per the multiple comparison procedure)	(-0.29, 0.15) for 1.5 mg; (-0.43, 0.01) for 3 mg

Source: Statistical and Clinical Reviewers created on 10/11/22

Subpopulation Analyses

Demographics

The demographics in the three efficacy trials, RGH-MD-75, 3111-301-001, and 3111-302-001, are generally balanced between treatment arms and similar among the trials (with a mix of international and U.S. populations). The safety populations for subjects with MDD consisted of 65 to 75% females, 25 to 35% males mostly aged 45 years; and all 70 to 85% white. The sex of the population of the cariprazine MDD studies is generalizable to the United States MDD population with women (10.4%) being twice as likely as men (5.5%) to have depression (Brody, Pratt, & Hughes, 2018). Based on the National Center for Health Statistics data brief, the prevalence of depression is lower among non-Hispanic Asian adults (3%) than in the cariprazine studies but occurred at similar rates compared with Hispanic, non-Hispanic black, or non-Hispanic white adults (8 to 9%) (Brody, Pratt, & Hughes, 2018). In the three cariprazine trials, the racial distribution of 70 to 85% white (instead of 8 to 9%) is likely representing which subjects enter clinical trials instead of representing the true prevalence of depression in the United States. Overall, the three cariprazine trials are reasonably generalizable to the United

States MDD population.

Also, the baseline characteristics of subjects with MDD, such as mean number of previous episodes of depression or the percentage of history of suicide attempts per assigned treatment arm, was generally balanced between treatment groups and similar among the three studies, as shown in Table 36.

Table 37: Baseline Depression Characteristics Across Studies (RGH-MD-75, 3111-301-001, 3111-301-001)

Study	Mean Number of Depressive Episodes (n)	History of Suicide Attempt Placebo (%)	History of Suicide Attempt Low-dose CAR (%)	History of Suicide Attempt High-dose CAR (%)
RGH-MD-75	4	11%	8%	10%
3111-301-001	6	10%	12%	13%
3111-302-001	5	10%	9%	6%

Source: Clinical Reviewer created on 10/12/22

Demographic Subpopulations

We conducted exploratory analyses of the demographic subgroups' change from baseline in MADRS total scores from the three studies, as displayed in Table 37, although noting that none of these subgroups were powered for definitive efficacy analyses. The demographic subgroups were age (< 55 years; ≥ 55 years), sex (male; female), and race (white; all other races). The Applicant proposed the age subgroup of over or under 55 years (which may be less clinically pertinent than an age 65 cutoff point). Since all participants were ≤ 65 years old, subgroup analysis by age is not discussed here. For the dose groups that demonstrated statistical significance in the two positive studies (RGH-MD-75, 3111-301-001), the subgroup analysis by sex showed the same trend in favor of cariprazine for both sexes although the results were numerically better in the female than in the male subgroup. Since the low-dose group in study RGH-MD-75 did not demonstrate efficacy, and the observed treatment effect for this dose was nearly neutral, inconsistent trends across subgroups are likely to occur as observed in sex subgroups for this dose group. For the two positive studies, subgroup analysis by race also trended in favor of cariprazine for both race subgroups. Subgroup analysis for the negative study 3111-302-001 is not discussed here because the observed overall treatment effect was very small.

The conclusion of the subgroup analysis is that, overall, no subgroup clearly responded differently to cariprazine low- or high-doses or 1.5 or 3 mg/day + ADT compared to the other subgroups.

Region-based Subgroups

Subjects from the United States make up approximately 50% of the total subject efficacy population across the three studies. Therefore, the clinical trials are probably generalizable to the United States MDD population, although we can also examine the results of the U.S. versus non-U.S. subgroups as follows. Again, for the dose groups that demonstrated efficacy in the two positive studies, subgroup analysis by region also trended in favor of cariprazine for both US and non-US regions.

It is important to point out that despite similar changes from baseline on the MADRS total scores between U.S. and non-U.S. regions' subjects, as seen in Table 37, the treatment difference from those assigned to the placebo groups in the three studies is somewhat smaller in the U.S. subjects than in the non-U.S. subjects. This difference is indicative of a higher placebo response in the U.S. MDD population (which is common in U.S. clinical trials for MDD). Still, overall, it did not appear that the non-U.S. subgroup was primarily driving efficacy results for these studies.

Table 38: Subgroups' Change from Baseline on MADRS (Efficacy Population) (RGH-MD-75, 3111-301-001, 3111-302-001)

	RGH-MD-75			3111-301-001			3111-302-001		
		Cariprazine			Cariprazine			Cariprazine	
Subgroup	Placebo (N=264)	1-2 mg (N=273)	2-4.5 mg (N=271)	Placebo + ADT (N=249)	1.5 mg + ADT (N=250)	3 mg + ADT (N=252)	Placebo + ADT (N=249)	1.5 mg + ADT (N=250)	3 mg + ADT (N=251)
Age									
< 55									
n	189	194	204	172	187	177	168	175	171
Mean at Baseline	29.1	29.2	29.5	32.2	32.9	33.0	33.0	32.3	32.1
LS Mean Change (SE)	-12.2 (0.66)	-13.8 (0.67)	-14.9 (0.67)	-11.7 (0.85)	-14.3 (0.82)	-13.7 (0.85)	-13.3 (0.88)	-13.7 (0.84)	-14.9 (0.87)
Treatment Difference (SE)	-	-1.5 (0.93)	-2.7 (0.93)	-	-2.7 (1.00)	-2.0 (1.02)	-	-0.3 (1.08)	-1.5 (1.10)
≥ 55									
n	75	79	67	77	63	75	81	75	80
Mean at Baseline	28.4	28.5	28.5	31.2	32.6	32.1	32.9	31.3	32.7
LS Mean Change (SE)	-12.3 (1.07)	-12.2 (1.05)	-13.9 (1.15)	-13.0 (1.20)	-15.6 (1.46)	-13.5 (1.35)	-13.6 (1.22)	-14.2 (1.29)	-14.7 (1.24)
Treatment Difference (SE)	-	-0.07 (1.48)	-1.6 (1.55)	-	-2.6 (1.54)	-0.5 (1.47)	-	-0.6 (1.55)	-1.1 (1.51)
Sex									
Female									
n	188	187	200	181	190	180	190	185	197
Mean at Baseline	28.9	29.6	29.3	31.8	32.9	32.6	33.1	32.1	32.6
LS Mean Change (SE)	-12.7 (0.66)	-14.1 (0.67)	-15.0 (0.67)	-11.3 (0.84)	-14.2 (0.82)	-12.8 (0.85)	-13.1 (0.82)	-14.5 (0.81)	-15.0 (0.81)
Treatment Difference (SE)	-	-1.4 (0.94)	-2.3 (0.93)	-	-3.0 (0.98)	-1.5 (0.99)	-	-1.34 (1.02)	-2.0 (1.01)
Male									
n	76	86	71	68	60	72	59	65	54
Mean at Baseline	28.9	27.7	29.1	32.1	32.4	33.1	32.8	31.7	30.9
LS Mean Change (SE)	-11.4 (1.06)	-11.4 (1.01)	-13.9 (1.14)	-12.3 (1.30)	-13.6 (1.37)	-13.7 (1.29)	-14.4 (1.39)	-11.2 (1.36)	-13.1 (1.44)
Treatment Difference (SE)	-	-0.03 (1.44)	-2.5 (1.55)	-	-1.3 (1.64)	-1.4 (1.57)	-	3.2 (1.77)	1.3 (1.86)
Race									
Non-White									
n	36	39	30	49	47	37	33	34	30
Mean at Baseline	30.4	29.8	31.6	34.1	34.6	34.0	34.9	33.1	33.6

	RGH-MD-75			3111-301-001			3111-302-001		
		Cariprazine			Cariprazine			Cariprazine	
Subgroup	Placebo (N=264)	1-2 mg (N=273)	2-4.5 mg (N=271)	Placebo + ADT (N=249)	1.5 mg + ADT (N=250)	3 mg + ADT (N=252)	Placebo + ADT (N=249)	1.5 mg + ADT (N=250)	3 mg + ADT (N=251)
LS Mean Change (SE)	-12.4 (1.83)	-12.9 (1.82)	-15.2 (2.11)	-11.0 (1.75)	-13.8 (1.91)	-12.3 (2.00)	-16.1 (1.91)	-12.3 (1.88)	-12.7 (1.99)
Treatment Difference (SE)	-	-0.6 (2.51)	-2.7 (2.75)	-	-2.8 (2.08)	-1.3 (2.22)	-	3.8 (2.61)	2.8 (2.68)
White									
n	228	234	241	200	203	215	216	216	221
Mean at Baseline	28.7	28.9	29.0	31.4	32.4	32.5	32.7	31.8	32.1
LS Mean Change (SE)	-12.7 (0.58)	-13.7 (0.58)	-14.7 (0.59)	-11.8 (0.74)	-14.2 (0.73)	-13.1 (0.72)	-13.1 (0.73)	-14.0 (0.73)	-15.0 (0.73)
Treatment Difference (SE)	-	-1.0 (0.81)	-2.0 (0.79)	-	-2.3 (0.85)	-1.3 (0.90)	-	-0.9 (0.94)	-1.9 (0.94)
Region									
Non-US									
n	116	116	118	101	99	99	123	123	123
Mean at Baseline	28.7	28.9	28.5	31.5	31.7	32.6	32.1	31.6	31.3
LS Mean Change (SE)	-12.2 (0.77)	-14.1 (0.78)	-14.3 (0.79)	-11.9 (0.90)	-14.9 (0.90)	-15.2 (0.92)	-13.3 (0.82)	-14.2 (0.81)	-15.3 (0.82)
Treatment Difference (SE)	-	-1.9 (1.09)	-2.1 (1.10)	-	-3.1 (1.21)	-3.3 (1.22)	-	-0.9 (1.14)	-2.0 (1.15)
US									
n	148	157	153	148	151	153	126	127	128
Mean at Baseline	29.0	29.0	29.9	32.2	33.5	32.8	33.8	32.4	33.1
LS Mean Change (SE)	-12.2 (0.79)	-12.4 (0.79)	-14.4 (0.82)	-12.8 (0.87)	-15.0 (0.87)	-13.2 (0.86)	-14.0 (0.99)	-13.7 (0.97)	-14.7 (1.00)
Treatment Difference (SE)	-	-0.2 (1.12)	-2.2 (1.14)	-	-2.2 (1.12)	-0.4 (1.12)	-	0.3 (1.32)	-0.8 (1.33)

LS = least squares; MMRM = mixed-effects model for repeated measures; SE = standard error
LS Mean Change was derived from an MMRM with treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates.
Source: Statistical Analyst

Additional Efficacy Considerations

None examined or conducted.

8.1.8. Integrated Assessment of Effectiveness

The Applicant's supplemental NDA submission for the indication (b) (4) consisted of five efficacy and safety studies. The Review Team's analyses of effectiveness primarily include Studies RGH-MD-75, 3111-301-001, and 3111-302-001 (with Studies 75 and 301 being statistically significant on their primary endpoints in one treatment arm each, and 302 being negative).

Substantial Evidence of Effectiveness

In order to consider a drug for regulatory approval, there must be substantial evidence of effectiveness (SEE). The Food and Drug Administration Modernization Act of 1997 states that the regulatory standard for SEE must be met in order to consider approval of an application. The 2019 FDA draft guidance on *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry* refers to both the quality and the quantity of the evidence of two adequate and well-controlled studies.

The Applicant did submit two adequate and well-controlled studies (i.e., RGH-MD-75 and 3111-301-001) in the sNDA 204370/ S-009 application, although only one and not two cariprazine treatment arms were positive in each study. Section II of the aforementioned Guidance says that to obtain SEE there should be substantiation of experimental results. On the surface, the Applicant's two registration trials do not appear to provide substantiation of results for one another. In Study RGH-MD-75, the high-dose cariprazine arm was positive, and in Study 3111-301-001, the low-dose arm was positive. However, the Review Team's analyses revealed that there is only a small difference between the 1.5 and 3-mg doses based on PK and biometric data. The difference in efficacy and PK levels is small enough that the two positive cariprazine arms in the two trials substantiate each other.

The next hurdle in demonstrating SEE is clinical meaningfulness. The primary efficacy endpoint of the MADRS has been accepted for trials in MDD for decades and represents a clinically meaningful outcome. However, in the Applicant's MDD trials, the amount of improvement on the MADRS scale was overall less than for other antipsychotics approved for adjunctive treatment of MDD. The treatment effects from the two positive trials RGH-MD-75 and 3111-301-001 range around -2.2 to -2.5 points placebo subtracted difference in least-squares mean change from baseline in the MADRS in Table 38.

Table 38: Treatment Effect for Atypical Antipsychotics in Adjunctive MDD Trials

Atypical antipsychotic approved for adjunctive MDD	Trials for approval	Placebo subtracted difference on MADRS (95% CI)
Cariprazine	2 trials each positive for 1 arm	1. 2 to 4.5 mg: -2.2 (-3.7, -0.6) 2. 1.5 mg: -2.5 (-4.2, -0.9)
Aripiprazole	2 positive trials of 5 to 20 mg/day	1. -2.8 (-4.5, -1.2) 2. -3.0 (-4.7, -1.4)
Brexpiprazole	1 positive 1 supportive	1. 2 mg: -3.2 (-4.9, -1.5) 2. 1 mg: -1.3 (-2.7, 0.1); 3 mg: -2.0 (-3.4, -0.5)
Quetiapine extended-release	2 positive trials	1. 150 mg: -1.9 (-3.9, 0.1); 300 mg: -3.0 (-5.0, -1.0) 2. 150 mg: -3.1 (-4.9, -1.2); 300 mg: -2.7 (-4.6, -0.8)

Source: Clinical Reviewer created 11/16/22

Also, the study population for the cariprazine adjunctive MDD trials were partial responders, i.e., usually more treatment-resistant at baseline relative to other standard MDD trials and getting some antidepressant therapy. For Study 301, the population may also have been more seriously ill at baseline on average than some of the other already approved adjunctive

antidepressant populations. The inclusion criterion of a minimum score of 22 on the HAMD-17 indicates moderate to severe depression (score of >17) in Study 301. This severity is worse than the "moderate" depression criterion in Study RGH-MD-75 and the quetiapine XR trials, and "mild to moderate" in the aripiprazole trials for the same indication. (Brexpiprazole baseline MADRS data was unavailable at this time.) Therefore, even more modest average treatment effect sizes on cariprazine may still be clinically beneficial for a subset of these more treatment-resistant patients already showing partial response.

Finally, the Guidance on SEE says that regulatory flexibility may be warranted for unmet medical need. At this time, there is not an unmet medical need. MDD is a common disease with a substantial armamentarium of treatment options. Refer to Analysis of Current Treatment Options. Like most psychiatric diseases, not every subject will have an adequate response to each treatment. This is one of the reasons that atypical antipsychotics, including cariprazine, are evaluated as adjunctive treatment to an ADT.

There are already four approved atypical antipsychotics for the treatment of MDD, either as adjunctive treatment for MDD or as monotherapy (for treatment-resistant depression). The antipsychotics for adjunctive use in Table 39 generally had larger treatment effects than cariprazine in their registration trials. However, as already mentioned, the same subject may or may not respond to each antipsychotic for adjunctive treatment of MDD. Also, given that these are partial responders, a significantly positive treatment effect may still be clinically beneficial for a subset of patients who respond to cariprazine.

The finding of SEE is necessary but not sufficient for FDA approval. The approval decision also requires a determination that the drug is safe for the intended use. Refer to Review of Safety section of this review.

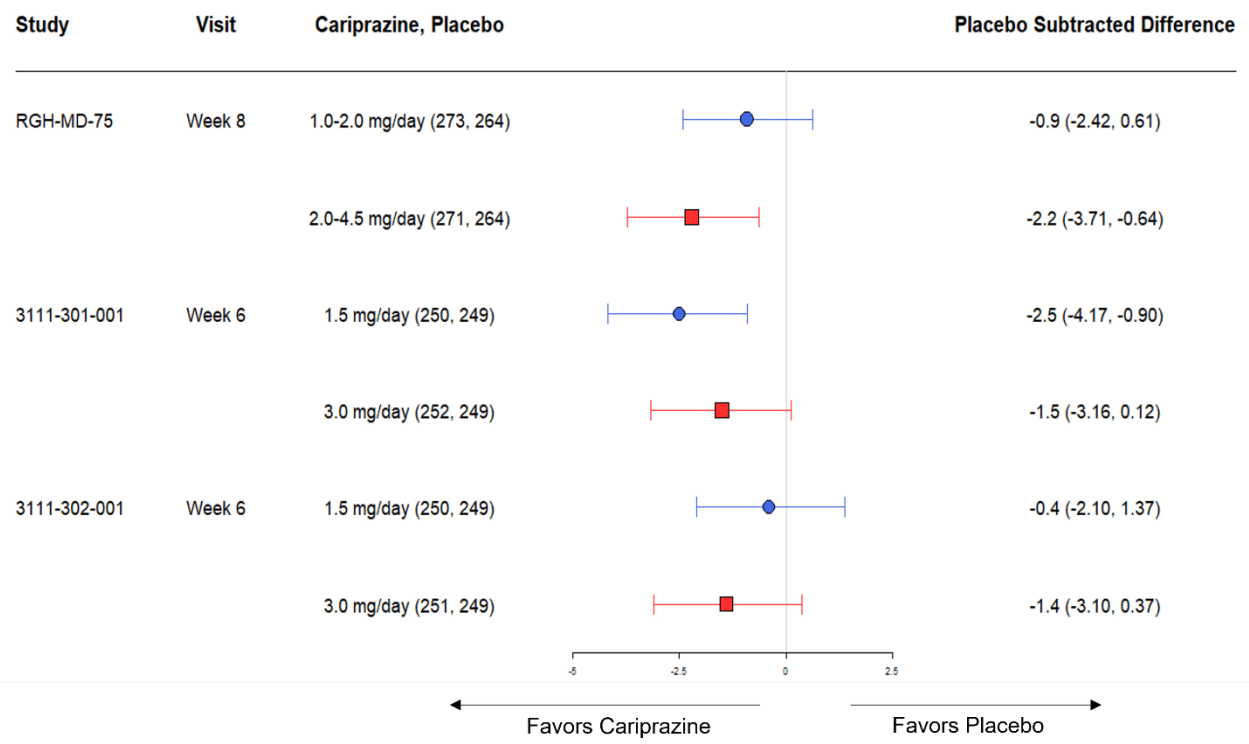
Dose Response

As noted earlier in this section of the review, there is an overall lack of dose response between the 1.5 and 3 mg/day doses. In Study RGH-MD-75, the mean dose (2.6 mg) from the positive high-dose arm is close to the cariprazine 3-mg dose. There is a subset of subjects who gained benefit from the higher dose of cariprazine if they could tolerate it.

Meta-analyses

To both explore the efficacy across the multiple studies and to address a recommendation by the MPPRC, the statistical review team conducted multiple descriptive analyses and meta-analyses.

Figure 14: Forest Plot of Change from Baseline in MADRS Total Score (Efficacy Population)



Source: Statistics Review Team

In Figure 14, all results (placebo subtracted treatment effect and unadjusted 95% confidence interval (CI)) for the CFB in MADRS score from studies 75, 301, and 302 are plotted with blue circles indicating the low doses (1 to 2 mg in study 75, 1.5 mg in studies 301 and 302) and with red squares the high doses (2 to 4.5 mg in study 75, 3 mg in studies 301 and 302). In Figure 14, note that all treatment effects favor cariprazine. However, some of the CIs for both the low dose band and high dose band include zero. Therefore, Figure 144 suggests an overall trend favoring cariprazine with moderate statistical evidence supporting this trend.

The Statistics reviewer conducted several post hoc, exploratory meta-analyses to better understand if there are any consistent signals of efficacy across studies 75, 301, and 302. The Reviewer first used Fisher's method to combine p-values for the low dose band (1 – 2mg in Study 75 and 1.5 mg in studies 301 and 302) and for the high dose band (2 – 4.5 mg in study 75 and 3 mg in studies 301 and 302). In addition, the Reviewer conducted a subject level meta-analysis using the same dose bands to explore what the average treatment effects were across all studies. Study 71 and 72 were not included in the subject level meta-analyses because of differences in the study design. Study 72 was a flexible dose design that did not have a clear low or high dose. Therefore, it is not easily linkable to the dose band or fixed dose study designs. Study 71 was a small, dose finding study with one of the arms investigating too low dose (cariprazine 0.1 to 0.3 mg/day + ADT) compared to the other trials. The second cariprazine arm was 1 to 2 mg/day + ADT. While the 1 to 2-mg arm could have been included in the low-dose

band for meta-analyses, it was determined that the lower dose arm indicated that the study design of Study 71 was different enough to potentially cause challenges to the meta-analyses. Therefore, it was excluded.

Fisher's method combines p-values from multiple studies to create the test statistic:

$$T = -2 \sum_{i=1}^{3} \log(p_i) \sim \chi^2(6),$$

where T is the test statistics, p_i is the p-value from the i^{th} study, and $\chi^2(6)$ is a chi-squared distribution with 6 degrees of freedom. This test statistic tests the global null hypothesis that all studies have no effect against the alternative of at least one study Combining the unadjusted p-values yields the Fisher's method p-values of:

Table 39: Fisher's Method Results of Studies RGH-MD-75 and 3111-301-001

Dose	p-value
Low doses	
75: 1 to 2 mg	0.0160
301 and 302: 1.5 mg	
High doses	
75: 2 to 4.5 mg	0.0029
301 and 302: 3 mg	

Source: Statistics Reviewer

The results from Fisher's method are similar to the combination of the results from studies 75 and 301. Therefore, the information from Study 302 adds minimal information about the efficacy of cariprazine. P-values from Fisher's method are smaller than the individual studies because it combines information from all three studies (majority of information from studies 75 and 301) to test if at least one study has a treatment effect not equal to zero in each dose band.

For the subject level meta-analysis, an MMRM analysis was used on a dataset that combined the MADRS score from all three studies. The MMRM model had fixed effects of dose band (treatment), study visit, baseline MADRS, and study ID, with interaction terms of baseline MADRS by visit and treatment by visit. An unstructured covariance matrix was used to account for the within-patient correlation. This model assumed a common treatment effect across studies. The common treatment effect model was compared to a model with a study by treatment interaction term via the likelihood ratio test. Both of these models may be misspecified; however, the standard confidence intervals were reported because this is an exploratory, post-hoc analysis. It was likely that any variance correction through the sandwich estimator was outweighed by the impact of the Reviewer having seen the unblinded data before both specifying and conducting these meta-analyses. For future meta-analyses intended to explore efficacy across an entire phase 3 program, the meta-analysis must be pre-specified including pre-specification of which studies will be included.

Results of the subject level meta-analysis suggest that both doses are superior to placebo where the low dose range showed an improvement of -1.4 points on the MADRS (95% CI: -2.7 to -0.6) and the high dose range showed an improvement of -1.7 points on the MADRS (95% CI: -2.4 to -0.4). In addition, there was no evidence that the treatment effect varied across studies with a likelihood ratio test p-value = 0.38.

Therefore, both exploratory, post-hoc meta-analyses suggest that the overall effect of cariprazine is an improvement in MADRS score of about -1.5 to -2 points. However, this meta-analysis was a post-hoc analysis, with the caveat that the statistical reviewer had seen the individual study results before developing the meta-analytic plan and statistical models. Therefore, all statistical test and interval estimates are likely influenced by this knowledge and should be interpreted carefully.

Summary/Conclusion about Efficacy

See Section 1.2.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant submitted safety data for five safety and efficacy trials in the sNDA submission and one open-label long-term safety extension trial, RGH-MD-76.

- RGH-MD-71- randomized, placebo-controlled, double-blind, flexible-dose, 8 weeks
- RGH-MD-72- randomized, placebo-controlled, double-blind, flexible-dose, 8 weeks
- RGH-MD-75- randomized, placebo-controlled, double-blind, flexible-dose, 8 weeks
- 3111-301-001- randomized, placebo-controlled, double-blind, fixed-dose, 6 weeks
- 3111-302-001- randomized, placebo-controlled, double-blind, fixed-dose, 6 weeks
- RGH-MD-76- open-label, 6 months, enrolled from Study -72 and *de novo*

The Applicant used Studies RGH-MD-75 and 3111-301-001 as the two registration trials based on positive efficacy results of the high and low dose cariprazine arms, respectively. The safety review will analyze the registrations trials, the pooled fixed dose studies, 3111-301-001 and 3111-302-001, the Applicant's Integrated Summary of Safety (ISS) which includes pooled data from all five efficacy trials listed above, and safety data from the 6-month safety extension trial, RGH-MD-76. The Summary of Clinical Safety submitted in the sNDA Module 2.7.4 was examined for ocular events.

The review of RGH-MD-71 only examines deaths and serious adverse events (SAEs) because it was a phase 2 study; one cariprazine dose arm was too low; and the trial results were negative for their primary endpoint. The review of RGH-MD-72 also only includes review of deaths and SAEs because it was a negative study, with a flexible-dose design ending with the modal cariprazine dose of about 3 mg/day.

This safety review focuses primarily on safety concerns of akathisia, extrapyramidal symptoms, dose-related AEs, and late-occurring AEs from the major metabolites of cariprazine, DCAR and DDCAR.

8.2.2. Review of the Safety Database

Overall Exposure

Subjects enrolled in the cariprazine adjunctive treatment of MDD development program received cariprazine or placebo for 6 or 8 weeks in the efficacy and safety trials. As shown in Table 38, a total of 149 subjects received cariprazine in Study -71, 269 in Study -72, 546 in Study -75, 504 in Study 301, and 501 in Study 302. The short-term, placebo-controlled exposure of cariprazine occurred in 1969 total subjects. The 6-month long-term exposure to cariprazine in the MDD program subject total was 345, in Study RGH-MD-76 (also in Table 38).

Table 40: Cariprazine Exposures in MDD Program

Study	Cariprazine+ADT mg/day (N=)	Cariprazine+ADT mg/day (N=)	Placebo+ADT (N=)	Total Cariprazine exposure DB-N=1969; OL-N=345
RGH-MD-71	0.1 to 0.3 Mean= 0.2 (76)	1 to 2 Mean= 1.1 (73)	(81)	149
RGH-MD-72	1.5 to 4.5 Mean at Week 8= 3.33; overall mean=2.97 (269)	—	(258)	269
RGH-MD-75	1 to 2 Mean=1.4 (273)	2 to 4.5 Mean=2.6 (273)	(266)	546
3111-301-001	1.5 (252)	3 (252)	(253)	504
3111-302-001	1.5 (250)	3 (251)	(250)	501
RGH-MD-76 (6-month, open-label)	0.5 to 4.5 Mean=2.8 (345)	—	—	345

Source: Clinical Reviewer created on 9/23/22

Adequacy of the Safety Database

The Applicant's safety database is deemed adequate for number of subjects and duration of exposure, based on the E1 International Conference on Harmonisation (ICH) Guidelines. The anticipated total number of subjects treated with an investigational drug for short-term exposure is (b) (4) The Applicant's development program had 1969 subjects taking cariprazine.

The E1 Guideline also says that a minimum of 100 subjects should be treated long-term for 1 year. However, cariprazine is approved for use in other indications where the safety profile has been previously adequately characterized. Therefore, during the June 18, 2012, Type C guidance meeting, the Division and Applicant agreed that 6-month exposure data on 100 participants would be acceptable. The median duration of exposure for the 345 subjects enrolled in RGH-MD-76 was 181 days (6 months).

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No technical data integrity issues were identified. Each of the six studies' data were in the Analysis Dataset format, in addition to the Tabulation datasets. The Review Team issued one information request to the Applicant about discrepancies in the number of subjects who prematurely discontinued Study RGH-MD-75 between the dataset and the clinical study report (CSR).

Categorization of Adverse Events

The Applicant categorized adverse events using Medical Dictionary for Regulatory Activities (MedDRA) versions as follows:

- 3111-301-001, version 24.0
- 3111-302-001, version 24.0
- RGH-MD-71, version 18.0
- RGH-MD-72, version 18.0
- RGH-MD-75, version 16.1
- RGH-MD-76, version 18.0

From the Applicant's sNDA submission, the AE-related datasets included lowest level terms that I incorporated into clinically appropriate dictionary-derived terms. The reason for recategorizing the terms is to adequately capture safety signals that may have slightly different terms but be clinically indicative of the same type of AE. The main examples, although not a comprehensive list from each study, are displayed in Table 41.

Table 41: Examples of MedDRA Lowest Level Terms Incorporated into Dictionary-derived Terms (RGH-MD-75, 3111-301-001, 3111-302-001)

Dictionary-derived term	Somnolence	Insomnia	Akathisia	Extrapyramidal symptoms
Lowest level terms	Hypersomnia	Initial insomnia	Feeling jittery	Increased salivation, Drooling
		Sleep disorder	Nervousness	Jaw stiffness, Limbs stiffness, stiff leg syndrome
		Middle insomnia		Sensation of heaviness
		Terminal insomnia		Rigidity, Neck rigidity, Cogwheel rigidity
		Poor sleep quality		Myoclonus, muscle disorder
		Insomnia		Parkinsonism, Dyskinesia
				Back muscle spasms
				Muscle tension, Muscle twitch, Muscle tightness, Muscle rigidity,
				Resting tremor, tremor

Source: Clinical Reviewer created from ADAE.xpt datasets

Routine Clinical Tests

The scheduling of routine clinical tests was adequate to support review of sNDA 204370/ S-009.

During Study RGH-MD-75, clinical laboratory tests, blood alcohol and urine drug screening, prolactin levels, electrocardiogram (ECG) monitoring, and serum pregnancy testing occurred at Screening, Week 4, and Week 8. Vital signs, suicidal ideation monitoring, EPS symptom scales, and AE reporting were collected weekly throughout the 8-week study.

During Studies 3111-301-001 and 3111-302-001, clinical laboratory testing and ECG monitoring occurred at Screening and at Week 6, the end of the double-blind period of the studies. Serum pregnancy tests were conducted at Screening, Week 6 and Week 7, the safety follow-up period. Vital signs, suicidal ideation monitoring, EPS symptom scales, and AE reporting were collected weekly throughout the study including at the Week 7.

8.2.4. Safety Results

Deaths

No deaths occurred during the double-blind periods of Studies 3111-301-001, 3111-302-001, RGH-MD-75, RGH-MD-72, or RGH-MD-71.

Study 3111-302-001
One death occurred during safety follow-up week at the end of Study 3111-302-001. Subject (b) (6) was a 48-year-old white male randomized to placebo plus ADT (amitriptyline) during Study 3111-302-001. His family reported his death during the safety follow-up week of Study 3111-302-001 from unknown causes, and no autopsy was performed.

RGH-MD-76
There were two deaths during the 6-month, open-label, safety extension trial RGH-MD-76. Subject (b) (6) was a 43-year-old white male enrolled from the parent Study RGH-MD-72. He received cariprazine 3 mg/day + venlafaxine. Scores on the C-SSRS were negative for suicidal ideation (SI) at each visit during Studies RGH-MD-72 and then RGH-MD-76. The subject reported akathisia on Day 29 of RGH-MD-76, and the cariprazine dose was reduced. His death by self-inflicted gunshot occurred at 11 days after the last dose (Day 64) of cariprazine.

Subject (b) (6) was a 56-year-old white female enrolled directly into RGH-MD-76 and not from the parent study, RGH-MD-72. At Visit 1, her C-SSRS lifetime score was positive for passive SI, then scores were negative at subsequent visits up to Visit 4, her last visit. The subject received cariprazine 3 mg/day + venlafaxine for 6 days. The CRF does not specify why the cariprazine was stopped; cariprazine was titrated to a final 3 mg/day dose during the 6 days. At 12 days post-last dose of cariprazine 3 mg + venlafaxine, she was struck by a vehicle while crossing the road and pronounced dead at the scene.

Reviewer's Comment: The death of Subject (b) (6) was not related to cariprazine because the subject was randomized to the placebo group.

The two deaths from the open-label safety trial (RGH-MD-76) which occurred 11 or 12 days after stopping cariprazine may be related to cariprazine although the Investigators judged them to be not related. Both deaths occurred shortly after stopping cariprazine. Subject (b) (6) had reached the steady-state plasma levels of cariprazine prior to stopping drug. Subject (b) (6) received cariprazine for 6 days that included doubling her dose to 3 mg/day.

None of the cariprazine adjunctive treatment of MDD protocols appeared to describe how the investigational drug is stopped at the end of the trial. The cariprazine was stopped immediately as needed, given the half-life 2 to 4 days for cariprazine, 1 to 2 days for DCAR, a major metabolite, and a long half-life of 1 to 3 weeks for DDCAR, the second metabolite. The mean concentrations for the two metabolites are widely variable (e.g., 30 to 400% of the cariprazine concentration) per the prescribing information, or package insert (PI). DDCAR is likely responsible for the late-occurring AEs including extrapyramidal symptoms (EPS) or akathisia, as described in the PI. After discontinuation, cariprazine, DCAR, and DDCAR plasma concentrations declined in a multi-exponential manner. Mean plasma concentrations of DDCAR decreased by about 50%, 1 week after the last dose and mean cariprazine and DCAR concentration dropped by about 50% in about 1 day. There was an approximately 90% decline in plasma exposure

within 1 week for cariprazine and DCAR, and at about 4 weeks for DDCAR. Following a single dose of 1 mg of cariprazine administration, DDCAR remained detectable 8 weeks post-dose, per the PI. Hence, DDCAR is slow to get to steady-state and may impart AEs after accumulation, and the metabolite is slow to disappear.

In the case of Subject (b) (6) *he reported an AE of akathisia during the trial, and after stopping the cariprazine, the half-life of DDCAR is so long that the metabolite's level would still be high enough to impart AEs 11 days post cariprazine. It is possible that akathisia or other effects from DDCAR were involved with the impulsive suicidal behavior.*

In the case of Subject (b) (6) *she had an 18-year history of depression with SI. During Study RGH-MD-76, she was titrated up to 3 mg/day of cariprazine over the first week, but then stopped the drug after Day 6. The reason for stopping is not described but is likely due to intolerability of cariprazine due to the fast titration. She did not report AEs during the trial. Although the CRF says that her "road accident" was a hit and run, it is possible that the accident was self-inflicted, maybe from lack of sufficient treatment response after medication discontinuation. Furthermore, 12 days after stopping the cariprazine, the DDCAR would still be accumulating and may cause AEs, as previously discussed.*

Serious Adverse Events

There were 33 (33/1969=1.7%) serious adverse events (SAEs) reported among the cariprazine adjunctive treatment of MDD studies, RGH-MD-71, RGH-MD-72, RGH-MD-75, 3111-301-001, and 3111-302-001 during the double-blind and safety follow-up periods. The SAEs are listed by treatment arm in Tables 42 and 43. The cases of certain SAEs that may be related to cariprazine are described below the tables. Except for depression, the psychiatric- or nervous system-related SAEs or AEs in the cases may be related to cariprazine and its metabolites.

SAEs during Double-Blind Periods

In Table 40, during the double-blind periods, 10 SAEs occurred in subjects randomized to the placebo + ADT group; 14 SAEs transpired in subjects randomized to the cariprazine + ADT groups. The SAEs in the placebo group were mostly medically related except for two cases of worsening depression, which makes sense because subjects did not have their ADT augmented with cariprazine.

Table 42: SAEs from Double-Blind Periods of Studies RGH-MD-71, RGH-MD-72, RGH-MD-75, 3111-301-001, & 3111-302-001

Dictionary-Derived Term	Cariprazine 1 to 2 mg/day + ADT (N=345)	Cariprazine 1.5 mg/day + ADT (N=502)	Cariprazine 1.5 to 4.5 mg/day + ADT (N=269)	Cariprazine 2 to 4.5 mg/day + ADT (N=273)	Cariprazine 3 mg/day + ADT (N=503)	Placebo + ADT (N=1108)
Agitation	0	0	0	1	0	0
Angina unstable	0	0	0	0	0	1
Animal bite	0	1	0	0	0	0
Atrial fibrillation	0	0	0	0	1	0
Cholelithiasis	0	0	0	0	0	1*
Chronic obstructive pulmonary disease	1	0	0	0	0	0
Depression	0	0	1*	0	0	2
Dyspnea	0	0	0	1*	0	0
Fall	0	1*	0	0	0	0
Fibula fracture	0	1*	0	0	0	0
Intestinal obstruction	0	0	0	0	0	1
Kidney infection	0	0	0	0	1	0
Ligament sprain	0	1*	0	0	0	0
Migraine	0	0	0	0	0	1
Multiple sclerosis	0	0	0	0	0	1
Non-cardiac chest pain	0	0	0	1*	0	0
Pancreatitis acute	0	0	0	0	0	1*
Panic attack	0	0	0	1*	0	0
Pulmonary embolism	0	0	0	0	0	1
Seizure	0	0	0	0	0	1
Social stay hospitalization	0	1	0	0	0	0
Suicidal ideation	0	0	1*	0	0	0
Total	**1 (0.3%)**	**5 (1.0%)**	**2 (0.7%)**	**4 (1.5%)**	**2 (0.4%)**	**10 (0.9%)**

*Denote multiple SAEs experienced by one subject in the same treatment group column

Source: Reviewer created from ISS dataset Group 2, ADAE using JMP Clinical 8.0 and Table 6-4.2 in Applicant's ISS

The subject from Study 3111-302-001 experiencing "moderate" atrial fibrillation was a 56 year-old Black male taking cariprazine 3 mg + venlafaxine. The atrial fibrillation resolved after 3 days and may be related to cariprazine (based on QTc data discussed in the QT section of this review). However, the episode did not appear to have any major permanent clinical sequelae.

Subject RGH-MD-75.(b) (6), a 53-year-old white female, discontinued Study RGH-MD-75 after experiencing an SAE of agitation while taking cariprazine 3 mg/day + sertraline. On Day 6, she experienced a nonserious AE of akathisia and was treated with benztropine. On Day 11, the subject had an SAE of agitation which led to loss of housing and subsequent inpatient hospitalization. The cariprazine was stopped, and the subject was discontinued from Study RGH-MD-75. The akathisia resolved on Day 23 and the agitation resolved on Day 29. The Investigator judged the akathisia but not the agitation to be related to cariprazine.

Reviewer's Comment: The akathisia and agitation are likely related to cariprazine; the akathisia may have led to the agitation. They both resolved as levels of DCAR and DDCAR diminished over time.

Subject RGH-MD-72.(b) (6), a 33-year-old Asian female in Study RGH-MD-72, taking cariprazine reported SAEs of depression and suicidal ideation (SI). She had a history of SI and during the trial she vacillated between positive and negative scores on the C-SSRS for SI. After the 8-week lead-in phase taking vilazodone, At Visit 6/ Day 57, she started cariprazine 1.5 mg/day + vilazodone and the dose was titrated to 4.5 mg/day during the first week of the double-blind period. At Visit 9/ Day 79, after 22 days of cariprazine, she again reported positive SI. On Day 86, 1 day post Visit 10, she developed severe anxiety (reported as nonserious AE). Treatment with cariprazine was discontinued on that day after only being administered 4 weeks out of an 8-week double-blind treatment period. The subject had ongoing anxiety and insomnia which were not treated with medication per the CRF. On Day 100, the subject experienced SAEs of SI of moderate intensity and depression of severe intensity. She was hospitalized and therefore discontinued from the trial (although the cariprazine had been already stopped at Day 86). The Investigator judged the SAEs of depression and SI not related to cariprazine. Per the ADAE dataset, the subject's SAE of depression did not lead to discontinuation of the study, but the SI did.

Reviewer's Comment: The subject had a 16-year history of depression and episodic SI while taking cariprazine and/or vilazodone. Her depression and SI is unlikely related to cariprazine 4.5 mg/day. However, the severe anxiety and insomnia started after about 4 weeks of cariprazine where the titration schedule was steep; accumulation of the major metabolites, DCAR and DDCAR may have caused her anxiety and insomnia. The CRF is unclear why the cariprazine was terminated prior to Week 8 of double-blind period and the end of the study; the subject's SAEs of depression and SI occurred 14 days after cariprazine was stopped. At that time, the metabolites would still have high levels and thus could have still led to AEs.

Subject RGH-MD-75.(b) (6), a 37-year-old female, randomized to cariprazine 2 to 4.5 mg/day + sertraline, experienced SAEs of dyspnea, non-cardiac chest pain, and panic attack on Day 19 of the study while taking cariprazine 3 mg/day. The panic attack resolved on the same day it occurred, and the anxiety (per CRF), dyspnea, and non-cardiac chest pain resolved on Day 21. The subject had presented to the emergency room for the chest pain. ECG findings were normal. The nonserious AE of anxiety was considered by the Investigator to still be of severe intensity and related to the investigational product. The SAEs of panic attack, dyspnea, and non-cardiac chest pain were considered by the Investigator to be of moderate intensity and not related to the investigational product.

Reviewer's Comment: The anxiety and subsequent panic attack which induced the chest pain and dyspnea may have been related to cariprazine. At Day 19, the major metabolites DCAR and DDCAR were still accumulating which could be responsible for these AEs.

Subject 3111-301-001.(b) (6), a 47-year-old white male, was assigned to the cariprazine 1.5 mg/day + sertraline arm of Study 3111-301-001. On Day 19, the subject was hospitalized at a psychiatric facility due to social reasons after relapsing by taking methamphetamine and losing his housing. The hospitalization counted as an SAE, and the cariprazine was discontinued. The Investigator judged the event to not be related to cariprazine.

Reviewer's Comment: I agree that this SAE of a social hospital stay was unrelated to treatment with cariprazine.

Conclusion/Summary: In Table 42, above, the total of 10 (0.9%) SAEs occurring in the placebo + ADT arm is similar to the rate of SAEs from any cariprazine arm (14 (14/1892=0.7%)). The cariprazine 2 to 4.5 mg/day + ADT had 1.5 % SAEs, but those four only occurred in two subjects, so again, technically the rate is about the same across treatment arms. Except for underlying depression symptoms with possibly insufficient treatment response, most of the psychiatric- or nervous system-related SAEs or AEs in these cases are likely directly related to cariprazine and its metabolites, particularly symptoms of akathisia and anxiety.

SAEs During Safety Follow-Up Periods

Subjects enrolled in Study RGH-MD-75 and the two fixed-dose Studies 3111-301-001 and 3111-302-001 entered a safety follow-up period after completion of the 8-week or 6-week double-blind treatment periods with cariprazine + ADT or placebo + ADT. Cariprazine or placebo were discontinued at the end of the double-blind period. Table 43 displays nine SAEs that subjects experienced during the safety follow-up period after discontinuing treatment.

Table 43: SAEs from Follow-Up Period of Studies RGH-MD-75, 3111-301-001, & 3111-302-001

Unique Subject Identifier	Dictionary-Derived Term	Previous Treatment
3111-301-001.(b) (6)	Abortion spontaneous	CAR 1.5 mg/day + sertraline
3111-301-001.(b) (6)	Fall	CAR 1.5 mg/day + fluoxetine
	Fibula fracture	
	Tibia fracture	
3111-301-001.(b) (6)	Appendicitis	CAR 3 mg/day + escitalopram
3111-301-001.(b) (6)	Depression	CAR 3 mg/day + duloxetine
3111-302-001.(b) (6)	Death	placebo + amitriptyline
3111-302-001.(b) (6)	Suicide attempt	CAR 1.5 + duloxetine
RGH-MD-75.(b) (6)	Myocardial ischaemia	CAR 2 to 4.5 mg/day + duloxetine

Source: Clinical Reviewer created using JMP Clinical 8.0, ISS dataset ADAE.xpt

Subject 3111-302-001.(b) (6) was discussed under the section on Deaths and had received placebo.

The SAEs of abortion spontaneous, fall and subsequent fractures, appendicitis, and myocardial ischemia (from undiagnosed coronary artery disease) occurred after stopping cariprazine. These SAEs are unlikely to be related to the drug.

Subject 3111-301-001.(b) (6), a 61-year-old white male, experienced an SAE of worsening depression during the follow-up period of Study 3111-301-001. He was randomized to receive cariprazine 3 mg/day + duloxetine. On Day 2, during titration, while receiving cariprazine 1.5 mg/day, the subject experienced a nonserious "moderate" AE of worsening of depression. The last dose of cariprazine was taken on Day 7 and was discontinued due to the depression. On Day 22 (the subject entered the follow-up period), the depression progressed to an SAE of "severe" depression requiring hospitalization. The Investigator judged the depression as not related to cariprazine. I agree, because the subject had taken it for only 1 week and had symptoms of depression with an inadequate response to ADT to enroll in the study.

Subject 3111-302-001.(b) (6), a 22-year-old white female, attempted suicide after discontinuing cariprazine 1.5 mg/day + duloxetine from the 6-week double-blind period of Study 3111-302-001. She had a history of SI. During the safety follow-up period, she had a

suicide attempt of moderate severity by drug overdose. She was hospitalized; she reported that the attempt was impulsive due to a quarrel with a friend. The Investigator and Applicant judged the SAE to be related to cariprazine.

Reviewer's Comment: Subject 3111-302-001. (b) (6) *did not report AEs during Study 3111-302-001. The subject's suicide attempt occurred 11 days post cariprazine 1.5 mg. As previously mentioned in this review, the half-life of DDCAR is so long that the metabolite's level would still be high enough to impart AEs such as akathisia which can leave to impulsivity or possible withdrawal symptoms at 11 days post cariprazine. The SAE may be related to stopping the cariprazine that was treating her depression or related to the DDCAR still at steady-state.*

Conclusion/Summary: Although more SAEs occurred after stopping cariprazine (8) than placebo (1) during the follow-up periods of the adjunctive treatment of MDD program, the only SAE that may be related to cariprazine was the suicide attempt from Subject 3111-302-001. (b) (6) *.*

SAEs from Open-Label Study RGH-MD-76

Subjects who participated in the flexible-dose cariprazine Study RGH-MD-72 could enroll into the 6-month, open-label, safety extension study, RGH-MD-76. The safety study also enrolled subjects directly. Table 44 shows the eight SAEs during Study RGH-MD-76. The pertinent cases are described below the table.

Table 44: SAEs from Open-Label Safety Study RGH-MD-76

Unique Subject Identifier	Dictionary-Derived Term	Comment
RGH-MD-76. (b) (6)	Road traffic accident	Case discussed under Deaths, above
RGH-MD-72.	Fall	Led to spinal cord injury
	Spinal cord injury	D/C'd trial at Day 31
RGH-MD-72.	Completed suicide	Case discussed under Deaths, above
RGH-MD-76.	Substance-induced psychotic disorder	D/C'd trial at Day 118
RGH-MD-72.	Suicide attempt	D/C'd trial at Day 132
RGH-MD-72.	Pneumonia	Completed trial
RGH-MD-72.	Blood creatinine phosphokinase increased	SAE was lab-related but anxiety led to D/C at Day 15

Source: Clinical Reviewer created from dataset RGH-MD-76 ADAE.xpt

Subject RGH-MD-76. (b) (6), a 42-year-old white male, had the SAE of substance-induced psychotic disorder. He received cariprazine + citalopram for 118 days. On Day 61, he started opioid pain medications for sciatica; by Day 100 the subject had nonserious substance abuse.

He was hospitalized for substance-induced psychotic disorder and the cariprazine was discontinued during the hospitalization.

Reviewer's Comment: It is unlikely that cariprazine, an antipsychotic, would cause substance-induced psychosis. I agree with the Investigator's assessment that the SAE was not related to cariprazine.

Subject RGH-MD-72.(b) (6), a 22-year-old white/Pacific Islander female experienced an SAE of a suicide attempt. The subject started cariprazine + fluoxetine and at Week 4, due to akathisia, the cariprazine dose was reduced to 1.5 mg/day. She continued the treatment for 132 days when she overdosed with zolpidem. The CFR says there was no precipitating incident, nor recent medication changes. The cariprazine was discontinued on Day 132 and the subject was followed-up at Days 142 and 148; she scored positive for SI at the follow-up.

Reviewer's Comment: The subject's suicide attempt does not appear to be related to cariprazine because she received it for 132 days prior to the attempt, and the dose had been stable for over 100 days.

Subject RGH-MD-72.(b) (6), a 24-year-old white male, experienced an SAE of increased creatinine phosphokinase (CPK). He was enrolled in Study RGH-MD-76 from RGH-MD-72 where he received placebo + venlafaxine. At screening, his GGT was 1.4 x UNL and ALT minimally elevated. On Day 1 cariprazine was started and titrated to 3 mg/day over 1 week. On Day 9, the subject's ALT was 3.6 × ULN and AST was 3.8 × ULN. On Day 15, the subject developed increased symptoms of anxiety; he did have a history of anxiety along with depression. The Investigator discontinued the cariprazine on Day 15 due to the anxiety. Labs from that day revealed CPK 35,290 U/L, an SAE, (reference range: 24-207 U/L), LDH 2.5 × ULN, AST 12.7 × ULN, ALT 5.6 × ULN, and GGT 2.1 × ULN. Also on Day 15, a urine toxicology screen was positive for cannabinoids.

On Day 18, labs decreased somewhat; CPK was 2792 U/L, AST was 2.7 × ULN, ALT was 3.6 × ULN, GGT was 1.7 × ULN. The same day, the urine toxicology screen was positive for benzodiazepine, cannabinoids, and opiates. On Day 31, CPK, LDH, AST, and ALT were within reference range, GGT was back to 1.4 × ULN; and urine screen was positive for benzodiazepine, cannabinoids, and phencyclidine. On Day 31, the SAE of blood creatine phosphokinase increased was resolved. The nonserious AE of anxiety resolved on Day 38. The Investigator considered the SAE of blood creatine phosphokinase increased and the AE of anxiety to be severe in intensity and related to investigational product.

Reviewer's Comment: The subject was assigned to the placebo + venlafaxine group prior to enrolling in the long-term cariprazine study. At screening, he already had increasing liver function tests (LFTs). The abnormal labs could have been related to venlafaxine (the postmarketing section of the PI says "abnormal liver function tests") or use of cannabinoids which also may cause increased LFTs and elevated CPK levels (Adedinsewo, 2016) (Fruman,

2021). *The cariprazine label lists blood CPK increased as known adverse reactions from the schizophrenia and bipolar I disorder trials. However, the timing of starting and stopping the cariprazine and likelihood of still having relatively high DDCAR levels about 3 weeks after stopping the cariprazine do not create a temporal relationship with the increased CPK and LFTs. In turn, the cariprazine, including the titration to 3 mg/day over 1 week is probably related to the subject's increased anxiety.*

Conclusion/Summary: Only two of the SAEs from the open-label safety study RGH-MD-76 may be related to cariprazine. Those are the deaths of Subjects 76. (b) (6) *and 72.* (b) (6)*, discussed in the section of this review under Deaths.*

Dropouts and/or Discontinuations Due to Adverse Effects

In all five safety and efficacy studies during the double-blind periods, subjects had more treatment emergent adverse events (TEAEs) leading to study discontinuation from the cariprazine arms (168 (168/1969=**8.5%**) compared to the placebo arms (34 (**3.1%**)), shown in Table 43. Those AEs include SAEs resulting in study discontinuation. More AEs leading to dropouts occurred in the higher dose cariprazine groups. The flexible-dose studies with high-dose arms (RGH-MD-72, RGH-MD-75) had 10% and 21% AEs leading to dropouts, which is more than from the high-dose, 3-mg cariprazine arm (7.2%) in the fixed-dose studies (3111-301-001, 3111-302-001).

Reviewer's Comment: Reasons for more subjects discontinuing from the flexible-dose studies than from the fixed-dose studies include a 2-week longer duration, dose titration over 1 week instead of 2 weeks, more limited rescue medication availability (i.e., no benzodiazepines), and some subjects took cariprazine at the higher dose of 4.5 mg/day. Cariprazine has dose-dependent AEs. It is notable that only one of the subjects with an SAE discussed above received cariprazine 4.5 mg/day + ADT; (The SAEs of depression and SI were not related to cariprazine 4.5 mg).

Table 45: Number of Dropouts by Treatment Arm (3111-301-001, 3111-302-001, RGH-MD-71, RGH-MD-72, RGH-MD-75)

	Cariprazine 0.1 to 0.3 mg/day + ADT (N=76)	Cariprazine 1 to 2 mg/day + ADT (N=346)	Cariprazine 1.5 mg/day + ADT (N=502)	Cariprazine 1.5 to 4.5 mg/day + ADT (N=269)	Cariprazine 2 to 4.5 mg/day + ADT (N=273)	Cariprazine 3 mg/day + ADT (N=503)	Placebo + ADT (N=1108)
Total n (%)	1 (1.3)	29 (8.4)	18 (3.6)	28 (10)	56 (21)	36 (7.2)	34 (3.1)

Source: Reviewer created from ISS ADAE.xpt dataset

Table 46, below, includes AEs and SAEs from the double-blind periods that led to study discontinuation from the five safety and efficacy studies. The listing is by system organ class

(SOC) and assigned treatment group. One or two asterisks denote one or two SAEs by the number of cases in the table. Discussion of certain cases and AEs that may be related to cariprazine are below the table.

Table 46: TEAEs & SAEs During Double-Blind Periods Leading to Study Discontinuation (3111-301-001, 3111-302-001, RGH-MD-71, RGH-MD-72, RGH-MD-75)

Dictionary-Derived Term	CAR 0.1 to 0.3 mg/day + ADT (N=76)	CAR 1 to 2 mg/day + ADT (N=346)	CAR 1.5 mg/day + ADT (N=502)	CAR 1.5 to 4.5 mg/day + ADT (N=269)	CAR 2 to 4.5 mg/day + ADT (N=273)	CAR 3 mg/day + ADT (N=503)	Placebo + ADT (N=1108)
Cardiac disorders							
Palpitations	0	1	0	0	0	0	0
Sinus tachycardia	0	1	0	0	0	0	0
Ventricular extrasystoles	0	0	0	0	0	1	0
Eye disorders							
Age-related macular degeneration	0	0	0	0	0	0	1
Blepharospasm	0	0	0	1	0	0	0
Vision blurred	0	0	1	4	1	1	0
Gastrointestinal disorders							
Abdominal pain upper	0	0	0	0	1	0	0
Constipation	0	1	0	0	0	0	0
Diarrhea	0	0	0	1	2	0	2
Dyspepsia	0	0	0	0	0	1	0
Dysphagia	0	0	0	0	0	1	0
Nausea	0	2	2	1	1	0	2
Vomiting	0	1	1	0	0	1	1
General disorders and administration site conditions							
Asthenia	0	0	0	0	1	1	1
Fatigue	0	2	0	1	4	2	2
Feeling abnormal	0	0	1	0	0	0	0
Immune system disorders							
Drug hypersensitivity	0	0	0	0	0	0	1

Dictionary-Derived Term	CAR 0.1 to 0.3 mg/day + ADT (N=76)	CAR 1 to 2 mg/day + ADT (N=346)	CAR 1.5 mg/day + ADT (N=502)	CAR 1.5 to 4.5 mg/day + ADT (N=269)	CAR 2 to 4.5 mg/day + ADT (N=273)	CAR 3 mg/day + ADT (N=503)	Placebo + ADT (N=1108)
Infections and infestations							
Pneumonia	0	0	0	0	0	0	1
Injury, poisoning and procedural complications							
Ligament sprain	0	1	0	0	0	0	0
Investigations							
Aspartate aminotransferase increased	0	1	0	0	0	0	0
Blood bilirubin increased	0	0	1	0	0	0	0
Blood pressure increased	0	1	0	0	0	0	0
Liver function test increased	0	0	0	1	0	0	0
Weight increased	0	0	0	0	0	0	1
Metabolism and nutrition disorders							
Dyslipidemia	0	1	0	0	0	0	0
Hyperglycemia	0	0	0	0	1	0	0
Musculoskeletal and connective tissue disorders							
Arthralgia	0	0	1	0	0	0	0
Intervertebral disc degeneration	0	0	0	0	1	0	0
Muscle fatigue	0	0	0	1	0	0	0
Muscle rigidity	0	0	0	0	1	0	0
Muscle spasms	0	1	0	1	1	0	1
Muscle tightness	0	0	0	0	1	0	1
Muscle twitching	0	0	1	0	0	0	0
Musculoskeletal pain	0	0	0	0	1	0	0
Myalgia	0	1	0	0	1	1	0

Dictionary-Derived Term	CAR 0.1 to 0.3 mg/day + ADT (N=76)	CAR 1 to 2 mg/day + ADT (N=346)	CAR 1.5 mg/day + ADT (N=502)	CAR 1.5 to 4.5 mg/day + ADT (N=269)	CAR 2 to 4.5 mg/day + ADT (N=273)	CAR 3 mg/day + ADT (N=503)	Placebo + ADT (N=1108)
Nervous system disorders							
Akathisia	0	2	3	6	13	11	3
Cognitive disorder	0	0	0	1	0	0	0
Disturbance in attention	0	0	0	0	1	0	0
Dizziness	0	0	0	0	4	1	0
Dyskinesia	0	0	0	0	0	0	1
Extrapyramidal disorder	0	0	0	1	0	0	0
Head discomfort	0	0	1	0	0	0	0
Headache	0	0	0	0	2	0	0
Migraine	0	0	0	0	0	0	1*
Multiple sclerosis	0	0	0	0	0	0	1*
Paraesthesia	0	0	0	0	0	1	0
Reduced facial expression	0	0	0	0	1	0	0
Restless legs syndrome	0	0	0	0	1	0	0
Seizure	0	0	0	0	0	0	1*
Somnolence	0	0	0	0	3	1	0
Stiff leg syndrome	0	0	1	0	0	0	0
Stupor	0	0	1	0	0	0	0
Syncope	0	0	0	0	0	1	0
Tension headache	1	0	0	0	0	0	0
Tremor	0	2	1	0	2	0	1
Psychiatric disorders							
Acute stress disorder	0	0	0	0	0	0	1
Agitation	0	0	0	0	2*	1	0
Alcohol abuse	0	0	0	1	0	0	0
Alexithymia	0	0	1	0	0	0	0
Anhedonia	0	0	0	0	1	0	0
Anxiety	0	0	0	1	1	1	2
Compulsive shopping	0	0	1	0	0	0	0

Dictionary-Derived Term	CAR 0.1 to 0.3 mg/day + ADT (N=76)	CAR 1 to 2 mg/day + ADT (N=346)	CAR 1.5 mg/day + ADT (N=502)	CAR 1.5 to 4.5 mg/day + ADT (N=269)	CAR 2 to 4.5 mg/day + ADT (N=273)	CAR 3 mg/day + ADT (N=503)	Placebo + ADT (N=1108)
Depression	0	1	0	0	1	1	2**
Disorientation	0	0	0	0	0	0	1
Insomnia	0	3	0	3	3	3	3
Poor quality sleep	0	0	0	0	0	0	1
Restlessness	0	2	0	2	3	2	0
Sleep disorder	0	1	0	0	0	0	0
Suicidal ideation	0	0	0	1*	0	0	0
Thinking abnormal	0	0	0	0	0	1	0
Renal and urinary disorders							
Glycosuria	0	0	0	0	1	0	0
Pollakiuria	0	1	0	0	0	0	0
Reproductive system and breast disorders							
Breast discomfort	0	0	0	0	0	1	0
Respiratory, thoracic, and mediastinal disorders							
Chronic obstructive pulmonary disease	0	1*	0	0	0	0	0
Skin and subcutaneous tissue disorders							
Hyperhidrosis	0	0	1	0	0	0	0
Rash	0	1	0	0	0	0	0
Rash maculo-papular	0	0	0	1	0	0	0
Rash pruritic	0	0	0	0	0	0	1
Urticaria	0	0	0	0	0	1	0
Vascular disorders							
Hot flush	0	1	0	0	0	1	0
Hypertension	0	0	0	0	0	0	1
Total n (%)	**1 (1.3)**	**29 (8.4)**	**18 (3.6)**	**28 (10)**	**56 (21)**	**36 (7.2)**	**34 (3.1)**

Source: Clinical Reviewer created from ISS ADAE.xpt dataset

Two subjects in the placebo + ADT groups from Studies 3111-301-001 and RGH-MD-75 had SAEs of worsening depression that led to study discontinuation. That is plausible due to lack of

efficacy of placebo, and subjects initially enrolled in the study already had an inadequate response to their ADT.

Reviewer's Comment: Table 47, below, tallies the dropouts by percentage and drug treatment arm by assigned dose. The most frequent AEs leading to study discontinuation and related to cariprazine are akathisia, restlessness, insomnia, fatigue, agitation, tremor, somnolence, dizziness, myalgia, muscle spasms, vomiting, nausea, and vision blurred. Discontinuations from different types of extrapyramidal symptoms (EPS) were also prevalent. These reasons for study discontinuation generally align with the reported TEAEs (discussed in section Treatment Emergent Adverse Events and Adverse Reactions) from all five safety and efficacy trials. The most frequent AEs leading to discontinuation that are dose-dependent are: akathisia, agitation, somnolence, and fatigue.

Table 47: Percent of Common Cariprazine AEs Leading to Dropout (3111-301-001, 3111-302-001, RGH-MD-71, RGH-MD-72, RGH-MD-75)

Dictionary-Derived Term of AE leading to D/C	All CAR + ADT N=1969 (%)	Placebo + ADT N=1108 (%)
Akathisia	35 (1.8)	3 (0.3)
Restlessness	9 (0.5)	0 (0)
Insomnia	12 (0.6)	3 (0.3)
Fatigue	9 (0.5)	2 (0.2)
Depression	3 (0.2)	2 (0.2)
Anxiety	3 (0.2)	2 (0.2)
Agitation	3 (0.2)	0 (0)
Tremor	5 (0.3)	1 (0.1)
Somnolence	4 (0.2)	0 (0)
Dizziness	5 (0.3)	0 (0)
Myalgia	3 (0.2)	0 (0)
Muscle spasms	3 (0.2)	1 (0.1)
Vomiting	3 (0.2)	1 (0.1)
Nausea	6 (0.3)	2 (0.2)
Diarrhea	3 (0.2)	2 (0.2)
Vision blurred	7 (0.4)	0 (0)

Source: Clinical Reviewer created from Table 44 in this review

In Study RGH-MD-75, there were major discrepancies in the number of AEs occurring during the double-blind period that led to study discontinuation, as in Table 46. We issued an information request to the Applicant on October 28, 2022. There were differences between the datasets from Study RGH-MD-75 and the integrated summary of safety (ISS). Regardless of the discrepancies, the number of AEs leading to dropouts from the high-dose arm of RGH-MD-75 is 21% which is concerning. The high-dose group is the arm of the study with positive efficacy

results. (We will further analyze this issue in a later section looking at AEs related to specific doses within the flexible dose arms.)

Table 48: Alternate Numbers of AEs Leading to D/C from Study RGH-MD-75

	CAR 1 to 2 mg/day + ADT (N=273) (%)	CAR 2 to 4.5 mg/day + ADT (N=273) (%)	Placebo + ADT (N=266) (%)
Applicant's CSR AE leading to dropout n (%)	18 (6.6) 18 subjects D/C from AE (Table 12.2.1-1)	36 (13) 36 subjects D/C from AEs	8 (3) 8 subjects D/C from AEs
Reviewer's from ISS ADAE.xpt (Study RGH-MD-75) AE leading to dropout n(%)	27 (10) Excluded 2 subjects that did not have phase of trial marked as DB or TEAE flag	56 (21) Excluded 2 subjects that did not have phase of trial marked as DB or TEAE flag	8 (3)
Reviewer's from RGH-MD-75 ADAE.xpt dataset	21 (7.7)	28 (10)	7 (2.6)
Applicant's Response AE leading to D/C	29 (11)	58 (21)	8 (3)

Source: Clinical Reviewer modified Table 12.2.1-1 from RGH-MD-75 CSR and ISS ADAE.xpt dataset

October 28, 2022 Information Request:

> Please provide data on the number of subjects per treatment group who discontinued (D/C) Study RGH-MD-75. In the CSR for RGH-MD-75, Table 10.1-1 Patient Disposition-Safety Population lists the number of subjects that D/C'd due to AEs. Those numbers are much smaller than the ADAE.xpt dataset list of subjects where the outcome of the AE was Discontinued Trial. For example, from the dataset, in the cariprazine 1 to 2 mg/day + ADT arm, there were a total of 27 (9.9%) AEs leading to D/C and in the 2 to 4.5 mg/day + ADT arm, there were 56 (21%). Also, The Table 10.1-1 also lists "withdrawal of consent"; are any of the reasons for withdrawal of consent AE-related? Please provide information for the discrepancy in number of subjects who D/C'd RGH-MD-75 for reasons of AEs.

November 2, 2022 Applicant's Response

> AbbVie confirms that there is no discrepancy between the CSR tables and ADAE.xpt dataset in the number of subjects who discontinued due to adverse events (AEs) in Study RGH-MD-75. AbbVie would like to clarify that some subjects who discontinued due to an AE had more than one AE that led to discontinuation. The number of subjects who prematurely discontinued due to AEs was 8 subjects in the placebo + ADT arm, 18 subjects in cariprazine 1 to 2 mg/day + ADT arm, and 36 subjects in cariprazine 2 to 4.5 mg/day + ADT arm as shown in the CSR Table 10.1-1 (source Table 14.1.3) and Table 12.2.1-1 (source Table 14.5.1.1A) as well as in ADAE.xpt dataset.

The Applicant provided the number of AEs leading to premature discontinuation in the last row of Table 46. They said that the difference in number of AEs leading to premature discontinuation in the ADAE.xpt dataset between AbbVie and the Agency may be due to SAS codes.

AbbVie confirms that, for subjects who prematurely discontinued due to withdrawal of consent, none of them were AE-related. That is based on their directions to Investigators about how AEs take precedence over other reasons for discontinuations.

Reviewer's Comment: In the RGH-MD-75 dataset, ADaM ADAE.xpt, I captured "Y" for all the subjects in the safety population, treatment emergent analysis flag, AE Leading to Drop Out Flag and Action Taken with Study Treatment. Subjects 75. (b) (6) *and 75.* (b) (6) *assigned to cariprazine 1 to 2 mg/day + ADT did not have any study period ("Phase" was column header) nor treatment emergent analysis flag listed. When I included those two subjects in my analysis, the number of AEs leading to dropouts (29 cariprazine 1 to 2 mg/day, 58 cariprazine 2 to 4.5 mg/day, 8 placebo) and the number of subjects who dropped out (18, 36, 8, respectively) matched the Applicant's. Some subjects in the cariprazine arms had more than one AE leading to discontinuation.*

Significant Adverse Events

The Applicant lists akathisia as a significant AE. Akathisia was the most frequent reason for study discontinuations and is dose-dependent. It appears to be worse when cariprazine is titrated in periods of time shorter than 2 weeks. However, during the fixed-dose studies where the cariprazine 3 mg/day arms were titrated over 2 weeks, there were almost the same number of dropouts due to akathisia (i.e., 11 versus 13) as in the high-dose arm of Study RGH-MD-75.

The onset of akathisia may be delayed by 4 weeks when the dose of cariprazine is increased due to the longer-lasting major metabolites of cariprazine, DCAR and DDCAR. Refer to 8.2.4 Safety Results for discussion of the metabolites' half-lives. When stopping cariprazine or reducing the dose due to akathisia, the akathisia will linger until the levels of DCAR and DDCAR have diminished, which may take weeks.

Treatment Emergent Adverse Events and Adverse Reactions

The most common AEs (>5%) from Studies 3111-301-001, 3111-302-001, and RGH-MD-75 are: akathisia, nausea, insomnia, restlessness, fatigue, somnolence, and extrapyramidal syndrome (EPS). These AEs align with the AEs leading to study discontinuation. The EPS AEs include many types of spasms, dystonias, and Parkinsonian symptoms.

Table 49 shows AEs that occurred >2% in the cariprazine + ADT groups and greater than in the placebo group in the 6-week, fixed-dose studies. All but five of the AEs are dose-dependent between the cariprazine 1.5 and 3 mg/day + ADT arms. The dictionary-derived MedDRA terms that were combined under akathisia, somnolence, EPS, and insomnia are listed under the table.

Table 49: AEs from 3111-301-001 and 3111-302-001

System Organ Class/ Dictionary-derived Term	CAR 1.5 mg/day + ADT (N=502) n (%)	CAR 3 mg/day + ADT (N=503) n (%)	Placebo + ADT (N=503) n (%)
Gastrointestinal Disorders			
Nausea	34 (6.8)	32 (6.4)	15 (3)
Dry Mouth	14 (2.8)	14 (2.8)	8 (1.6)
Constipation	12 (2.4)	12 (2.4)	7 (1.4)
Vomiting	7 (1.4)	10 (2)	4 (0.8)
General Disorders			
Fatigue	14 (2.8)	13 (2.6)	10 (2)
Investigations			
Weight increased	10 (2)	11 (2.2)	3 (0.6)
Nervous system disorders			
Akathisia	34 (6.8)	51 (10)	10 (2)
Somnolence	28 (5.6)	31 (6.2)	3 (0.6)
Extrapyramidal Symptoms	32 (6.4)	32 (6.4)	15 (3)
Psychiatric disorders			
Anxiety	8 (1.6) rounds to 2	5 (1)	0 (0)
Insomnia	43 (8.6)	48 (9.5)	30 (6)
Restlessness	18 (3.6)	12 (2.4)	0 (0)
Skin and subcutaneous disorders			
Hyperhidrosis	4 (0.8)	12 (2.4)	7 (1.4)
Eye disorders			
Vision blurred	2 (0.4)	8 (1.6) rounds to 2	1 (0.2)

Source: Clinical Reviewer created from ISS ADAE.xpt dataset

[a]**Akathisia terms:** psychomotor hyperactivity, feeling jittery, nervousness, tension
[b]**Somnolence terms**: hypersomnia, sedation, lethargy, somnolence
[c]**Extrapyramidal symptoms terms**: drooling, dyskinesia, extrapyramidal disorder, hypotonia, muscle contractions involuntary, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, myoclonus, oromandibular dystonia, parkinsonism, psychomotor hyperactivity resting tremor, restless legs syndrome, stiff leg syndrome, salivary hypersecretion, stiff tongue, tardive dyskinesia, stiff tongue, tremor, trismus
[d]**Insomnia terms**: initial insomnia, insomnia, middle insomnia, poor sleep quality, sleep disorder, terminal insomnia

Table 48 shows AEs that occurred >2% in the cariprazine + ADT groups and greater than in the placebo group in the 8-week, flexible-dose study, RGH-MD-75. Like the fixed-dose studies, most of the AEs appear dose-dependent, especially those AEs that led to study discontinuation. The dictionary-derived MedDRA terms that were combined under akathisia, somnolence, EPS, and insomnia are listed under the table.

Table 50: AEs from RGH-MD-75

System Organ Class/ Dictionary-derived Term	CAR 1 to 2 mg/day + ADT (N=273) (%)	CAR 2 to 4.5 mg/day + ADT (N=273) (%)	Placebo + ADT (N=266) (%)
Cardiac disorders			
Palpitations	6 (2.2)	1 (0.4)	2 (0.8)
Eye disorders			
Vision blurred	4 (1.5)	10 (3.7)	2 (0.8)
Gastrointestinal disorders			
Constipation	6 (2.2)	14 (5.1)	5 (1.9)
Dry mouth	14 (5.1)	10 (3.7)	7 (2.6)
Nausea	19 (7)	35 (13)	13 (4.9)
Vomiting	4 (1.5)	7 (2.6)	1 (0.4)
General disorders			
Asthenia	3 (1.1)	5 (1.8)	0 (0)
Fatigue	18 (6.6)	26 (9.5)	11 (4.1)
Edema	6 (2.2)	3 (1.1)	1 (0.4)
Infections			
Nasopharyngitis	10 (3.7)	4 (1.5)	6 (2.3)
Rhinitis	0 (0)	4 (1.5)	0 (0)
Investigations			
Weight increased	6 (2.2)	7 (2.6)	3 (1.1)
Increased appetite	6 (2.2)	14 (5.1)	4 (1.5)
Musculoskeletal and connective tissue disorders			
Back pain	5 (1.8)	7 (2.6)	2 (0.8)
Myalgia	3 (1.1)	7 (2.6)	0 (0)
Pain in extremity	4 (1.5)	2 (0.7)	1 (0.4)
Nervous system disorder			
Akathisia	19 (7)	62 (23)	7 (3)
Dizziness	11 (4)	15 (5.5)	5 (1.9)
Extrapyramidal symptoms	32 (12)	47 (17)	12 (5)
Somnolence	29 (11)	30 (11)	16 (6)
Psychiatric disorders			
Agitation	1 (0.4)	7 (2.6)	1 (0.4)
Anxiety	3 (1.1)	8 (2.9)	1 (0.4)
Restlessness	21 (7.7)	25 (9.2)	7 (2.6)
Insomnia	40 (15)	45 (16)	21 (7.9)
Renal and urinary disorders			
Pollakiuria	4 (1.5)	2 (0.7)	2 (0.8)
Skin and subcutaneous tissue disorders			

System Organ Class/ Dictionary-derived Term	CAR 1 to 2 mg/day + ADT (N=273) (%)	CAR 2 to 4.5 mg/day + ADT (N=273) (%)	Placebo + ADT (N=266) (%)
Rash	4 (1.5)	0 (0)	1 (0.4)

Source: Clinical Reviewer created from RGH-MD-75 ADAE.xpt and ISS ADAE.xpt datasets

[a]**Akathisia terms:** psychomotor hyperactivity, feeling jittery, nervousness, tension
[b]**Extrapyramidal symptoms terms**: cogwheel rigidity, drooling, dyskinesia, extrapyramidal disorder, hypertonia, jaw stiffness, muscle contractions involuntary, muscle disorder, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, nuchal rigidity, parkinsonism, psychomotor retardation, reduced facial expression, resting tremor, restless legs syndrome, sensation of heaviness, salivary hypersecretion, tremor
[c]**Somnolence terms**: hypersomnia, sedation, lethargy, somnolence
[d]**Insomnia terms**: initial insomnia, insomnia, middle insomnia, terminal insomnia, sleep disorder, poor sleep quality

Reviewer's Comment:

Subjects in the 8-week, flexible-dose study, RGH-MD-75, reported more AEs compared to the incidence of AEs in the 6-week fixed-dose studies. Fixed-dose studies are generally better than flexible-dose studies for characterizing the safety profile of a drug in a particular indication.

The mean doses per cariprazine treatment arms in Study RGH-MD-75 were 1.4 mg/day in the 1 to 2 mg/day + ADT group and 2.6 mg/day in the 2 to 4.5 mg/day + ADT group. Because the mean doses are slightly less than the cariprazine 1.5 and 3 mg/day doses in the fixed-dose studies, we would expect fewer AEs. However, that was not the outcome of the rate comparison of AEs between the fixed- and flexible-dosed studies for cariprazine here. As previously discussed, reasons for a greater number of AEs from the flexible-dose Study RGH-MD-75 may be related to a longer study duration (8 weeks), where the DDCAR can accumulate to steady state; also there was a steeper titration schedule to a higher maximum dose of 4.5 mg as compared to the fixed-dose studies and more availability of rescue medications such as benzodiazepines in the fixed-dose studies to mitigate AEs.

Known Cariprazine Safety Profile:

In the schizophrenia development program, 6-week trials included dosage arms of 1.5 to 3 mg/day. Observed AEs are similar as those in the two adjunctive MDD fixed-dose studies (3111-301-001 and 3111-302-001) and Study RGH-MD-75. The incidence of AEs in the schizophrenia trials was higher for EPS (15%) than the 6% observed in the fixed-dose MDD studies, but nearly the same as in the flexible-dose MDD low- (12%) and high-dose (17%) arms.

More of the following AEs were observed in the adjunctive MDD development program than in the schizophrenia program:

- Akathisia 23% vs. 9%.
- Restlessness 8 to 9% vs. 4%.
- Somnolence 11% (flex-dose) vs. 5%.

- Fatigue 3% (fixed-dose) to 10% (2 to 4.5 mg) vs. 1% (1.5 to 3 mg) to 3% (4.5 to 6 mg)

Comparisons are more difficult to the 3-week trials of subjects with manic and mixed episodes in bipolar I disorder which were of shorter duration using higher dosages. The cariprazine low dose for acute mania was 3 to 6 mg/day, which is higher than in the adjunctive MDD program. Generally, the rates of akathisia, EPS, and gastrointestinal-related symptoms were higher in the mania in bipolar I disorder trials compared to rates in the adjunctive MDD trials, likely reflecting dose-dependent issues.

Subjects being treated with adjunctive cariprazine for MDD reported more types of AEs than subjects taking the drug for treatment of depressive episodes of bipolar I disorder for 6 or 8 weeks with the same dosages (i.e., 1.5 or 3 mg/day). Where the AEs were the same between the populations, the incidences were still similar when both populations took fixed-dose cariprazine 1.5 or 3 mg. When taking Study RGH-MD-75 into account, the rates and types of AEs were still overall greater in the MDD population than in subjects with depressive episodes of bipolar I disorder.

In conclusion, subjects with MDD have reported more akathisia, restlessness, somnolence, and fatigue than for other approved indications at the same dosages, and these seem to be dose- and duration-dependent. Reasons for this potential difference otherwise remain unclear. This trend mirrors similar tolerability patterns across indications to quetiapine XR **(Wang, 2011)**.

Anticholinergic Properties:

Subjects taking cariprazine reported many anticholinergic-related AEs, such as blurred vision, dry mouth, and constipation. Like most atypical antipsychotics, cariprazine has anticholinergic properties. Anticholinergic drugs were also administered in the studies to treat AEs of EPS and akathisia, yet subjects receiving cariprazine still experienced 7 to 23% AE rates of akathisia and EPS. The concomitant use of propranolol (not an anticholinergic) was 2.4% for treatment of akathisia in Study 3111-301-001 and benztropine 4% in Study RGH-MD-75. In Study 3111-302-001, there was less than 2% use of any allowed rescue medications for symptoms of akathisia or EPS. The relatively low amount of rescue medications compared to the amount of reported akathisia and EPS appears counterintuitive. Yet, the study discontinuations from akathisia and EPS (individual terms such as muscle spasms, etc.) were relatively high compared to dropouts for other reasons.

Study RGH-MD-75 AEs from Cariprazine 4.5 mg/day + ADT:

In the 8-week, flexible-dose study RGH-MD-75, the safety population contains 812 subjects. Of those, 266 were randomized to the placebo + ADT arm, 273 to cariprazine 1 to 2 mg/day + ADT, and 273 to cariprazine 2 to 4.5 mg/day + ADT. In the high-dose cariprazine group, 91 subjects took cariprazine 4.5 mg/day.

I conducted a safety analysis of the 91 subjects who received cariprazine 4.5 mg/day for at least part of the 8-week double-blind period to assess if this cohorts' AEs were driving the 21% (56/273) rate of study discontinuation from the high-dose treatment group. After experiencing AEs, some Investigators reduced the subjects' dose to 3 mg or the subjects dropped out of the trial. Of the 91 subjects taking cariprazine 4.5 mg/day + ADT, three (3.4%) of them experienced an AE leading to study discontinuation. The AEs were akathisia, somnolence, and in one subject: vision blurred, fatigue, and insomnia.

Of those 91 subjects who were titrated to cariprazine 4.5 mg, 64 (70%) experienced AEs. Some subjects had one AE, the maximum number of AEs per subject was 9, and the average number of AEs was 2.5. The overall rate of AEs per treatment arm of Study RGH-MD-75 was 69% in the 1 to 2 mg/day + ADT arm, 55% in the 2 to 4.5 mg/day + ADT arm (excludes subjects on 4.5 mg), and 60% rate of AEs in the placebo + ADT arm, shown in Table 49.

Table 51: Overall Rate of AEs per Treatment Arm (RGH-MD-75)

	CAR 1 to 2 mg/day + ADT (N=273)	CAR 2 to 4.5 mg/day + ADT (N=273) Includes subjects on 4.5 mg	CAR 4.5 mg/day + ADT (N=91)	Placebo + ADT (N=266)
Subjects with at least 1 AE	189 (69%)	214 (79%)	64 (70%)	157 (60%)
		150 (55%) excludes 4.5 mg subjects		
Average # AE/subject	2.5	2.7	2.5	2.2
		2.8 excludes the 4.5 mg subjects		

Source: Reviewer created from ADAE.xpt RGH-MD-75

Table 50 displays the AEs over 2% experienced by those subjects who received cariprazine 4.5 mg + ADT (N=91) compared to the placebo + ADT (N=266) arm. Additionally, Table 50 shows all subjects' AEs of those assigned to high-dose group (N=273) and AEs in the high-dose group excluding the AEs from the subjects who received 4.5 mg/day + ADT (N=182). The AEs are similar between all three cariprazine dosage groups; however, the greatest rates were generally experienced by those subjects in the cariprazine 2 to 4.5 mg/day + ADT group not including those taking 4.5 mg/day (i.e., cariprazine 2 to 3 mg/day). The most common (>5%) AEs in the 4.5 mg/day cohort were: nausea, fatigue, arthralgia, akathisia, somnolence, tremor, and insomnia. For purposes of the analysis of AEs in subjects taking cariprazine 4.5 mg/day + ADT, I

did not incorporate the lower level terms into higher levels one (e.g., middle insomnia added to the number of AEs for insomnia).

Table 52: AEs >2% in Cariprazine 4.5 mg + ADT arm vs. Placebo + ADT

Body System	Dictionary Derived Term	CAR 4.5 mg/day + ADT (N=91 (%))	CAR 2 to 4.5 mg/day + ADT (N=182 (%))	CAR 2 to 4.5 mg/day + ADT (N=273 (%))	Placebo + ADT (N=266 (%))
Eye disorders	Vision blurred	3 (3.3)	7 (3.8)	10 (3.7)	2 (0.8)
Gastrointestinal disorders	Constipation	4 (4.4)	10 (5.5)	14 (5.1)	5 (1.9)
	Dry mouth	4 (4.4)	6 (3.3)	10 (3.7)	5 (1.9)
	Nausea	9 (9.9)	26 (14)	35 (13)	13 (4.9)
	Vomiting	2 (2.2)	5 (2.7)	7 (2.6)	1 (0.4)
General disorders	Fatigue	13 (14)	13 (7.1)	26 (9.5)	11 (4.1)
Infections	Rhinitis	2 (2.2)	2 (1.1)	4 (1.5)	0 (0)
	Urinary tract infection	2 (2.2)	2 (1.1)	0 (0)	5 (1.9)
Investigations	Gamma-glutamyltranferase increased	2 (2.2)	3 (1.6)	0 (0)	4 (1.5)
Metabolism and nutrition disorders	Increased appetite	4 (4.4)	10 (5.5)	14 (5.1)	4 (1.5)
Musculoskeletal and connective tissue disorders	Arthralgia	5 (5.5)	3 (1.6)	0 (0)	4 (1.5)
	Back pain	2 (2.2)	5 (2.7)	7 (2.6)	2 (0.8)
Nervous system disorders	Akathisia	13 (14)	53 (29)	62 (23)	6 (2.3)
	Dizziness	4 (4.4)	11 (6)	15 (5.5)	5 (1.9)
	Somnolence	8 (8.8)	20 (11)	30 (11)	13 (4.9)
	Tremor	7 (7.7)	14 (7.7)	19 (7)	4 (1.5)
Psychiatric disorders	Anxiety	2 (2.2)	6 (3.3)	8 (2.9)	1 (0.4)
	Insomnia	8 (8.8)	30 (17)	45 (16)	16 (6)

Source: Reviewer created ADAE.xpt from RGH-MD-75

Reviewer's Comment: The purpose of tabulating the AEs in the subjects who received cariprazine 4.5 mg/day + ADT was to assess if those AEs were driving the high rate (21%) of

study discontinuation and the incidence of AEs in the high-dose cariprazine arm (2 to 4.5 mg/day) of Study RGH-MD-75. The subjects in that treatment arm experienced the greatest rates of AEs in the adjunctive treatment of MDD phase 3 program (i.e., Studies 3111-301-001, 3111-302-001, RGH-MD-75). Yet, the efficacy of the high-dose arm was positive so the benefits of taking cariprazine >1.5 mg/day should be weighed against the risks. The Applicant's proposed recommended doses are 1.5 and 3 mg/day + ADT.

With the exception of the AEs of arthralgia and fatigue in the 91 subjects taking 4.5 mg, the percentages of AEs were higher in the 182 subjects who received 2 to 3 mg/day in the high-dose arm of Study RGH-MD-75, indicating that this cohort experienced more AEs, including those leading to study discontinuation. For example, the 29% akathisia AEs (Table 50) led to a 6.6% rate of dropouts due to akathisia. Only one subject taking 4.5 mg/day dropped out of the study from akathisia. Subjects who received 4.5 mg/day and experienced AEs did not drive the higher incidence of AEs in the high-dose arm of Study RGH-MD-75.

The high-dose (2 to 4.5 mg/day) arm of the flexible-dose study had a discontinuation rate of 21%. The rate in the low-dose (1 to 2 mg/day) arm was 8.4%. (Refer to Table 43.) Based on the subject listings in the CSR for RGH-MD-75, a portion of the 273 subjects in the high-dose arm remained at 1.5 or 2 mg/day during the 8-week study. The mean dose of this treatment arm was 2.6 mg/day. Most of the 273 subjects in the high-dose arm were actually receiving cariprazine 1.5 to 3 mg/day, yet reported more AEs and had a higher rate of study discontinuation than subjects taking 4.5 mg or those in the low-dose cariprazine arm. In contrast, in the fixed-dose studies, the drop-out rate in the high-dose (3 mg/day) arm was 7.2%, not 21%. The greater tolerability (than the high-dose flexible study arm) and lower dropout rate of the fixed-dose studies (3111-301-001, 3111-302-001) is likely from a slower titration schedule over 2 weeks, rather than 1 week. However, we will still not recommend the 4.5-mg dose, given that there is still a increased risk of additional AEs (given the overall dose-dependent nature of AEs with cariprazine) without any confirmed additional benefit.

Laboratory Findings

The laboratory safety profile for cariprazine from Studies RGH-MD-75, 3111-301-001, and 3111-302-001 was generally consistent with the drug's known safety profile.

Hematology Parameters
In Study RGH-MD-75, the hematology-related findings were similar between the cariprazine groups and the placebo group.

In Studies 3111-301-001 and 3111-302-001, the hematology-related findings were similar between the cariprazine groups and the placebo group.

Chemistry Parameters
The chemistry panels included sodium, chloride, potassium, magnesium, calcium, total protein, uric acid, lactate dehydrogenase, fasting and nonfasting glucose, creatinine, and blood urea

nitrogen.

In Study RGH-MD-75, the findings on the chemistry panels over time were similar between the cariprazine groups and the placebo group. The change from baseline to the end of the 8-week trial in mean fasting glucose is shown in Table 53. Changes are small and similar among treatment groups. One subject reported elevated glucose in the high-dose arm of Study RGH-MD-75.

Table 53: Change from Baseline in Fasting Glucose (Study RGH-MD-75)

Glucose mmol/L	n	Placebo + ADT (N=266)	n	CAR 1 to 2 mg/day + ADT (N=273)	n	CAR 2 to 4.5 mg/day + ADT (N=273)
Baseline	262	5.2 ± 0.7	265	5.2 ± 0.8	263	5.2± 0.7
Change from baseline to end of trial	262	0.1 ± 0.8	265	0.1 ± 0.9	263	0.2 ± 0.8

Source: Clinical Reviewer modified Table 12.4.2.1.2-1 from RGH-MD-75

In Studies 3111-301-001 and 3111-302-001, the findings on the chemistry panels (except for fasting glucose) over time were similar between the cariprazine groups and the placebo groups.

Table 54 displays the number of subjects with changes in fasting glucose from baseline. The shifts from normal to high were greatest in the cariprazine 3 mg/day + ADT group (3.2%) compared to the cariprazine 1.5 mg/day + ADT (2%) and placebo + ADT group (1.3%). There was also a dose-related change >10 mg/dL in the cariprazine 3 mg/day + ADT group (28%) that was greater than occurred with the cariprazine 1.5 mg/day + ADT (22%) or placebo + ADT groups (20%).

In Study 3111-301-001 there was one case of Type 2 diabetes reported during the follow-up period of the cariprazine 1.5 mg/day arm. One subject had elevated glucose in the cariprazine 1.5 mg/day arm of Study 3111-301-001.

Table 54: Shifts in Fasting Glucose by Treatment Arm (3111-301-001, 3111-302-001)

Fasting Glucose mg/dL	Baseline	Postbaseline	Placebo + ADT (N=503) (%)	CAR 1.5mg/day + ADT (N=502) (%)	CAR 3mg/day + ADT (N=503) (%)
Normal to High	< 100	>= 126	4/297 (1.3)	6/302 (2)	10/309 (3.2)
Normal to Impaired	< 100	>= 100 & < 126	56/297 (19)	54/302 (18)	65/309 (21)
Impaired to High	>= 100 & < 126	>= 126	7/90 (7.8)	9/96 (9.4)	8/87 (9.2)
Normal/Impaired to High	< 126	>= 126	11/387 (2.8)	15/398 (3.8)	18/396 (4.5)

Change >= 10 mg/dL	Any Value	Increase >= 10	80/402 (20)	91/413 (22)	112/405 (28)

Source: Clinical Reviewer modified Table 19 from Module 2.7.4 Summary of Clinical Safety

Reviewer's Comment: Metabolic syndrome, including increases in blood glucose, is a known risk of atypical antipsychotic treatment. Cariprazine treatment appears to be associated with dose-related elevations in fasting glucose. Even the pooled cariprazine dose groups have a 25% rate of changes > 10 mg/dL compared to 20% in the placebo group from Studies 3111-301-001 and 3111-302-001. (For reference, in the trials for adjunctive treatment of MDD with brexpiprazole, 32% of subjects in the all brexpiprazole + ADT group had a postbaseline fasting glucose (any visit) that increased >10 mg/dL, compared with 29% of subjects in the placebo + ADT group.)

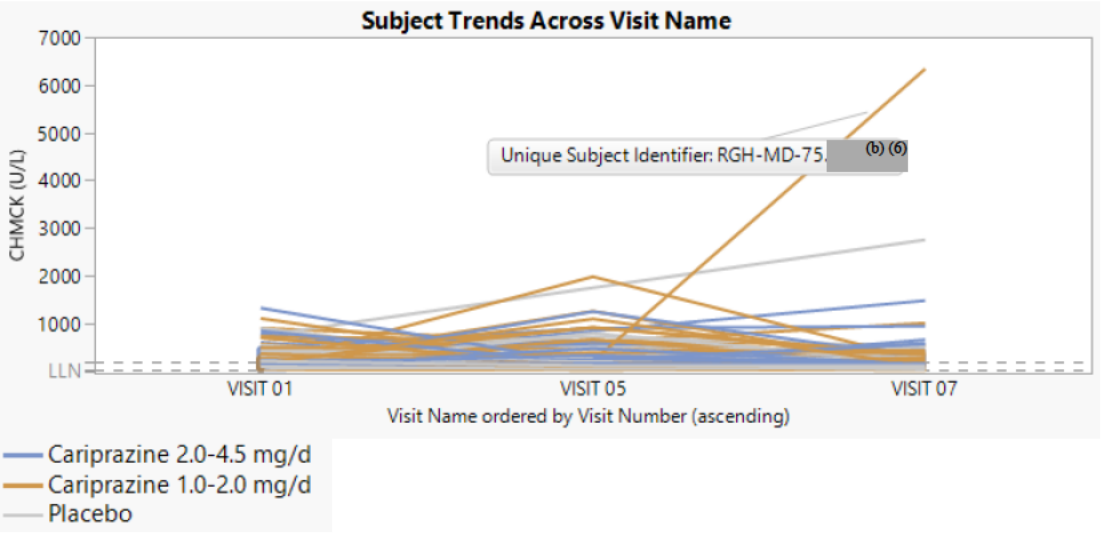
The mean change in glucose levels is relatively small, but could be clinically meaningful for susceptible subjects, especially over time.

Creatinine Phosphokinase

In Study RGH-MD-75, the chemistry panels among treatment groups were similar except for mean CPK elevations in the low- and high-dose cariprazine + ADT arms. The mean change from baseline creatinine kinase after 8 weeks in the placebo group was 8.2 U/L, low-dose cariprazine was 18 U/L, and high-dose cariprazine 9.8 U/L. Figure 18 displays the trend of increasing CPK over time. Four cases of CPK increased occurred in the study with two subjects in each cariprazine group (0.7%). No cases of CPK increased occurred in the placebo group.

Figure 18 illustrates CPK over time in RGH-MD-75, with a notable outlier in Subject (b) (6) assigned to cariprazine 1 to 2 mg/day + duloxetine. This subject had a baseline CPK of 125 U/L that increased to 6336 U/L at Week 8. The CPK value decreased to 199 U/L 6 days after cariprazine 2 mg/day was discontinued at the end of the trial.

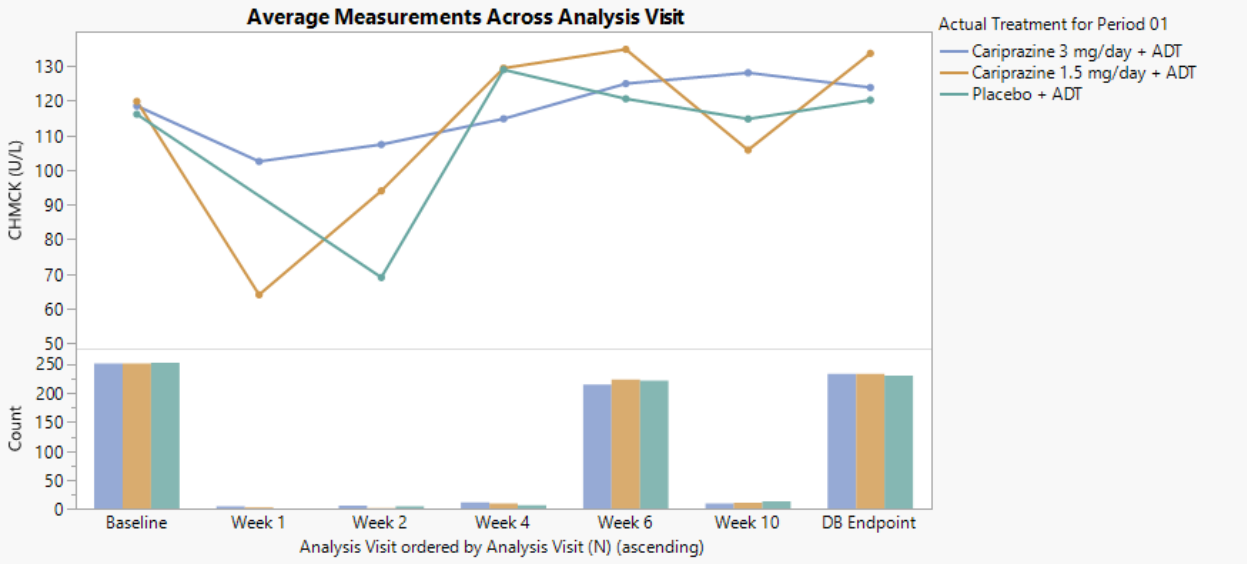
Figure 15: Creatinine Phosphokinase Over Time (RGH-MD-75)



Source: Reviewer created using JMP Clinical 8.0

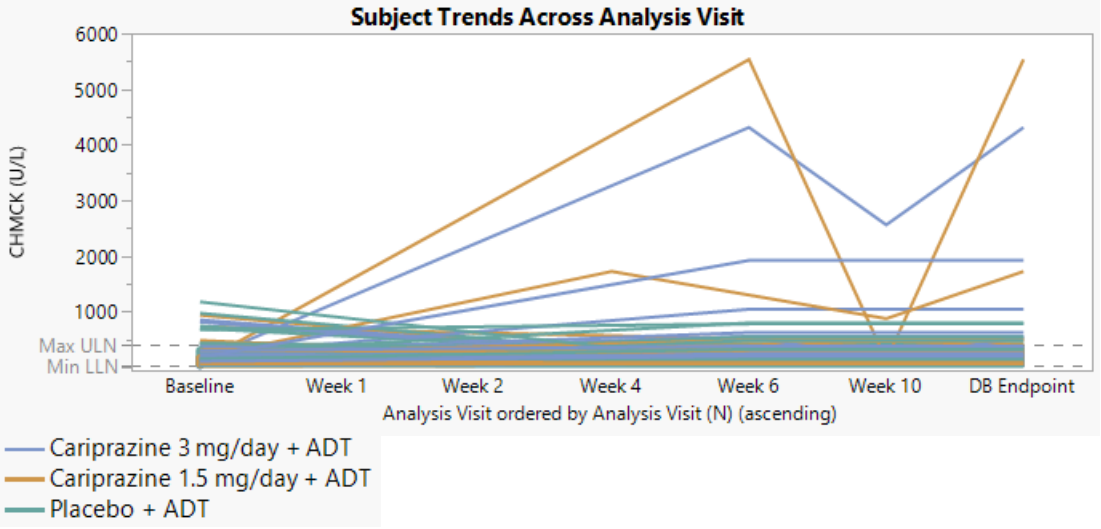
In Studies 3111-301-001 and 3111-302-0001, there were more cases of increased CPK in the cariprazine 1.5 mg/day (4/502=0.8%) and 3 mg/day (4/503=0.8%) arms than in the placebo (0) arms. In Figure 19 from Study 3111-301-001 and Figure 20 from 3111-302-001, the increased CPK values over time in the cariprazine groups are noticeable.

Figure 16: Increased Creatinine Phophokinase Over Time (Study 3111-301-001)



Source: Reviewer created using JMP Clinical 8.0

Figure 17: Increased Creatinine Phosphokinase Over Time (Study 3111-302-001)



Source: Reviewer created using JMP Clinical 8.0

No AEs of rhabdomyolysis were reported during Studies RGH-MD-75, 3111-301-001, nor 3111-

302-001 or any other signs of neuroleptic malignant syndrome.

In the long-term open-label Study RGH-MD-76, there was an SAE of CPK increased to 35,290 U/L. The SAE resolved. The case is discussed in the section on Serious Adverse Events.

Reviewer's Comment: Although Figures 15, 16, and 17 display trends of CPK increasing over time, there were relatively few cases of CPK increased during the adjunctive treatment of MDD development program. The rate of elevated CPK based on cases per treatment arm in the fixed-dose studies (3111-301-001, 3111-302-001) and the flexible-dose study (RGH-MD-75) was, respectively, 0.7% and 0.8% for both cariprazine dose arms versus 0% in the placebo arms of the three studies.

As mentioned under Product Introduction, doses of cariprazine 9 to 12 mg/day for treatment of schizophrenia were associated with elevated CPK levels; the original NDA application initially received a complete response action due to dose-dependent safety signals, including increased CPK. Cariprazine was ultimately approved with a lower range of recommended doses. According to the current PI for cariprazine, the rate of CPK increased in subjects with schizophrenia taking cariprazine 1.5 to 3 mg/day is 1% vs. 1% in placebo subjects. In the acute mania in bipolar I disorder program, 2% of subjects in the cariprazine 3 to 6 mg/day group (the lowest dosage range for that indication) experienced increased CPK compared to 2% in the placebo arm. CPK increased is not listed in the adverse reactions table for bipolar I depression where the cariprazine dose was 1.5 or 3 mg/day.

> *From the PI: The proportions of patients with elevations of creatine phosphokinase (CPK) greater than 1000 U/L in 6-week schizophrenia trials ranged between 4% and 6% for VRAYLAR-treated patients, increasing with dose, and was 4% for placebo-treated patients. The proportions of patients with elevations of CPK greater than 1000 U/L in 3-week bipolar mania trials was about 4% in VRAYLAR and placebo-treated patients. The proportions of patients with elevations of CPK greater than 1000 U/L in 6-week and 8-week bipolar depression trials ranged between 0.2% and 1% for VRAYLAR-treated patients versus 0.2% for placebo-treated patients.*

The excerpt from the cariprazine PI lists the proportion of subjects with elevated CPK where levels were >1000 U/L. The two cases of elevated CPK during the cariprazine adjunctive treatment of MDD program were much higher than 1000 U/L (i.e., 6336; 35,000+ U/L) but resolved after stopping cariprazine. The proportion of subjects with MDD who experienced increased CPK was smaller than in the schizophrenia or bipolar I disorder mania development programs.

Liver Test Parameters
In Study RGH-MD-75, the individual tests were alanine aminotransferase (ALT), alkaline phosphatase, aspartate aminotransferase (AST), and bilirubin. The bilirubin findings (e.g., total, direct, and indirect) in both cariprazine groups were slightly less (i.e., –0.006 ± 0.836 to –0.400 ± 3.430 µmol/L) at the end of the trial compared to the placebo group.

There were a few individual subjects with elevations in LFTs. All from Study RGH-MD-75 were taking SSRIs except one who was taking duloxetine. Two subjects (2/273=0.7%) experienced increased bilirubin >1.5 x ULN; one resolved while taking cariprazine 1 to 2 mg/day + ADT and the other worsened but was judged not related to cariprazine 1 to 2 mg/day. In the cariprazine low-dose arm, four subjects (1.5%) had increased ALT or AST ≥ 3 × ULN but no increased bilirubin. Two subjects (0.7%) reported AEs of increased AST; one had increased AST related to alcohol use, and the subject discontinued the study. The other subject had concurrent AEs of AST increased and blood CPK (i.e., 6336 U/L above), both AEs were considered related to cariprazine. In the cariprazine high-dose (2 to 4.5 mg/day + ADT) arm, there were three (3/273=1.1%) cases of increased ALT and one (0.4%) of increased AST. In the placebo group, there were four subjects (4/266=1.5%) with both increased ALT and AST.

In Studies 3111-301-001 and 3111-302-001, cases of increased alkaline phosphatase occurred at similar rates across the cariprazine 1.5 (3/502=0.6%) and 3 mg/day (2/503=0.4%) and the placebo (2/503=0.4%) arms. The cariprazine 1.5 mg/day + ADT groups experienced more LFT elevations than in the cariprazine 3 mg/day + ADT or the placebo + ADT groups. For example, there were four (0.8%) cases of increased ALT > 3 x ULN, four (0.8%) AST > 3 x ULN, and three (0.6%) total bilirubin >1.5 x ULN compared to zero in the 3 mg or placebo groups. But overall rates even in the drug arms were still very low.

The aforementioned three subjects in Study 3111-302-001 in the cariprazine 1.5 mg/day group had total bilirubin > 2 x ULN or ALT > 3 x ULN in Figures 21 and 22 marked with a tan triangle per subject. Subject 3111-302-001. (b) (6) experienced increased total bilirubin >2xULN and had an AE of cholelithiasis but continued the study. The two other subjects with elevated ALT did not report AEs.

Figure 18: Findings of ALT and Total Bilirubin (Study 3111-302-001)

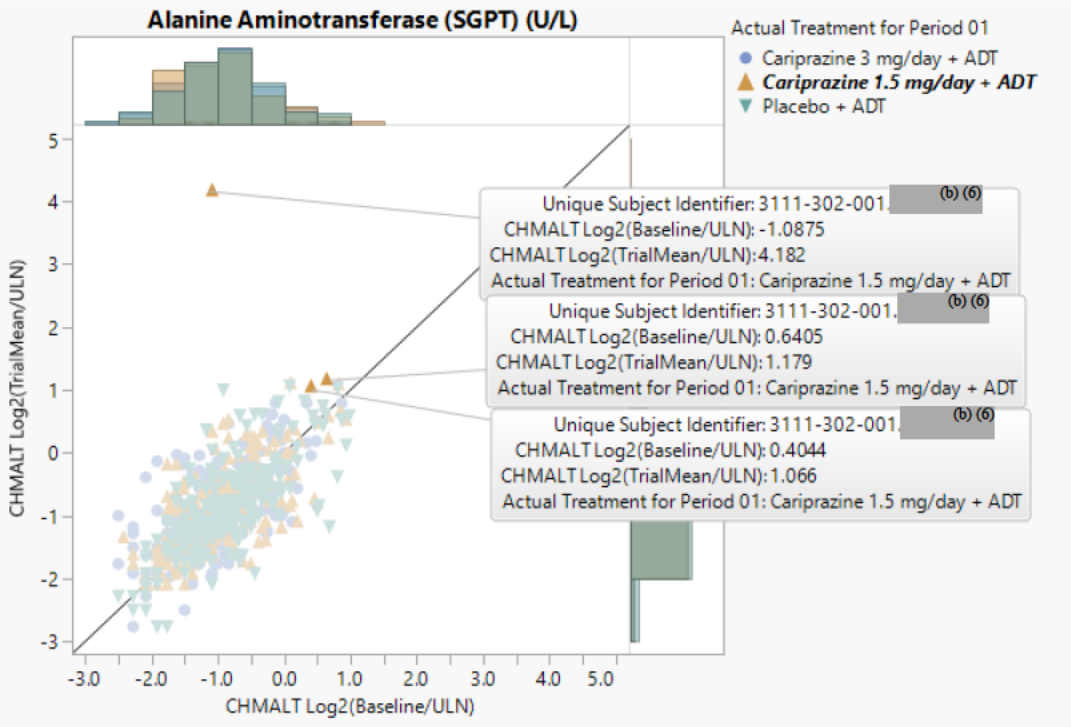
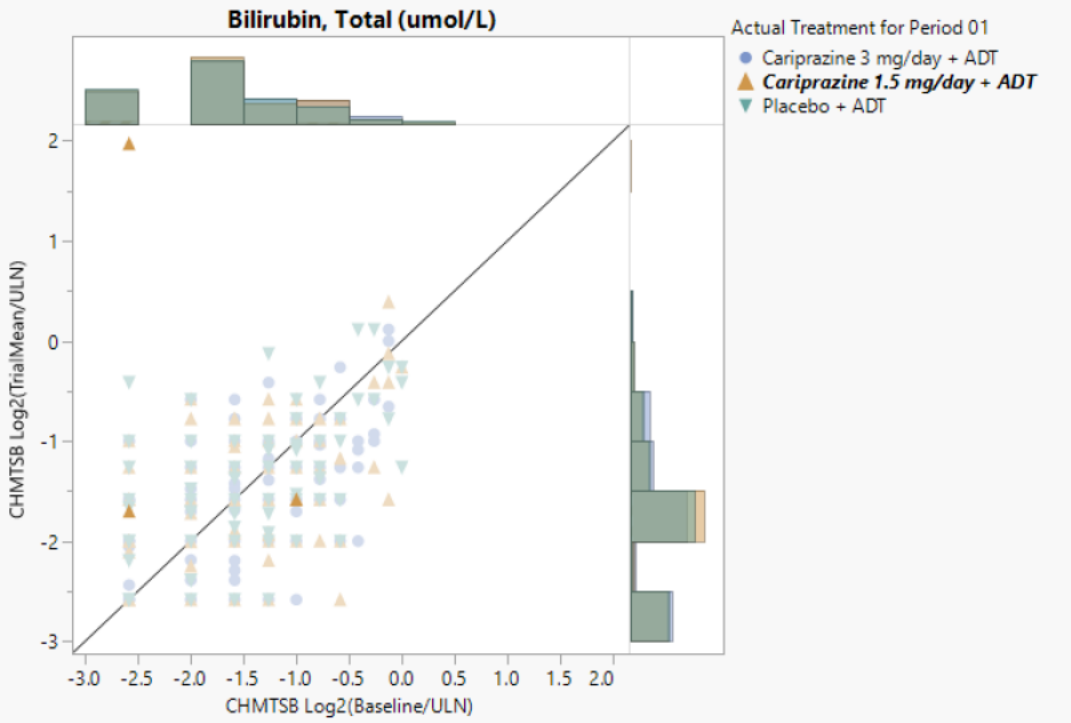


Figure 19: (Continued) Findings of ALT and Total Bilirubin (Study 3111-302-001)



Source: Reviewer created using JMP Clinical 8.0 from 3111-302-001

Reviewer's Comment: In Study RGH-MD-75, rates of elevated LFTs including bilirubin, alkaline

phosphatase, AST, or ALT were similar across treatment arms (i.e., <1 to 1.5%). In the fixed-dose Studies 3111-301-001 and 3111-302-001 the rate of was < 1% among treatment arms. Increased LFTs appear to occur in the subjects with MDD at a very low rate and similar to rates observed in other disorders treated with cariprazine. The incidence of "hepatic enzymes increased" (including terms hepatic enzymes increased, alkaline phosphatase, AST, or ALT) in the current cariprazine PI is 1% in the low-dose arms compared to <1% in the placebo arm for the schizophrenia and bipolar I disorder indications. No cases of increased LFTs are listed for bipolar I depression.

Metabolic Parameters
In Study RGH-MD-75, the mean changes from baseline in cholesterol (high-density lipoprotein HDL), low-density lipoprotein (LDL), and total cholesterol), triglycerides, and serum glucose were small (e.g., <1 mmol/L) and similar between the placebo and both cariprazine treatment groups. However, the mean values for serum insulin increased by the end of the 8-week study in the all treatment groups, but with a greater increase in the low-dose (+12.1 pmol/L) and high-dose (+20.1 pmol/L) cariprazine arms compared to the increased insulin in the placebo arm (+8.5 pmol/L). No intervention was necessary. In Study RGH-MD-75, a subject experienced dyslipidemia while assigned to the placebo group.

In Studies 3111-301-001 and 3111-302-001, the proportion of subjects with shifts in total cholesterol, fasting LDL, HDL, and fasting triglycerides were similar in patients treated with cariprazine or placebo. However, one subject had an AE of dyslipidemia in the cariprazine 1.5 mg/day arm and one subject had an AE of Type 2 diabetes (after the cariprazine 1.5 mg/day period), indicating increased glucose levels.

Reviewer's Comment: No safety signal for changes in cholesterol parameters was identified in the MDD trials of cariprazine. As in the schizophrenia and bipolar I disorder indications, the incidence of mean changes from baseline were small and similar between subjects treated with cariprazine and those treated with placebo. There was a small dose-dependent signal though for serum insulin increase in the 8-week study, so longer-term effects on diabetes risk may be something to monitor.

Prolactin Levels
In Study RGH-MD-75, the mean change from baseline after 8 weeks was greater in the low-dose (3.8 ng/mL) and high-dose (4.1 ng/mL) cariprazine groups compared to in the placebo group (0.7 ng/mL). No AEs related to increased prolactin levels were reported during the study.

In Studies 3111-301-001 and 3111-302-001, 5.4% of subjects in the placebo arms had increased prolactin levels >1 x ULN. The percentage of subjects with elevated prolactin taking cariprazine was greater than in the placebo groups; 7.3% in the cariprazine 1.5 mg/day groups and 8.8% in the 3 mg/day groups (ISS data).

Reviewer's Comment: Most antipsychotic drugs increase prolactin levels. The current PI for cariprazine does not discuss elevated prolactin levels. The PI for brexpiprazole, another antipsychotic with the indication of adjunctive treatment of MDD, lists blood prolactin increased ≥1% and greater than placebo observed during the premarket evaluation of brexpiprazole.

Conclusion/Summary for Laboratory Parameters: Overall, laboratory parameters were consistent with those previously seen for cariprazine; any existing concerns are already addressed in labeling.

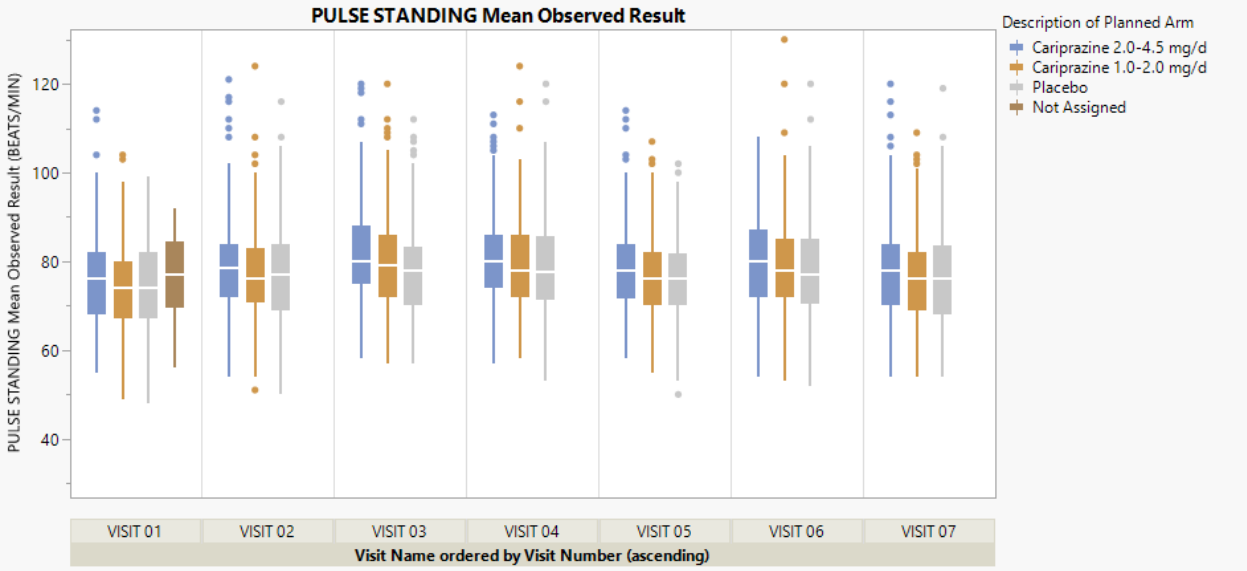
Vital Signs

Mean changes in blood pressure between subjects receiving placebo and cariprazine low or high-dose were similar and not clinically meaningful. The mean changes in pulse among treatment groups was also similar but increased slightly over time. The subjects in the cariprazine + ADT groups experiences a larger weight gain than those assigned to the placebo + ADT groups.

In Study RGH-MD-75, the systolic blood pressure (SBP) and diastolic blood pressure (DBP) findings were similar across treatment groups.

The difference in mean change from baseline to Week 8 in the findings for standing pulse between treatment groups was +2.14 in the cariprazine 2 to 4.5 mg/day + ADT arm, +2.11 in the cariprazine 1 to 2 mg/day + ADT arm, and +2.31 in the placebo + ADT arm. Figure 20 indicates that the high-dose cariprazine group had a slightly higher mean baseline pulse rate but likely not clinically significant.

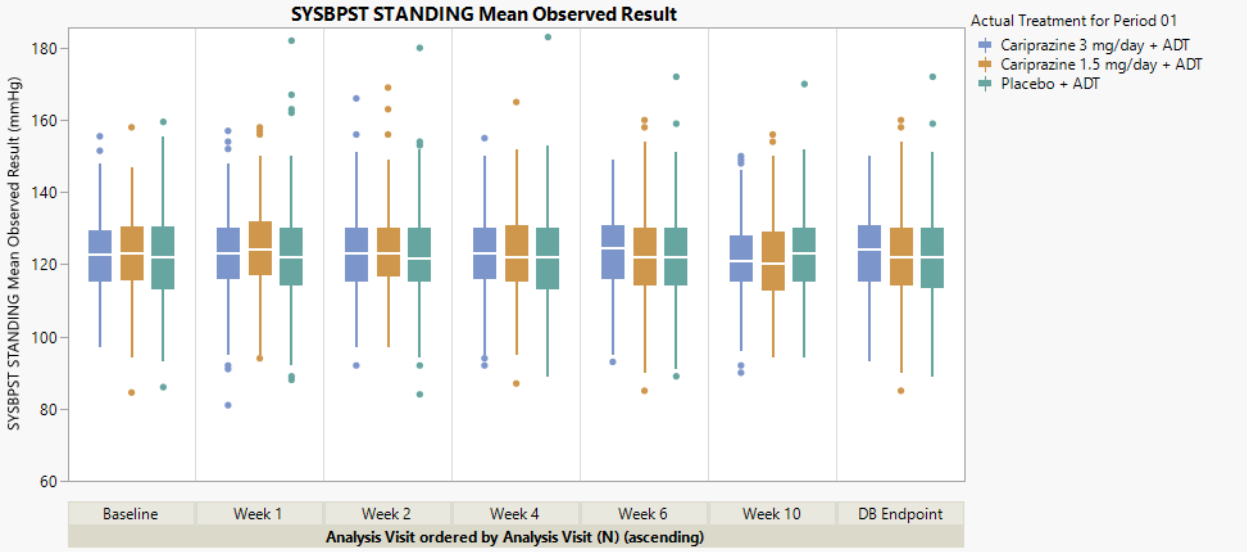
Figure 20: Change in Standing Pulse Over Time (RGH-MD-75)



Source: Reviewer created using JMP Clinical 8.0

In the 6-week, fixed-dose Studies 3111-301-001 and 3111-302-001, there was very little difference in BP readings between the cariprazine 1.5 mg/day + ADT, cariprazine 3 mg/day + ADT, and placebo + ADT. For example, the mean change from baseline to Week 6 (end of double-blind treatment) for systolic blood pressure (SBP) was -0.1 mmHg in the cariprazine 3 mg/day + ADT treatment group, -0.7 mmHg in the cariprazine 1.5 mg/day + ADT treatment group, and -0.1 mmHg in the placebo + ADT treatment group. Mean change from baseline to Week 6 for diastolic blood pressure (DBP) was 0.1 mmHg, 0.1 mmHg, and 0.2 mmHg in the aforementioned treatment groups, respectively. Each of the supine and standing SBP and DBP look similar to the box plots over time in Figure 21 for both studies. There also appeared to be no difference among treatment groups for change from baseline for pulse.

Figure 21: Change in Systolic Blood Pressure (3111-301-001)



Source: Reviewer created using JMP Clinical 8.0

In Study RGH-MD-75, the mean weight change from baseline to Week 8 was +1.5 kg in the cariprazine 2 to 4.5 mg/day + ADT arm, +1.44 kg in the cariprazine 1 to 2 mg/day + ADT arm, and 0.01 kg in the placebo + ADT arm. Hence, 2% of subjects taking cariprazine gained about 1.5 kg where the 1% of subjects in the placebo group had a negligible weight gain at Week 8.

In Studies 3111-301-001 and 3111-302-001, there was slightly more weight gain in the cariprazine arms compared to the placebo arms by the end of the double-blind period at Week 6. Table 55 displays the percentage of subject with changes in weight per treatment group. The percentage change in kilograms in Table 55 converts to a mean change of 0.72 kg in the cariprazine 3 mg/day arms, 0.68 kg in the cariprazine 1.5 mg/day arms, and 0.16 kg in the placebo arms.

Table 55: Weight Change Over 6 Weeks (3111-301-001, 3111-302-001)

Weight in kg Baseline to Week 6	Placebo + ADT (N=503) n (%)	CAR 1.5 mg/day + ADT (N=502) n (%)	CAR 3 mg/day + ADT (N=503) N (%)
Increase > 7%	4 (0.8)	11 (2.2)	8 (1.6)
Decrease > 7%	4 (0.8)	3 (0.6)	3 (0.6)

Source: Reviewer modified Table 9-2.1.1 from ISS

Reviewer's Comment: There were no unexpected findings for vital sign parameters in the adjunctive MDD studies for cariprazine. BP changes were a concern highlighted in labeling for some other indications but showed no difference between drug and placebo here. Mean weight did increase in a dose-dependent fashion in the studies, which is a known concern for cariprazine, included already in labeling.

Electrocardiograms (ECGs)

Electrocardiogram (ECG) findings during the adjunctive treatment of MDD development program are consistent with the known safety profile for cariprazine. In the five clinical trials (RGH-MD-71, RGH-MD-72, RGH-MD-75, 3111-301-001, 3111-302-001), there were no postbaseline clinically significant ECG findings.

In the fixed-dose studies, there was one subject assigned to cariprazine 3 mg/day + ADT who experienced an SAE of atrial fibrillation which resolved. Refer to the section of this review about SAEs. One subject had a QTcB interval increase > 60 msec in the cariprazine 1.5 mg/day + ADT treatment group but it was not recorded as an AE, nor was the treatment changed. There were two AEs of QTc prolongation, but one subject was in the placebo group, and the other subject had entered the safety follow-up period post-cariprazine dosing.

According to the Applicant's ISS for the five trials, the percentage of subjects with a postbaseline QTcB interval increase > 60 msec was 0.4% in the pooled cariprazine + ADT group and 0.3% in the placebo + ADT group. The percentages of subjects with a postbaseline QTcF interval increase > 60 msec were the same (0.1%) in these groups.

Table 56 displays the cardiovascular-related AEs derived from ECG monitoring during Studies RGH-MD-71, RGH-MD-72, RGH-MD-75, 3111-301-001, and 3111-302-001. The flexible-dose cariprazine arms of 1 to 2 mg/day and 1.5 to 4.5 mg/day have an incidence of almost 3% compared to 1.3% in subjects who were assigned to the placebo arm.

Table 56: Cardiovascular AEs by Treatment Arm (RGH-MD-71, RGH-MD-72, RGH-MD-75, 3111-301-001, 3111-302-001)

Dictionary-Derived Term	Placebo + ADT (N=1108)	Cariprazine 1 to 2 mg/day + ADT (N=346)	Cariprazine 1.5 mg/day + ADT (N=502)	Cariprazine 1.5 to 4.5 mg/day + ADT (N=269)	Cariprazine 2 to 4.5 mg/day + ADT (N=273)	Cariprazine 3 mg/day + ADT (N=503)
Angina pectoris	0	0	0	1	0	1
Angina unstable	1	0	0	0	0	0
Atrial fibrillation	0	0	0	0	0	1
Atrioventricular block first degree	2	0	1	1	0	0
Bundle branch block left	1	0	0	0	0	1
Bundle branch block right	0	1	0	0	0	0
Myocardial ischaemia	0	0	0	0	1	0
Palpitations	5	6	2	3	1	2
Sinus bradycardia	2	0	0	0	0	0
Sinus tachycardia	1	1	0	0	0	0
Tachycardia	2	2	3	2	0	3
Ventricular extrasystoles	0	0	0	0	1	1
Total	**14 (1.3%)**	**10 (2.9%)**	**6 (1.2%)**	**7 (2.6%)**	**3 (1.1%)**	**9 (1.8%)**

Source: Reviewer created from ISS Group 2 dataset using JMP Clinical 8.0

Reviewer's Comment: The ECG abnormalities were few and of similar rates between cariprazine and the placebo groups. The higher percentages of cardiovascular AEs in two cariprazine cohorts (2.9 and 2.6%) appear to be driven by the number of palpitation cases. These resolved without intervention. Palpitations and tachycardia were the most frequent cardiovascular AEs reported. Tachycardia is a labeled AE in the PI based on the premarket schizophrenia trials. The ECG changes appear to be consistent with the known safety profile of cariprazine.

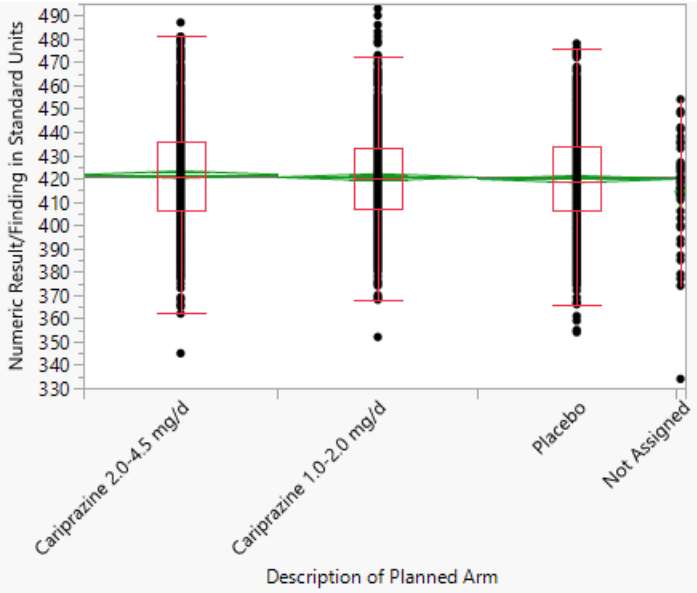
QT

The approved cariprazine PI describes a thorough QT study conducted prior to initial approval; cariprazine does not prolong the QTc interval to clinically relevant extent. Pooled ECG findings from Studies 3111-301-001, 3111-302-001, RGH-MD-71, RGH-MD-72, and RGH-MD-75, are

consistent with this conclusion as there does not appear to be a clinically meaningful difference in QT prolongation between subjects assigned to placebo or any cariprazine dose.

Figure 22 is an example of ECG results using the Bazett correction in Study RGH-MD-75. Similar ECG findings were observed in the other adjunctive MDD studies.

Figure 22: ECG Results and QTc Prolongation from RGH-MD-75



Source: Reviewer created from Study RGH-MD-75 using JMP Clinical 8.0

The Applicant's CSR from RGH-MD-75 notes that three subjects assigned to placebo + ADT (3/1108= 0.3%) experienced a QTc prolongation of > 60 msec (Bazett correction), while 0.7% (13/1969) of subjects taking cariprazine + ADT experienced QTc prolongation > 60 msec. The QT prolongation in subjects assigned to cariprazine did not appear to be dose-related given that prolongation was reported in all dose groups of cariprazine + ADT.

Using the Fridericia correction formula in the five aforementioned studies, one subject taking placebo + ADT and four taking cariprazine + ADT had QTc prolongation > 60 msec.

In pooled datasets from Studies 3111-301-001 and 3111-302-001, there were three cases of QT prolongation reported as an AE, one case in each cariprazine treatment arm (1.5 and 3 mg/day + ADT) and one during the safety follow-period. These cases are also mentioned in the ECG section, above.

Reviewer's Comment: As discussed in the above section on ECGs, the QTc prolongations are consistent with the safety profile of cariprazine and were of similar rates between cariprazine and placebo groups. No ECG changes led to significant AEs or permanent arrhythmias.

Immunogenicity

In the Applicant's sNDA 204370/ S-009, there were 12 (12/1969=0.6%) cases of rash in subjects assigned to the cariprazine + ADT treatment arms compared to five cases in the subjects taking placebo + ADT (5/1108=0.5%). Hence, there was no difference between treatment groups. There were no cases of anaphylaxis or hypersensitivity reactions.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Ocular Adverse Events

The primary review team consulted the Division of Ophthalmology to review the reported ocular AEs. The CSR for the open-label long-term safety study lists 25 cases of shift to Lens Opacity Classification System (LOCS) III Grades.

Nonclinical data analyzed during the original review of NDA 204370 identified cataracts in the dog species. Section 6 of the cariprazine label describes the incidence of cataracts in both nonclinical and clinical studies. Also in Section 6 of the label, blurred vision is documented in the cariprazine arm of short-term bipolar mania trials.

The consult review from the Division of Ophthalmology dated August 19, 2022, concluded that blurred vision was reported in 1 to 2-3% and 1 to 6% of subjects taking cariprazine in the double-blind and open-label long-term trials in this supplemental application, respectively. The incidence of blurred vision in the MDD clinical trials was consistent with the incidence in other indications.

The consult also concluded that the MDD studies are too short in duration to accurately assess whether the drug product increases lens opacities. Over the period monitored in these trials there is approximately an equal number of positive and negative shifts. Given that lens changes do not resolve, these shifts are more likely to represent variability in the grading and not true increases or decreases in the lenses.

In Study 3111-302-001, Subject (b) (6) a 62-year-old white female was diagnosed with mild bilateral cataracts on Day 59 during a routine ophthalmologist examination. The subject completed the 6-week double-blind period in the cariprazine 3 mg/day + escitalopram group. According to our consultant, the MDD trials are too short to be associated with cataract development. The subject's cataracts are unlikely related to cariprazine.

The Division of Ophthalmology consultant also reviewed ocular AEs in the Applicant's Periodic Adverse Drug Experience Report. Refer to the 8.2.9 Safety in the Postmarket Setting. The consultant reviewer's comments dated February 22, 2022 were: Reporting the incidence of cataracts based on 16 week trials is misleading because cataract typically take at least 12 months to be recognized and reported. It is recommended that the reported incidence be deleted.

Reviewer's Comment: I agree with the consultant's review from the Division of Ophthalmology that the incidence of blurred vision in the MDD trials is the same as with other approved indications of cariprazine.

The short-term and long-term (open-label, 6-month) trials for the adjunctive treatment of MDD with cariprazine do not point to a likely cause of lens opacities.

Currently, the PI reads:

> *In the long-term uncontrolled schizophrenia (48-week) and bipolar mania (16-week) trials, the incidence of cataracts was 0.1% and 0.2%, respectively. The development of cataracts was observed in nonclinical studies. The possibility of lenticular changes or cataracts cannot be excluded at this time.*

I agree with the consultant about inaccurate text in the PI and recommend changing the language under the PI heading Cataracts to say:

> *The development of cataracts was observed in nonclinical studies. Adverse events of cataracts were reported during the premarket clinical trials of cariprazine; however, the duration of trials was too short to assess the association to cariprazine usage.*

8.2.5.2 Suicidal Ideation and Behavior

During the five clinical trials, the Investigators used the Columbia Suicide Severity Rating Scale (C-SSRS) to monitor for suicidal ideation at each visit in addition to recording any suicidal ideation or behavior (SI/B) as an AE. Table 55 provides the counts per study sample size.

In Study RGH-MD-72, an 8-week, flexible-dose study with an 8-week ADT lead-in period, one subject experienced SAEs of suicidal ideation and depression while receiving cariprazine 1.5 mg/day + ADT. In Study 3111-302-001, one subject attempted suicide while taking cariprazine 1.5 mg/day + ADT. Refer to the section of this review on SAEs.

During the 6-month, open-label cariprazine Study RGH-MD-76, four subjects reported SI (4/345=1.2%). One of these subjects attempted suicide and is recorded as an SAE. Refer to the section of this review on SAEs. A fifth subject died by suicide 11 days after stopping cariprazine. Refer to section on Deaths.

Table 57: AEs of Suicidal Attempts or Behavior (RGH-MD-72, 3111-302-001, RGH-MD-76)

Study Name	Flex CAR 1.5 mg/day + ADT N=269; placebo=258	Fixed CAR 1.5 mg/day + ADT N=250; placebo=250	CAR flexible open-label + ADT N=345
RGH-MD-72	1 (0.4%) vs. 0%	--	--
3111-302-001	--	1 (0.4%) vs. 0%	--

Study Name	Flex CAR 1.5 mg/day + ADT N=269; placebo=258	Fixed CAR 1.5 mg/day + ADT N=250; placebo=250	CAR flexible open-label + ADT N=345
RGH-MD-76 CAR 4.5mg	--	--	1 (0.3%)
RGH-MD-76 CAR 3mg	--	--	2 (0.6%)
RGH-MD-76 CAR 1.5 mg	--	--	2 (0.6%)

Source: Reviewer created from ISS ADAE.xpt

The C-SSRS was administered at each scheduled study visit of the five safety and efficacy trials. There was a total of 3066 subjects in the C-SSRS ISS datafile. Table 56 breaks down the number of subjects who answered the C-SSRS by dosage arm; the number of subjects is not the same as the safety population. Table 58 also displays the number and percent of subjects with positive SI per treatment arm. Table 59 shows subjects who expressed positive SI, if they had intent, and if they had a specific plan. That table's data is classified via all-cariprazine treatment arms (0.1 to 4.5 mg) with pooled visits and during the double-blind period of the trial.

Table 58: Subjects with Positive SI of Those Who Answered C-SSRS by Treatment (All Studies)

CAR 0.1 to 0.3 mg/day + ADT	CAR 1 to 2 mg/day + ADT	CAR 1.5 mg/day + ADT	CAR 1.5 to 4.5 mg/day + ADT	CAR 2 to 4.5 mg/day + ADT	CAR 3 mg/day + ADT	Placebo + ADT
N=76 (%)	346 (%)	500 (%)	267 (%)	271 (%)	503 (%)	1103 (%)
20 (26)	64 (19)	83 (17)	50 (19)	33 (12)	72 (14)	190 (17)

Source: Reviewer created from ISS ADCSSRS.xpt

Table 59: Subjects with Positive SI on C-SSRS (3111-301-001, 3111-302-001, RGH-MD-71, RGH-MD-72, RGH-MD-75)

Questions 1 to 5 on C-SSRS	CAR 0.1 to 4.5 mg/day + ADT N=1963 (%)	Placebo + ADT N=1103 (%)
Suicidal ideation (Y)	322 (16)	190 (17)
Wish to be dead (Y)	168 (8.6)	120 (11)
Non-specific active suicidal thoughts (Y)	44 (2.2)	19 (1.7)
Suicidal ideation without intent (Y)	21 (1.1)	12 (1.1)
Suicidal ideation with some intent and no plan (Y)	1 (0.1)	3 (0.3)

Questions 1 to 5 on C-SSRS	CAR 0.1 to 4.5 mg/day + ADT N=1963 (%)	Placebo + ADT N=1103 (%)
Suicidal ideation with specific plan and intent (Y)	0 (0)	0 (0)

Source: Reviewer created from ISS ADCSSRS.xpt

Reviewer's Comment: During the MDD safety and efficacy trials reviewed here, there were two AEs of SI/B recorded in subjects randomized to cariprazine and none in placebo. There were five AEs recorded during the 6-month, long-term safety study; however, there is no comparator drug during the longer trial. More SI/B AEs could tend to occur during a longer timeframe in subjects with MDD (who also have increased background risks of SI/B).

The rates of positive SI on the C-SSRS appear similar between subjects taking cariprazine or placebo + ADT. The percentage of SI dropped during the 6- or 8-week MDD trials for treatment groups. This trend could be due to the drug treatment or because the subject is receiving attention while enrolled in the trial (i.e., placebo effect).

The CSRs for each of the individual MDD trials tallied the C-SSRS data in the same way I did in Table 59. However, in the Applicant's ISS, SI/B was presented in a table that compiled rates of SI/B based on subjects who experienced akathisia or restlessness from scores on the Barnes Akathisia Rating Scale (BARS). I do agree that akathisia can lead to agitation and impulsiveness, and there is a potential relationship with SI/B. However, the cariprazine MDD trials enrolled subjects with depression, some with a history of or current SI/B. Safety data about SI/B may be better presented against the mean change from baseline score per visit by treatment group in order to assess if subjects are improving over time, although not every depressed subject is positive for SI. The C-SSRS does not capture longitudinal SI/B data like that using a total score.

Overall, there were no significant trends for SI/B events on cariprazine.

8.2.5.3 EPS and Akathisia

In Study RGH-MD-75, cariprazine-treated subjects reported an increased frequency of extrapyramidal symptoms (EPS) compared with subjects taking placebo. Excluding akathisia and restlessness, the EPS-related AEs occurred in 5% of patients in the placebo group, 12% in the low-dose (1 to 2 mg/day) cariprazine group, and 17% in the high-dose (2 to 4.5 mg/day) cariprazine group. Akathisia occurred in 3%, 7%, and 23% of patients in the placebo, low-dose, and high-dose cariprazine groups, respectively. The cariprazine treated subjects reported restlessness at a rate of 7.7% in the low-dose arm, 9.2% in the high-dose arm, and 2.6% by those taking placebo. See Table 48: AEs from RGH-MD-75 in 8.2.4 Safety Results.

In the fixed-dose studies, 3111-301-001 and 3111-302-001, subjects who received 1.5 or 3 mg/day cariprazine + ADT experienced more frequent and dose-dependent AEs of EPS than

those in the placebo + ADT arms. The rate of EPS excluding akathisia or restlessness was 4.4 and 4.6%, respectively, in the cariprazine 1.5 and 3 mg/day + ADT arms, whereas the rate in the placebo arm was 3.2%. The total incidence of any EPS AEs is driven by the akathisia and restlessness; 13% in the cariprazine 1.5 mg/day arm and 17% reported by subjects taking cariprazine 3 mg/day + ADT. The subjects taking placebo reported 6% EPS.

Table 60: EPS and Akathisia AEs by Treatment (3111-301-001, 3111-302-001)

Dictionary-Derived Term	Placebo + ADT (N=503)	CAR 1.5 mg/day+ ADT (N=502)	CAR 3 mg/day + ADT (N=503)
	N (%)	N (%)	N (%)
Subjects with any EPS including akathisia/restlessness	30 (6)	63 (13)	84 (17)
Subjects with any EPS AE excluding akathisia/restlessness	16 (3.2)	23 (4.6)	22 (4.4)
Subjects with any Akathisia/Restlessness	19 (3.8)	48 (9.6)	65 (13)
Akathisia	10 (2)	32 (6.4)	49 (9.7)
Restlessness	9 (1.8)	18 (3.6)	19 (3.8)
Dystonia cluster	2 (0.4)	2 (0.4)	1 (0.2)
Myoclonus	1 (0.2)	0 (0)	1 (0.2)
Trismus	1 (0.2)	1 (0.2)	0 (0)
Oromandibular dystonia	0 (0)	1 (0.2)	0 (0)
Parkinsonism cluster	13 (2.6)	18 (3.6)	20 (4)
Drooling	2 (0.4)	0 (0)	2 (0.4)
Dyskinesia	0 (0)	1 (0.2)	1 (0.2)
Extrapyramidal disorder	0 (0)	2 (0.4)	4 (0.8)
Muscle tightness	2 (0.4)	0 (0)	0 (0)
Muscle rigidity	1 (0.2)	1 (0.2)	0 (0)
Salivary hypersecretion	1 (0.2)	1 (0.2)	2 (0.4)
Tremor	7 (1.4)	14 (2.8)	12 (2.4)
Parkinsonism	0 (0)	1 (0.2)	0 (0)
Musculoskeletal stiffness	2 (0.4)	3 (0.6)	0 (0)
Tardive dyskinesia	0 (0)	0 (0)	1 (0.2)

Source: Reviewer modified ISS Table 10

Reviewer's Comment: The subjects in the flexible-dose adjunctive treatment for MDD trial (23%) reported more akathisia than the schizophrenia indications (9%). They also reported double the rate of restlessness; 8 to 9% in MDD compared to 4% in subjects with schizophrenia. It is possible that in subjects with MDD, the AEs could be more pronounced compared to subjects with schizophrenia, whose first-line treatment tends to be an atypical antipsychotic medication;

those subjects may have developed some tolerance to this drug class. On the other hand, general EPS was less frequent in the MDD trials than in the schizophrenia trials of cariprazine.

In the fixed-dose studies, EPS was dose-dependent, and the rate of over 10% is driven mainly by restlessness and akathisia AEs. (In the flexible-dose trial, EPS was also dose-dependent.) The subjects who received placebo + ADT reported 6% EPS, but it may be because some antidepressants are associated with akathisia. Based on the breakdown of types of EPS, cariprazine appears to cause mainly Parkinsonian-type EPS, especially tremor, in addition to akathisia and inner restlessness.

As previously discussed, akathisia was the most common AE resulting in Study RGH-MD-75 discontinuation among patients treated with cariprazine (0.4% and 4.8% of patients in the low-dose and high-dose groups of RGH-MD-75, respectively). Also previously mentioned, akathisia can cause impulsivity, anxiety, agitation, and suicidal ideation. Akathisia starts early when subjects start taking cariprazine and gets worse weeks after a dose increase due to the long-lasting metabolites accumulating to steady state.

Summary/Conclusion: There is no doubt that cariprazine can cause akathisia, inner restlessness, and EPS (especially tremor) in subjects with MDD. These AEs are not only dose-dependent but titration rate dependent. The most frequent reason for study discontinuation was related to these AEs. Subjects who are prescribed adjunctive cariprazine + ADT should be counseled about the potential for intolerability. Because the fixed-dose studies (3111-301-001, 3111-302-001) had a slower titration rate than the flexible-dose studies, and at the doses for potential approval (i.e., 1.5 and 3 mg/day, but not 4.5 mg/day) the rate of EPS including akathisia and restlessness was less, albeit 13 and 17% which is still relatively high. The Dosing and Administration information in the PI of cariprazine will describe the starting dose of 1.5 mg/day and increase only after 14 days if necessary to a maximum dose of cariprazine 3 mg/day.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant conducted subject-related clinical outcome assessment scales to assess tolerability of EPS using a standard method, such as the Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), and the Simpson=Angus Scale (SAS). Nearly all of the scores on each scale for each study visit were zeros, indicating that no major movement concerns. That outcome is counterintuitive to the high percentages of EPS in the subjects taking cariprazine. Clearly, AE reporting was a more precise method of capturing the types of EPS. (See the previous section for more details.)

The Applicant used the C-SSRS for monitoring suicidal ideation as discussed in section 8.2.5.2.

8.2.7. Safety Analyses by Demographic Subgroups

There were no clinically significant differences in AEs between the demographic subgroups of race, sex, or age among subjects assigned to the placebo or cariprazine treatment arms in any of the cariprazine studies.

Subjects over 55-years-old had slightly more falls (i.e., eight vs. six) and Parkinsonian AEs (four vs. zero) than subjects under age 55 (but no differences for overall EPS or akathisia AE rates) in Studies 3111-301-001, 3111-302-001, RGH-MD-71, RGH-MD-72, and RGH-MD-75. Both AEs are known to be age-related.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant conducted a 6-month, open-label, safety extension trial of cariprazine (flexible-dose) + ADT, Study RGH-MD-76. The subjects participating in Study RGH-MD-76 were enrolled directly or from those who completed the flexible-dose efficacy Study RGH-MD-72. The AEs in this trial were consistent with the placebo-controlled trials of cariprazine as in Table 60. The most frequent AEs were akathisia 16%, headache 13%, anxiety 10%, restlessness 10%, insomnia 9.9% and dizziness 6.7%. The most frequent reason for discontinuing the study was akathisia and restlessness at rates of 2% and 1.7%, respectively.

Notably, subjects reported 8.4% increased weight over the 6-month trial. Two subjects (0.6%) discontinued due to increased weight in Table 60. Cariprazine was associated with mean change from baseline in weight of 1.7 kg at Week 26/End of Trial. Using vital sign collection to measure weight change over the 6-month trial, 19% of subjects demonstrated a ≥7% increase in body weight, and 5% demonstrated a ≥7% decrease in body weight.

Table 61: Outcome of AEs (2%) from 6-month Open-Label Cariprazine Study RGH-MD-76

Open-label cariprazine flexible-dose + ADT (N=345)										
		None		Study Drug Dose Reduced		Subject D/C'd Study		Drug Stopped Temporarily		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Count	%	Count	%	Total AEs n (%)
Nervous system disorders	Akathisia	22	6.4%	26	7.5%	7	2%	.	.	55 (16)
	Headache	37	10.7%	5	1.4%	.	.	1	0.30%	43 (13)
	Dizziness	19	5.5%	4	1.2%	.	.	.	.	23 (6.7)
	Sedation	12	3.5%	7	2%	2	0.6%	.	.	21 (6.1)
	Somnolence	7	2%	4	1.2%	.	.	1	0.30%	12 (3.5)
	Tremor	8	2.3%	4	1.2%	.	.	.	.	12 (3.5)
Psychiatric disorders	Anxiety	26	7.5%	5	1.4%	4	1.2%	.	.	35 (10)
	Restlessness	11	3.2%	18	5.2%	6	1.7%	.	.	35 (10)
	Insomnia	28	8.1%	5	1.4%	1	0.3%	.	.	34 (9.9)
	Irritability	3	0.9%	4	1.2%	.	.	1	0.30%	8 (2.4)
	Agitation	1	0.3%	4	1.2%	1	0.3%	.	.	6 (1.7)
Gastrointestinal disorders	Nausea	15	4.3%	6	1.7%	.	.	.	.	21 (6.1)
	Diarrhea	15	4.3%	1	0.3%	.	.	.	.	16 (4.6)
	Vomiting	10	2.9%	1	0.3%	1	0.3%	.	.	12 (3.5)
	Constipation	7	2%	2	0.6%	1	0.3%	.	.	10 (2.9)
	Dry mouth	10	2.9%	.	.	.	.	.	.	10 (2.9)
	Dyspepsia	8	2.3%	.	.	.	.	.	.	8 (2.4)
Infections and infestations	Nasopharyngitis	32	9.3%	.	.	.	.	.	.	32 (9.3)
	Upper respiratory tract infection	15	4.3%	.	.	.	.	.	.	15 (4.3)
	Urinary tract infection	10	2.9%	.	.	.	.	1	0.30%	11 (3.1)
Investigations	Weight increased	29	8.4%	3	0.9%	2	0.6%	.	.	34 (9.9)
Musculoskeletal and connective tissue disorders	Back pain	7	2%	.	.	.	.	.	.	7 (2)
	Myalgia	6	1.7%	.	.	.	.	.	.	6 (1.7)

General disorders and administration site conditions	Fatigue	15	4.3%	12	3.5%	3	0.9%	1	0.30%	31 (9)
	Pyrexia	6	1.7%	.	.	.	.	.	.	6 (1.7)
Eye disorders	Vision blurred	7	2%	3	0.9%	.	.	.	.	10 (2.9)
Metabolism and nutrition disorders	Increased appetite	11	3.2%	1	0.3%	.	.	.	.	12 (3.5)
Cardiac disorders	Palpitations	3	0.9%	3	0.9%	.	.	.	.	6 (1.7)

Source: Reviewer created using JMP Clinical 8.0

Summary/Conclusion: In study RGH-MD-76, the most frequent AEs and reasons for study discontinuation were the same as in the safety and efficacy studies except for headache and the rate of anxiety (i.e., akathisia, anxiety, restlessness, insomnia, and dizziness). Anxiety occurred at a higher rate (10%) than in the short-term trials (1 to 2%); this higher rate may be related to monitoring a longer timeframe of the subjects' life events.

The metabolic AEs of cariprazine such as weight gain (10%), increased serum glucose levels, and potentially dyslipidemia were more concerning after 6 months on cariprazine compared to the short-term 6- and 8-week trials. The CSR said there were no mean increases from baseline at the end of the trial for lipid parameters, with the exception of fasting triglycerides (+11.2 mg/dL). Mean increases from baseline were observed for fasting glucose (4.44 mg/dL) and insulin (7.2 mcIU/mL). Although there was a small change from baseline for hemoglobin A1c (0.1%), 7% of subjects with normal hemoglobin A1c baseline values developed elevated levels (> 6%). Also, 7 percent of subjects with MDD having hgbA1c elevation is greater than the 4% of subjects with schizophrenia or bipolar I disorder described in the PI from long-term, open-label trials in these indications. One concern of these increased, long-term metabolic effects is the propensity to develop Type 2 diabetes mellitus. The PI already lists metabolic changes in the Highlights: Warnings and Precautions and suggests that prescribers "monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain," and these findings are described in the respective adjunctive treatment of MDD sections of the warnings and precautions.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Division of Pharmacovigilance did not identify postmarket safety concerns with cariprazine during the review of this supplemental NDA.

The Applicant submitted their most recent Periodic Adverse Drug Experience Report (PADER) for our assessment of postmarket data as part of this sNDA. I identified no new safety signals.

Upon my review of the PADER, I consulted the Division of Ophthalmology to assess the ocular report portion of the PADER. The Consultant Wiley Chambers, MD recommended that the cariprazine PI language about cataracts be updated. Refer to the sections of this review on Ocular Adverse Events. He did not feel additional postmarketing cohort studies to track cataract signals would be helpful, as background rates for comparison would be difficult to determine.

Expectations on Safety in the Postmarket Setting

Although the Applicant is granted a full pediatric study plan waiver for pediatric subjects ages 0 to 17, it is possible that off-label use of cariprazine for treatment of MDD in adolescents may occur and should be monitored by surveillance.

8.2.10. Integrated Assessment of Safety

Safety results from the cariprazine adjunctive treatment of MDD program generally align with the safety profile of cariprazine for the other indications of schizophrenia, acute treatment of manic or mixed episodes of bipolar I disorder, and treatment of depressive episodes of bipolar I disorder. No new safety signals to be labeled were identified.

The MDD development program included five efficacy and safety studies, for which the safety review focused on one 8-week flexible-dose study and two 6-week fixed-dose studies. The safety of cariprazine hinges on (1) slow titration of 2-weeks (as in the fixed-dose studies) for each dose increase, (2) monitoring for late-occurring akathisia or other AEs due to the slow rate to reach steady state for the metabolites DCAR and DDCAR at each dose increase, and (3) a maximum dose in the MDD population of 3 mg/day + ADT.

The most common AEs are akathisia, nausea, insomnia, restlessness, fatigue, somnolence, and extrapyramidal syndrome (EPS). These same AEs are consistent with the reasons for subjects' study discontinuation. The safety profile of cariprazine is similar to other atypical antipsychotics that are approved for the adjunctive treatment of MDD.

We determined that the higher-dose arm of flexible-dose Study RGH-MD-75 had a 21% study discontinuation rate, due to apparent intolerability of cariprazine. However, our safety analysis revealed that the highest 4.5 mg/day dose was not driving the large number of AEs; instead, it was most likely the steep titration schedule of the lower doses between 1.5 (starting dose) and 4.5 mg/day in that high-dose arm. Therefore, the Applicant's recommended high-dose of 3 mg/day, if titrated slowly (i.e., over 2 weeks), could still have more tolerability than seen in the flexible-dose studies of cariprazine for adjunctive treatment of MDD (and was shown to be effective). The dosing and administration section 2.5 of the PI should provide instructions accordingly to reduce intolerability. The section for adjunctive treatment of MDD should read: *the starting dosage for VRAYLAR is 1.5 mg once daily. Depending upon clinical response and tolerability, the dosage can be increased to 3 mg once daily on Day 15. Maximum recommended dosage is 3 mg once daily.* (b) (4)

(b) (4)

Since the nonclinical data regarding a potential ocular signal was reviewed prior to the initial cariprazine approval in 2015, the Division has been concerned with ocular AEs including cataract formation. Over time, the Applicant and Division changed the subject ocular monitoring parameters to conduct extensive monitoring such as slit-lamp examinations for clinical trials over 6 months in duration. The Division has consulted the Division of Ophthalmology at least six times about ocular AEs in the cariprazine development programs. Given that cataracts take about 1 year to form, it is unlikely cataract development in humans is related to cariprazine during any short-term studies. The Cataracts section of the PI will be updated per recommendations from the Division of Ophthalmology.

Aside from the aforementioned updates, cariprazine's current labeling covers existing safety concerns for the newly indicated population.

8.3. **Statistical Issues**

The statistics team recommends approval based on the presence of two positive studies. Exploratory post-hoc meta-analyses can be helpful to understand the data but not to base regulatory decisions. All additional exploratory, post-hoc analyses on the MADRS endpoint support that cariprazine likely has a small effect on improving MDD symptoms. If the true efficacy of cariprazine is small (~1.5 to 2 units on the MADRS) and has little to no dose response between these doses, the expected results for underpowered studies is that sometimes a 1.5-mg dose beats 3 mg, sometime vice versa, and other times neither dose shows statistical evidence of efficacy. This pattern is what is observed in studies 75, 301, and 302. Therefore, the statistics team determined that there is still evidence of efficacy. However, the clinical effect supported by studies 75, 301, 302 is likely less than 2 units on the MADRS. The statistics team defers to the clinical team to determine if this effect is clinically meaningful and if the benefits outweigh the risks. In addition, the statistics team recommends the inclusion of all arms of study 75, 301, and 302 as not to potentially misrepresent the magnitude of the treatment effect.

In these meta-analyses, we can presuppose that the results of both study and patient level meta-analyses will show a smaller treatment effect and p-value compared to the positive individual studies. The smaller treatment effect is caused by the inclusion of the smaller treatment effects from the negative studies/treatment arms. This smaller estimate results from averaging treatment effect estimates ranging from -0.3 to -2.5. The smaller p-value results from the greater amount of information we obtain from combining across studies. The exploratory meta-analyses conducted by both OCP and OB support a small effect size but consistent.

These three studies were designed to detect a standardized effect of 0.286. This effect size is equivalent to 3 point improvement (δ) on the MADRS compared to placebo at an assumed standard deviation (σ) of 10.5. For example, in study 301, the 1.5 mg arm had an observed

effect size of 0.28 (δ = -2.5, σ = 9) and the 3 mg arm had an effect size of 0.17 (δ = -1.5, σ = 9). Because the mean treatment differences were smaller in Study 302 (δ ranging from -0.3 to -1.3), the effect size was similarly smaller under an assumption of a similar variance. Similar trends were seen in Study 75. The smaller, average observed treatment effect sizes indicate that these studies may have been underpowered to detect the effect of cariprazine on MADRS total score. Therefore, it is not surprising that only two study arms (the 2 to 4.5 mg arm in Study 75 and the 1.5 mg arm in Study 301) showed any efficacy signal.

8.4. Conclusions and Recommendations

The Applicant has provided substantial evidence of effectiveness for cariprazine 1.5 to 3 mg/day as adjunctive treatment for MDD in adults. This supplemental application included two positive adequate and well-controlled studies. Statistics noted that due to a small overall average treatment effect on the MADRS (around -1.5 to 2) with cariprazine in the studies reviewed, the dose response could overlap if the studies were insufficiently powered, while substantiation of efficacy was still occurring. Also, an analysis by clinical pharmacology noted that there was substantial overlap in the PK exposure levels for the two positive studies between 1.5 and 3 mg, indicating that while dose response for efficacy was flat for the two doses, this PK overlap also meant that the two doses were essentially functioning similarly in the study populations. Therefore, efficacy for the total dose range of 1.5 to 3 mg was indeed substantiated. We also determined that the small treatment effect was clinically meaningful, given that it is similar to the effect observed in other atypical antipsychotics approved for adjunctive treatment for MDD.

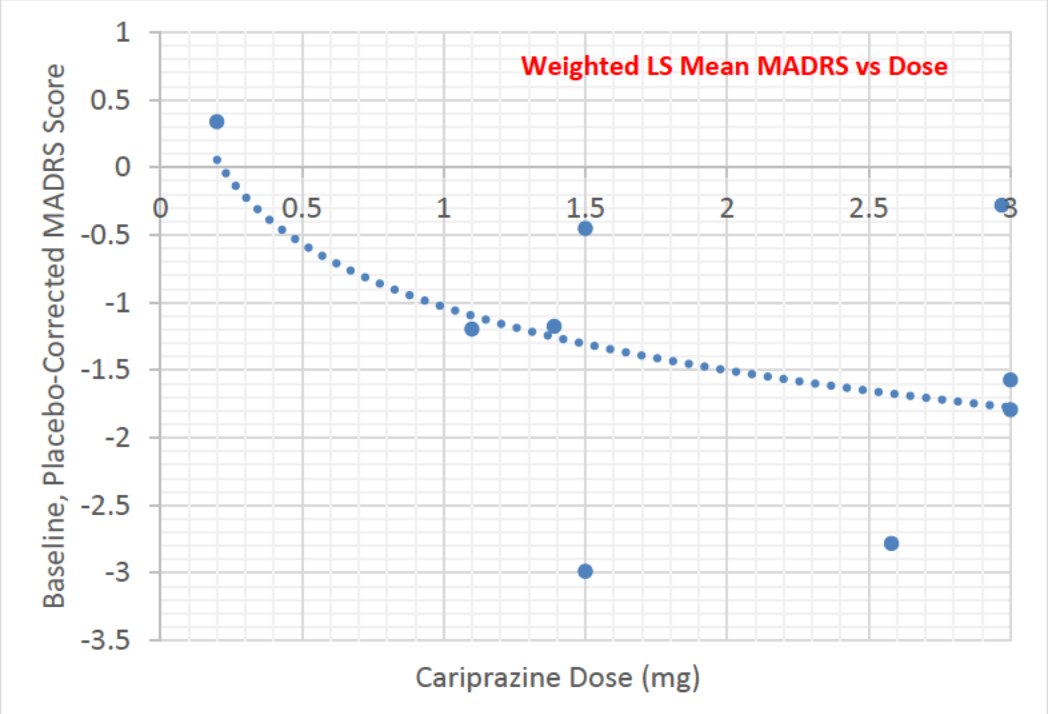
The review team has also determined that the benefits of treatment outweigh cariprazine's potential risks for the adjunctive treatment of MDD in adults. A dose response was more clearly evident for AEs and dropouts, particularly in the higher-dose 2 to 4.5 mg arm in the flexible-dose Study RGH-MD-75 vs. the lower-dose arm, and to a lesser extent with the fixed-dose of 3 vs. 1.5 mg/day + ADT. Our safety analyses suggest that the steep cariprazine titration over 1 week in the flexible-dose Study RGH-MD-75 likely contributed to the higher AE and dropout rates as compared to the fixed-dose studies (which titrated over 2 weeks). Cariprazine is not well-tolerated with a rapid titration, with higher rates of early akathisia which causes agitation and anxiety, followed by accumulating AEs from cariprazine's long-acting major metabolites. With the slower fixed-dose study titration, it appears that the 3-mg dose, while having more AEs than 1.5 mg, was still better tolerated than the high dose arm of the flexible dose study. The rate and types of AEs for both 1.5 and 3 mg remain within a similar range to other approved antipsychotics, and to those seen for other cariprazine indications. Accordingly, both doses of 1.5 and 3 mg will still be recommended as safe and effective for the adjunctive treatment of MDD.

9 Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting. There was a CDER Medical Policy and Program Review Committee (MPPRC) meeting on October 12, 2022, to discuss substantial evidence of effectiveness in the development program for adjunctive treatment of MDD.

The Council expressed concerns with the lack of dose response (and how to inform dosages in labeling), and they were interested in possible results of a meta-analysis to inform or support Studies RGH-MD-75 and 3111-301-001. The council voted 7:5 that the cariprazine application (b) (4) did not have substantial evidence of effectiveness, but some of the later analyses (i.e., clinical pharmacology and statistics examining dose overlap between 1.5 and 3 mg) providing explanations for the lack of dose response had not been completed before or presented at the meeting.

Figure 23: Weighted Dose-Response Across Five Studies. LSMEAN Estimates vs. Dose



10 Pediatrics

FDA issued an agreed iPSP on November 3, 2016, with a planned request for waiver in all pediatric age groups.

A full waiver is granted in all pediatric age groups for cariprazine as an adjunctive treatment for MDD because necessary studies are impossible or highly impracticable.

APPEARS THIS WAY ON ORIGINAL

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The review team made the decision in Section 6 Adverse Reactions from Adjunctive Treatment of MDD Trials to separate the adverse reactions from the fixed-dose studies, 3111-301-001 and 3111-302-001, and the flexible-dose study, RGH-MD-75, into two tables. The rationale for having two AE tables in a label for the same indication is that the study designs are different by dosage arms of cariprazine (e.g., fixed-dose 1.5 or 3 mg/day + ADT, flexible-dose 1 to 2 mg/day or 2 to 4.5 mg/day + ADT) and by duration of the trials, 6- or 8-week.

The population of the adjunctive MDD studies was majority white and female and, therefore, we lack complete evidence about the treatment effect for other races. (There is, however, enough race information to generalize to the U.S. MDD population for purposes of a recommendation for action on the sNDA 204370/S-009; see Section 8.1.7 Assessment of Efficacy Across Trials).

The review team discussed whether to add the same safety tables for this indication as the previous indications' tables. There are currently designated numerical tables for Blood Pressure, Weight, and Extrapyramidal Symptoms (EPS) for each previously approved indication. In the case of Blood Pressure and Weight Gain, the team decided to remove these tables for all indications because the data between treatment groups in the tables were already adequately conveyed in text and did not show clinically meaningful differences. The review team ultimately decided to keep the Blood Pressure tables for the indications of schizophrenia and mania in bipolar I disorder because the 6 to 9 mg/day doses were associated with clinically meaningful increased blood pressure. The rationale for deleting the EPS tables was that the adverse reaction data was already conveyed in the 2% tables under 6.1 Clinical Trials Experience. The text about the number of akathisia, restlessness, and EPS events leading to study discontinuation was kept in the section of the label specifically describing EPS.

The section in the PI about cataracts will be updated based on consultations with the Division of Ophthalmology. The PI currently says:

> In the long-term uncontrolled schizophrenia (48-week) and bipolar mania (16-week) trials, the incidence of cataracts was 0.1% and 0.2%, respectively. The development of cataracts was observed in nonclinical studies. The possibility of lenticular changes or cataracts cannot be excluded at this time.

The updated language under the PI heading Cataracts is as follows:

> The development of cataracts was observed in nonclinical studies *[see Nonclinical Toxicology (13.2)]*. Cataracts were reported during the premarketing clinical trials of cariprazine; however, the duration of trials was too short to assess any association to cariprazine usage.

12 Risk Evaluation and Mitigation Strategies (REMS)

There is no REMS plan for this supplement.

APPEARS THIS WAY ON ORIGINAL

13 Postmarketing Requirements and Commitment

No new postmarketing requirements or commitments will be issued.

APPEARS THIS WAY ON ORIGINAL

14 Division Director Comments

The review above reflects my feedback and edits. I agree with the conclusions of the primary review team.

APPEARS THIS WAY ON ORIGINAL

15 Appendices

15.1. Financial Disclosure

The Applicant certified that they did not enter into any financial arrangements with clinical investigators for the registrations trials in this sNDA application, RGH-MD-75 and 3111-301-001.

Covered Clinical Study (Name and/or Number): RGH-MD-75

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 403		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 3111-301-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 658		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

15.2. OCP Appendices (Technical documents supporting OCP recommendations)

Refer to the Clinical Pharmacology section for technical graphs.

16 References

Adedinsewo, D. O. (2016). Acute Rhabdomyolysis Following Synthetic Cannabinoid Ingestion. *N Am J Med Sci*, 256-258.

Allergan. (Submitted 12/2/2022). *Investigator's Brochure, 20th Edition.* Sponsor's Development Safety Update Report (DSUR).

American Psychiatric Association. (2013). *Diagnostic And Statistical Manual Of Mental Disorders, Fifth Edition.* Arlington: American Psychiatric Association. Retrieved from Psychiatry Online: https://doi.org/10.1176/appi.books.9780890425596

Brody, D., Pratt, L., & Hughes, J. (2018, February). *National Center for Health Statistics, Prevalence of Depression Among Adults Aged 20 and Over: United States, 2013–2016*. Retrieved from Centers for Disease Control and Prevention: https://www.cdc.gov/nchs/products/databriefs/db303.htm

Fruman, A. S. (2021). Creatine kinase levels in psychotic patients who use cannabinoids. *Int Clin Psychopharmacol*, 45-49.

Hollon, S., Jarrett, R., & Nierenberg, A. e. (2005). Psychotherapy and Medication in the Treatment of Adult and Geriatric Depression: Which Monotherapy or Combined Treatment? *J Clin Psychiatry*, 455-468.

Kleeblatt, J., Betzler, F., Kilarski, L., & al., e. (2017). Efficacy of off-label augmentation in unipolar depression: A systematic review of the evidence. *Eur Neuropsychopharmacol*, 423-441.

National Institute of Mental Health. (2022, January accessed 9/16/22). *Major Depression*. Retrieved from Mental Health Information: https://www.nimh.nih.gov/health/statistics/major-depression

Papakostas, G., M, F., L, B., & al., e. (2015). Ziprasidone augmentation of escitalopram for major depressive disorder: efficacy results from a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*, 1251-1258.

Wang, Z. K. (2011). Comparisons of the tolerability and sensitivity of quetiapine XR in the acute treatment of schizophrenia, bipolar mania, bipolar depression, major depressive disorder, and generalized anxiety disorder. *Int J Neuropsychopharmacol*, 131-142.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204370Orig1s009

CLINICAL REVIEW(S)

Medical Officer's Review of NDA 204370/S-009
Ophthalmology Consult for Supplement 9

Consult Request Date:	July 26, 2022
Submission Dates:	February 18, 2022
Review completed:	August 19, 2022

Name: Vraylar (cariprazine) capsules

Applicant: Allergan

Requested: DP is consulting the Division of Ophthalmology about our efficacy supplement for cariprazine (NDA 204370/S-009) for the (b) (4).
The NDA includes five efficacy studies and one open-label trial of patients with MDD taking cariprazine or placebo plus their antidepressant pharmacotherapy. In Module 2.7.4, the Summary of Clinical Safety, ocular adverse events are listed. Please advise DP if any of the ocular AEs or changes to visual acuity are related to cariprazine therapy or are serious. For examples of the changes, a table in study RGH-MD-76 lists 25 cases of shift to LOCS III Grades.

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As you may know, cariprazine is labeled in Section 6 Adverse Reactions for “vision blurred” from trial data and “cataracts” from long-term data, based on nonclinical dog findings of cataracts.

Study IDs
3111-301-001 a fixed-dose, 6-week study
3111-302-001 a fixed-dose, 6-week study
RGH-MD-71 a flexible-dose, 8-week study
RGH-MD-72 a flexible-dose, 8-week study
RGH-MD-75 a flexible-dose, 8-week study
RGH-MD-76 a 6-month, open-label safety extension study enrolling patients from RGH-MD-72 or new patients

Labeling Planning Meeting: 9/15/2022
Labeling Meeting #1: 10/6/2022
Labeling Meeting #2: 10/20/2022
Labeling Meeting #3: 11/3/2022
Wrap-Up Meeting: 11/17/2022
PDUFA Goal Date: 12/18/2022 (Sunday)/ Action Date: 12/16/2022
EDR: \\CDSESUB1\evsprod\NDA204370\0190

Reference ID: 5032993

Submitted:

Table 5-2.1.1 Number (%) of Participants with Treatment-Emergent Adverse Events during the Double-Blind Treatment Period by System Organ Class and Preferred Term
Group 1 Safety Population

	Placebo+ADT	Cariprazine 1.5 mg/day+ADT	Cariprazine 3 mg/day+ADT	Cariprazine Overall+ADT
System Organ Class	(N=503)	(N=502)	(N=503)	(N=1005)
Preferred Term	n (%)	n (%)	n (%)	n (%)
Vision blurred	1 (0.2%)	2 (0.4%)	8 (1.6%)	10(1.0%)
Photophobia	0	1 (0.2%)	2 (0.4%)	3 (0.3%)
Blepharochasis	0	0	1 (0.2%)	1 (0.1%)
Diplopia	0	0	1 (0.2%)	1 (0.1%)
Eye pruritus	0	0	1 (0.2%)	1 (0.1%)
Eye allergy	0	1 (0.2%)	0	1 (0.1%)
Vitreous floaters	0	1 (0.2%)	0	1 (0.1%)
Blepharospasm	1 (0.2%)	0	0	0

Reviewer's Comments: *Blurred vision is reported in 1-2% of subjects.*

Table 5-2.2.1 Number (%) of Participants with Treatment-Emergent Adverse Events during the Double-Blind Treatment Period by System Organ Class and Preferred Term
Group 2 Safety Population

	Placebo + ADT		Cariprazine <1.5mg/day + ADT		Cariprazine 1.5 mg/day +ADT		Cariprazine 2mg/day +ADT		Cariprazine 3mg/day +ADT		Cariprazine 4.5 mg/day +ADT		Cariprazine Overall	
System Organ Class	N=1108		N=213		N=619		N=265		N=699		N=173		N=1969	
Preferred Term	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Eye disorders	12	1.1%	6	2.8%	10	1.6%	9	3.4%	29	4.1%	8	4.6%	62	3.1%
Vision blurred	6	0.5%	4	1.9%	5	0.8%	5	1.9%	21	3.0%	3	1.7%	38	1.9%
Photophobia	0		0		2	0.3%	1	0.4%	2	0.3%	3	1.7%	8	0.4%
Blepharospasm	1	0.1%	1	0.5%	0		0		3	0.4%	0		4	0.2%
Dry eye	0		1	0.5%	0		1	0.4%	0		1	0.6%	3	0.2%
Eye pain	0		0		0		1	0.4%	1	0.1%	0		2	0.1%
Lacrimation increased	0		0		0		1	0.4%	1	0.1%	0		2	0.1%
Lenticular opacit	0		0		0		0		0		1	0.6%	1	0.1%

Reviewer's Comments: *Blurred vision is reported in 1-3% of subjects.*

Reference ID: 5032993

Table 5-2.3 Number (%) of Participants with Treatment-Emergent Adverse Events during the Open-Label Treatment Period by System Organ Class and Preferred Term
Group 3 Safety Population

	Cariprazine 1.5 mg/day +ADT	Cariprazine 3 mg/day +ADT	Cariprazine 4.5 mg/day +ADT	Cariprazine Overall+ADT
	N=103	N=183	N=59	N=345
Preferred Term	n (%)	n (%)	n (%)	n (%)
Eye disorders	10 (10%)	7 (4%)	3 (5%)	20 (6%)
Vision blurred	6 (6%)	3 (1.6%)	1 (2%)	10 (3%)
Dry eye	2 (2%)	0	1 (2%)	3 (1%)
Blepharospasm	1 (1%)	1 (0.5%)	0	2 (1%)
Vitreous floaters	2 (2%)	0	0	2 (1%)
Photophobia	0	0	1 (2%)	1 (0.3%)
Mydriasis	0	1 (0.5%)	0	1 (0.3%)
Retinal haemorrhage	0	1 (0.5%)	0	1 (0.3%)
Visual impairment	0	1 (0.5%)	0	1 (0.3%)
Vitreous detachment	0	1 (0.5%)	0	1 (0.3%)

Reviewer's Comments: *Blurred vision is reported in 1-6% of subjects.*

Tables 14.5.7.6 and 15.5.7.7 Combined Incidence of Lenticular Shifts Safety Population

		Class I	Class II	Class III
Increase	End of Open-label Treatment Period	17/290 (5.9%)	8/290 (2.8%)	10/290 (3.4%)
Decrease	End of Open-label Treatment Period	16/290 (5.5%)	7/290 (2.4%)	5/290 (1.7%)
Increase	Anytime During Open-label Treatment Period	24/290 (8.3%)	8/290 (2.8%)	13/290 (4.5%)
Decrease	Anytime During Open-label Treatment Period	18/290 (6.2%)	9/290 (3.1%)	6/290 (2.1%)

The definitions of positive/negative lenticular shifts Class I, II, III are: Class I: increase/decrease from baseline in LOCS III grade of >= 0.5 (nuclear opalescence), or >= 0.8 (cortical), or >= 0.5 (posterior subcapsular); Class II: increase from baseline in LOCS III grade of >= 0.9 (nuclear opalescence), >= 1.5 (cortical), or >= 0.9 (posterior subcapsular); Class III: LOCS III grade of >= 2.0 for any type of opacity (nuclear opalescence, cortical, or posterior subcapsular) and increase/decrease from baseline in LOCS III grade of >= 0.9 (nuclear opalescence), >= 1.5 (cortical), or >= 0.9 (posterior subcapsular), at the same visit, or cataract surgery since baseline.

Reviewer's Comments: *The studies are too short in duration to accurately assess whether the drug product increases lens opacities. Over the period monitored in these trials there is approximately an equal number of positive and negative shifts. Since lens changes do not resolve, these shifts are more likely to represent variability in the grading and not true increases or decreases in the lenses.*

Reference ID: 5032993

Current Labeling of Ocular Events:

6.1 Clinical Trials Experience

Table 6. Adverse Reactions Occurring in ≥ 2% of VRAYLAR-treated Patients and > Placebo-treated Adult Patients in 3-Week Bipolar Mania Trials			
	Placebo (N= 442) **%**	**VRAYLAR*** 3 - 6 mg/day (N=263) (%)	**VRAYLAR*** 9 - 12 mg/day° (N=360) (%)
Eye Disorders			
Vision blurred	1	4	4

Cataracts
In the long-term uncontrolled schizophrenia (48-week) and bipolar mania (16-week) trials, the incidence of cataracts was 0.1% and 0.2%, respectively. The development of cataracts was observed in nonclinical studies *[see Nonclinical Toxicology (13.2)]*. The possibility of lenticular changes or cataracts cannot be excluded at this time.

Reviewer's Comments: *The incidence of blurred vision in the MDD clinical trials was consistent with the incidence in other indications. Reporting the incidence of cataracts based on 16-week trials is misleading because cataract typically take at least 12 months to be recognized and reported. It is recommended that the reported incidence be deleted.*

Reference ID: 5032993

Summary

1. The incidence of blurred vision in the MDD clinical trials was consistent with the incidence in other indications.

2. The current labeling provides a misleading incidence of cataracts because of the duration of the clinical trials in which the cataracts were reported was too short to obtain an accurate incidence. It is recommended that the labeling include cataract development has been reported in post-market reporting, but that the incidence is uncertain.

Wiley A. Chambers, M.D.
Supervisory Physician, Ophthalmology

Reference ID: 5032993

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILEY A CHAMBERS
08/19/2022 10:54:49 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204370Orig1s009

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 204-370
Supplement #:	9
Related IND #:	104,466
Product Name:	VRAYLAR (Cariprazine)
Indication(s):	(b) (4)
Applicant:	AbbVie, Inc
Dates:	Submission date: 2/18/2022, PDUFA date: 12/18/2022
Review Priority:	Standard (10 month)
Biometrics Division:	DB1
Statistical Reviewer:	Andrew N. Potter, PhD; Emily Nguyen, MS
Concurring Reviewers:	Peiling Yang, PhD
Medical Division:	Division of Psychiatry
Clinical Team:	Nancy Dickinson, PharmD
Project Manager:	Sarah Seung, PharmD

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

The Applicant submits five clinical trials (RGH-MD-53, RGH-MD-54, RGH-MD-56) to support an efficacy claim for the (b) (4)

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
RGH-MD-75	Multicenter, randomized, double-blind, placebo-controlled, parallel-group; flexible-dose	Cariprazine 1-2 mg/day + ADT / 273 Cariprazine 2-4.5 mg/day + ADT / 273 Placebo + ADT / 266	Primary: Change from baseline to week 8 in MADRS score. Secondary: Change from baseline to week 8 in CGI-S scale.	Primary: 1-2 mg \ -0.9 (p=0.2404) 2.0-4.5 mg \ -2.2 (p = 0.0114) Secondary: 1-2 mg \ -0.1 (p=0.1965)

Reference ID: 4966959

				2.0-4.5 mg \ -0.2 (p = 0.0233)
3111-301-001	Multicenter, randomized, double-blind, placebo-controlled, parallel-group; fixed-dose	Cariprazine 1.5 mg/day + ADT / 252 Cariprazine 3 mg/day + ADT / 252 Placebo + ADT / 253	Primary: Change from baseline to week 6 in MADRS score. Secondary: Change from baseline to week 6 in CGI-S scale.	Primary: 1.5 mg \ -2.5 (p=0.0050) 3.0 mg \ -1.5 (p = 0.0727) Secondary: 1.5 mg \ -0.3 (p=0.0727) 3.0 mg \ -0.2 (p = 0.0944)
3111-302-001	Randomized, double-blind, placebo-controlled, fixed-dose, multi-center study to assess dose-response	Cariprazine 1.5 mg/day + ADT / 250 Cariprazine 3 mg/day + ADT / 251 Placebo + ADT / 250	Primary: Change from baseline to week 6 in MADRS score. Secondary: Change from baseline to week 6 in CGI-S scale.	Primary: 1.5 mg \ -0.4 (p = 0.6798) 3 mg \ -1.4 (p=0.1245) Secondary: 1.5 mg \ -0.1 (p=0.5152) 3.0 mg \ -0.2 (p = 0.0573)
RGH-MD-71	Multicenter, randomized, double-blind, placebo-controlled, parallel-group; flexible-dose	Cariprazine 0.1-0.3 mg/day + ADT / 76 Cariprazine 1-2 mg/day + ADT / 73 Placebo + ADT / 81	Primary: Change from baseline to week 8 in MADRS score. Secondary: Change from baseline to week 8 in CGI-I scale.	Primary: 0.1-0.3 mg \ 0.5 (p=0.746) 1-2 mg \ -1.8 (p = 0.227) Secondary: 0.1-0.3 mg \ 0.0 (p=0.879) 1-2 mg \ -0.2 (p = 0.167)
RGH-MD-72	Multicenter, randomized, double-blind, placebo-controlled, parallel-	Cariprazine 1.5-4.5 mg/day + ADT / 269 Placebo + ADT / 258	Primary: Change from baseline to week 8 in MADRS score. Secondary: Change from baseline to week 8 in SDS.	Primary: 1.5-4.5 mg \ -0.2 (p=0.7948) Secondary: 1.5-4.5 mg \ -0.7 (p=0.2784)

Reference ID: 4966959

group;
flexible-dose

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	N/A – no interim analyses.
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	Non future dependent pattern mixture model for sensitivity analysis. Dropouts in all arms are imputed using the same imputation model (shared shift parameter between cariprazine and placebo arms). This model assumes that all dropouts did worse than completers by a common amount.
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Yes.

1 – MMRM is mixed model for repeated measures
2 – PMM is pattern mixture model

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA204370\0190\m5\datasets
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	Both

Reference ID: 4966959

Content Parameter	Response/Comments
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	• RGH-MD-75: adeff • 3111-301-001: adeff • 3111-302-001: adeff • RGH-MD-71: deff • RGH-MD-72: adeff
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Defer to the clinical team.

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc..	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.).	X			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups.	X			The Sponsor only conducted descriptive statistical analyses of the subgroups.
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			

Reference ID: 4966959

Content Parameter	Yes	No	NA	Comments
Application appears to be free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements.	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

No.

5.2. Information Requests/Review Issues

IR sent to Sponsor on Apr 6, 2022 for SAS code used to create plots in label.

Reference ID: 4966959

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREW N POTTER
04/11/2022 01:15:11 PM

EMILY P NGUYEN
04/13/2022 11:10:31 AM

PEILING YANG
04/13/2022 11:35:45 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204370Orig1s009

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA-204370-SUPPL-9**
   sNDA Recommendation: Approval
   sNDA Managed by: OND

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA Efficacy	2/18/22	2/18/22	2/18/22	12/18/22	11/9/2022
Amendment		4/15/22	4/15/22			

3. **Provides For:** a new indication: (b) (4)

4. **Review #**: 1

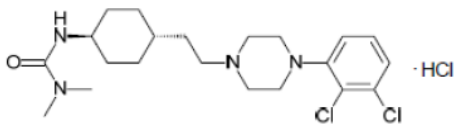
5. **Clinical Review Division**: CDER/OND/ON/DP

6. **Name and Address of Applicant**:
   Allergan Sales, LLC
   5 Giralda Farms,
   Madison, NJ 07940

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Vraylar (cariprazine) capsules	Capsule	1.5 mg, 3 mg, 4.5 mg, 6 mg	Oral	Rx	No

8. **Chemical Name and Structure of Drug Substance**:

	**USAN:** Cariprazine HCl **Chemical name:** *trans*-N-{4-[2-[4-(2,3 dichlorophenyl)piperazine-1-yl]ethyl]cyclohexyl}-N',N'-dimethylurea hydrochloride **Molecular formula:** $C_{21}H_{32}Cl_2N_4O \cdot HCl$ **MW:** 463.87 g/mol **CAS:** 1083076-69-0

9. **Indication**: Treatment of depressive episodes associated with bipolar I disorder (bipolar depression)

10. Supporting/Relating Documents: Seq-0190 and -0192

11. Consults: N/A

12. Executive Summary:

This PA efficacy supplement provides for a new indication: [redacted] (b) (4) .

The original NDA was approved on 9/17/2015 for the acute treatment of manic or mixed episodes associated with bipolar I disorder and the treatment of schizophrenia. Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) was approved on 5/24/2019 via Efficacy Supplement-6. On a Type B pre-submission meeting dated January 12, 2022, the Division of Psychiatry agreed with submission of the supplemental NDA for use of VRAYLAR [redacted] (b) (4), based on the clinical data contained in the meeting briefing package.

A claim for categorical exclusion from the requirement to prepare an environmental assessment (EA) is submitted in accordance with 21 CFR 25.31 (b) for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. The required statement of no extraordinary circumstances also was provided, in accordance with 21 CFR 25.15. The claimed categorical exclusion is acceptable.

There are no new CMC information in Module 2 and Module 3 of this supplement. The proposed labeling changes include an update from the [redacted] (b) (4) trademark to the registered trademark which impacts the Carton and Container labels (See Attachment). There are no CMC related changes made to the carton and container labels. CMC relevant changes were made to Section 11 and Section 16 of the updated prescribing information through team discussions (See SharePoint Link: 204370 -> S-9 for the updated PI). There are no outstanding CMC issues.

13. Conclusions & Recommendations:

This supplement is recommended for approval from a CMC standpoint.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:
Lin Qi, Ph.D., CMC Reviewer, Branch 3, DPMA1, OLDP, OPQ

16. Secondary Reviewer:
Gurpreet Gill Sangha, Ph.D., Branch Chief, Branch 3, DPMA1, OLDP, OPQ

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Lin Qi

Digitally signed by Lin Qi
Date: 11/09/2022 11:28:01AM
GUID: 508da72000029f8811bc57ddc6dd073c

Gurpreet Gill Sangha

Digitally signed by Gurpreet Gill Sangha
Date: 11/09/2022 11:41:20AM
GUID: 5135f2ad000117842392c50c36c7f28a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204370Orig1s009

OTHER REVIEW(S)

Division of Psychiatry

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: 204370/S-009

Name of Drug: Vraylar (cariprazine) capsules

Applicant: Allergan Sales, LLC

BACKGROUND

- The Agency first approved new drug application (NDA) 204370 on September 17, 2015, for the treatment of schizophrenia in adults and acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. The indication "treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults" was added under S-006 (approved 5/24/2019).

- NDA 204370/S-009 is an Efficacy Supplement (ES) that proposes the addition of a new indication of "adjunctive therapy to antidepressants for the treatment of major depressive disorder in adults."

- The most recent and pending supplements with changes to labeling are provided in the table below.

NDA	Supplement (S) #	Type	Submission Date	Provides for	Status
204370	S-006	PAS	7/24/2018	A new indication of treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults. Results from a drug interaction study that fulfill PMR 2947-7.	Approved 5/24/2019
	S-009	ES	2/18/2022	Addition of a new indication "adjunctive therapy to antidepressants for the treatment of major depressive disorder in adults"	Pending

PAS = prior approval supplement
ES = efficacy supplement

REVIEW

- The Applicant submitted proposed changes to the Prescribing Information (PI) and the Medication Guide (MG). The proposed labeling was reviewed by:

- Division of Psychiatry Clinical Team: Nancy Dickinson, PharmD (Clinical Reviewer) and Jean Kim, MD (Team Leader)

- Office of Clinical Pharmacology: Huixia Zhang, PhD (Reviewer) and Luning (Ada) Zhuang, PhD (Team Leader); Atul Bhattaram, PhD (Pharmacometrics Team Leader)

- Office of Biostatistics: Andrew N. Potter, PhD (Reviewer), Emily Nguyen (Analyst) and Peiling Yang, PhD (Team Leader)

- Office of Pharmaceutical Quality: Lin Qi, PhD (CMC Reviewer), Joyce Crich (Quality Application Lead) and Gurpreet Gill Sangha, PhD (Branch Chief)

- Office of Prescription Drug Promotion: Domenic D'Alessandro, PharmD, MBA, CDE (Regulatory Review Officer)

- Division of Medication Error Prevention and Analysis: Loretta Holmes, BSN, PharmD (DMEPA Safety Evaluator) and Madhuri R. Patel, PharmD, (DMEPA Team Leader (Acting))

- Division of Medical Policy Programs: Laurie Buonaccorsi, PharmD (Patient Labeling Reviewer)

- The last approved labeling, for comparison purpose, was the labeling attached to the May 24, 2019, Agency approval letter for NDA 204370/S-006.

- The review team concluded that there is substantial evidence submitted in this ES for approval. Therefore, the new indication, along with associated data from the trials supporting the new indication were added to labeling. The Applicant originally proposed the indication [redacted] (b) (4) [redacted]" however, to be consistent with other drug products with the same indication, the team revised the language to "adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults." Other editorial and clarification changes to the prescribing information and the medication guide are specified in the attached annotated labeling.

- The Applicant submitted carton and container (C&C) labels for reference purposes. DMEPA confirmed that the C&C labels did not contain any proposed revision, so the C&C labels provided in this ES were not reviewed.

- The labeling review was coordinated by the Associate Director of Labeling, Kimberly Updegraff, PharmD.

RECOMMENDATIONS

1. The Agency and Applicant attained labeling agreement in an e-mail dated December 16, 2022.
2. I recommend that an approval letter be issued for this pending supplemental application.

{See appended electronic signature page}

CDR Sarah Seung, PharmD, MS
Regulatory Project Manager

{See appended electronic signature page}

CAPT Keith Kiedrow, PharmD, MS, RAC
Chief, Project Management Staff

ATTACHMENT

- Labeling agreement e-mail
- Annotated labeling

From: Seung, Sarah
To: Yang, Guang
Subject: RE: [EXTERNAL] RE: NDA 204370/S-9 VRAYLAR (cariprazine): Labeling Comments
Date: Friday, December 16, 2022 10:01:00 AM
Attachments: image001.png

Good Morning Guang,

I confirm receipt. As you have accepted all our edits and you have not proposed any further edits, we now have labeling agreement.

Regards,
Sarah

From: Yang, Guang <guang.yang@abbvie.com>
Sent: Friday, December 16, 2022 9:25 AM
To: Seung, Sarah <Sarah.Seung@fda.hhs.gov>
Subject: [EXTERNAL] RE: NDA 204370/S-9 VRAYLAR (cariprazine): Labeling Comments

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Good morning Sarah,

Attached please find the revised final draft USPI (redline and clean versions of the Word files), accepting all recommendations from the Division. We will also submit this officially to the NDA today.

Kindly confirm receipt.

Kind Regards,
Guang

Guang Yang (She/Her/Hers)
Associate Director, Regulatory Affairs
Global Regulatory Strategy
AbbVie Inc.
Office: +1 847-935-4716
Cell: +1 224-478-3722
Email: guang.yang@abbvie.com

From: Seung, Sarah <Sarah.Seung@fda.hhs.gov>
Sent: Thursday, December 15, 2022 8:45 PM
To: Yang, Guang <guang.yang@abbvie.com>
Subject: [EXTERNAL] NDA 204370/S-9 VRAYLAR (cariprazine): Labeling Comments

Dear Guang,

Please find attached our last comments for the prescribing information (PI) for NDA 204370/S-009.

Use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please provide your response via email by **12:00pm on Friday, December 16, 2022**.

Kindly confirm receipt.

Regards,
Sarah

Sarah Seung, PharmD, MS
Senior Regulatory Project Manager

Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation & Research
Tel: 240-402-3879
sarah.seung@fda.hhs.gov

50 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SARAH H Seung
12/16/2022 02:00:33 PM

KEITH J KIEDROW
12/16/2022 02:48:41 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 22, 2022
To:	Sarah Seung, PharmD, MS Regulatory Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Domenic D'Alessandro, PharmD, MBA, CDE Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	VRAYLAR (cariprazine)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 204370
Supplement Number:	S-009
Applicant:	Allergan Sales, LLC

1 INTRODUCTION

On February 18, 2022, Allergan Sales, LLC submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved New Drug Application (NDA) 204370 for VRAYLAR (cariprazine) capsules. With this supplement, the Applicant seeks approval for use of VRAYLAR (cariprazine) capsules as an adjunctive treatment to antidepressant in adults patients with major depressive disorder.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DP) on April 7, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VRAYLAR (cariprazine) capsules.

2 MATERIAL REVIEWED

- Draft VRAYLAR (cariprazine) capsules MG received on April 15, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 18, 2022.
- Draft VRAYLAR (cariprazine) capsules Prescribing Information (PI) received on April 15, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 18, 2022.
- Approved VRAYLAR (cariprazine) capsules labeling dated May 24, 2019.
- Approved CAPLYTA (lumateperone) and REXULTI (brexpiprazole) comparator labeling dated April 26, 2022 and December 27, 2021, respectively.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

LAURIE J BUONACCORSI
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DOMENIC G DALESSANDRO
11/22/2022 11:13:55 AM

SHARON R MILLS
11/22/2022 12:27:39 PM

LASHAWN M GRIFFITHS
11/22/2022 12:39:56 PM

MEMORANDUM

REVIEW OF LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 16, 2022
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 204370/S-009
Product Name and Strength:	Vraylar (cariprazine) capsules, 1.5 mg, 3 mg, 4.5 mg, and 6 mg
Applicant/Sponsor Name:	Allergan Sales, LLC (Allergan)
TTT ID #:	2022-2113
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

Allergan submitted efficacy supplement NDA 204370/S-009 on February 18, 2022 "to seek approval for use of Vraylar as an adjunctive treatment to antidepressant in adult patients with major depressive disorder."

The Division of Psychiatry (DP) requested that we review the proposed Prescribing Information (PI) for Vraylar (Appendix A) to determine if it is acceptable from a medication error perspective.

2 ASSESSMENT

We reviewed the proposed Prescribing Information (PI), submitted on February 18, 2022, as well as DP's current edits to the PI (as of November 14, 2022). We focused on the Dosage and Administration sections of the PI and did not identify any areas that are prone to medication errors. We also considered whether the revisions made to provide for S-009 require subsequent updates to the Vraylar container labels to ensure consistency and to minimize the risk of confusion. We did not identify any areas where updates (e.g., proprietary name, dosage form, route of administration, or usual dosage statement) to the container labels are needed. As such, we have no comments regarding the revised PI or container labels.

3 CONCLUSION

We find the Prescribing Information acceptable from a medication error perspective. Therefore, we have no recommendations at this time.

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Reference ID: 5078865

APPENDIX A. LINK TO THE UPDATED PRESCRIBING INFORMATION RECEIVED ON FEBRUARY 18, 2022

The proposed Prescribing Information can be accessed in docuBridge via this link:

Annotated version: \\CDSESUB1\EVSPROD\nda204370\0190\m1\us\draft-labeling-text-redlined.pdf

Clean version: \\CDSESUB1\EVSPROD\nda204370\0190\m1\us\draft-labeling-text-clean.pdf

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LORETTA HOLMES
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MADHURI R PATEL
11/18/2022 11:34:01 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 16, 2022

To: Sarah Seung, PharmD, Regulatory Project Manager, DP

Nancy Clark Dickinson, PharmD, DP

Kimberly Updegraff, PharmD, MS, Associate Director for Labeling, DP

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for VRAYLAR® (cariprazine) capsules, for oral use

NDA: 204370, S-9

Background:
In response to DP's consult request dated April 7, 2022, OPDP has reviewed the proposed Prescribing Information (PI) for supplement 9 for Vraylar. This supplement provides for a new indication of adjunctive therapy to antidepressants for the treatment of major depressive disorder in adults.

PI and Medication Guide
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 10, 2022, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide, and comments will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at 301-796-3316 or domenic.dalessandro@fda.hhs.gov.

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/s/

DOMENIC G DALESSANDRO
11/16/2022 11:44:47 PM

Clinical Inspection Summary

Date	11/16/2022
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D., Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sarah Seung, Program Coordinator Nancy Dickinson, Pharm.D., Senior Clinical Analyst Jean Kim, M.D., Lead Physician Division of Psychiatry Products (DPP)
NDA	204370 S-09
Applicant	Allergan Sales, LLC (subsidiary of AbbVie, Inc.)
Drug	Cariprazine (Vraylar®)
NME	No
Proposed Indication	(b) (4)
Consult Request	4/7/2022
CIS Goal Date	12/1/2022
Action Goal Date	12/16/2022
PDUFA Date	12/18/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Allergan Sales, LLC seeks to extend the approval of cariprazine (Vraylar®) to include (b) (4) The two major studies supporting this sNDA (3111-301-001, RGH-MD-75) were audited at good clinical practice (GCP) inspections of four clinical investigators (CIs), Drs. Booker, Kunovac, Horwitz, and Shiovitz. Two sites per study were selected based on large subject enrollment and site-specific efficacy effect, no recent inspection history, and relatively large number of protocol deviations.

No significant GCP violations were observed. The two studies appear to have been conducted in adequate compliance with GCP principles and regulations. The audited data for the four CI sites appear acceptable in support of the adjunctive use of cariprazine for MDD as proposed in the sNDA.

Reference ID: 5079068

II. BACKGROUND

Cariprazine (Vraylar®) is an orally active dopamine agonist first approved in 2015 as an atypical antipsychotic agent for use in adults to treat schizophrenia. Dopaminergic pathways in the mesolimbic system of the brain are known to be important in modulating mood and behavior (motivation, pleasure, and reward) and logically believed to be important also as the anatomic-pharmacologic target in treating loss of motivation and anhedonia, the core symptom of depression.

- Clinical experience indicates that cariprazine may be effective in enhancing cognition, improving negative symptoms, and stabilizing mood swings.
- Relatively few important adverse effects have been observed. Long-term safety concerns appear to be limited to modest weight gain, increased glucose and lipid levels, and readily manageable extrapyramidal symptoms.

The current approval of cariprazine includes use in bipolar mania (acute episodes). In this sNDA, the sponsor proposes its use as an (b) (4), as an agent to be added to the baseline antidepressant therapy (ADT) regimen. The two major studies (randomized controlled trials) supporting the sNDA are further described below, with emphasis on protocol features as audited at GCP inspections.

Study Protocol 3111-301-001: *A Double-Blind, Placebo-Controlled Study of Cariprazine as an Adjunct to Antidepressants in the Treatment of Patients with Major Depressive Disorder Who have had an Inadequate Response to Antidepressants Alone*

This randomized, double-blinded, placebo-controlled study was conducted over three years (2018–21) in 759 subjects randomized at 116 CI sites in the United States (US), United Kingdom (UK), Germany, Bulgaria, Estonia, Hungary, and Ukraine. The primary study objective was to evaluate the utility of cariprazine (2 dose levels, relative to placebo) as an adjunctive agent in treating MDD that respond inadequately to baseline ADT.

The study consisted of three periods: (1) 14 - 21 days of screening and washout of prohibited medications; (2) 6 weeks of blinded treatment; and (3) 4 weeks of safety follow-up monitoring. The *major efficacy endpoints* were the changes in evaluation instrument scores from baseline to Week 6 in: *Montgomery-Asberg Depression Rating Scale* (MADRS, *primary*) and *Clinical Global Impressions – Severity* (CGI-S, *major secondary*). Subjects were randomized in equal ratio to three groups (once daily orally for 6 weeks):

- Cariprazine 1.5 mg/day + ADT for 6 weeks
- Cariprazine 1.5 mg/day + ADT for 2 weeks, then 3.0 mg/day + ADT for 4 weeks
- Placebo + ADT for 6 weeks

Subjects were selected for age (18-65 years) and the diagnosis of MDD according to the criterial specified in *Diagnostic and Statistical Manual of Mental* Disorders, *Fifth Edition* as assessed at subject screening using *Structured Clinical Interview*, AND:

- Current major depressive episode (8 weeks to 24 months in duration) with an inadequate response (< 50% improvement) to treatment using up to three antidepressants (adequate dose and duration)

- Overall score ≥ 22 on *Hamilton Depression Rating Scale – 17 Items* (HAMD-17) with a subscore ≥ 2 on Item 1, at both screening and baseline visits (Visits 1 and 2)
- Subjects were excluded for a diagnosis of any current psychiatric diagnosis other than MDD, history of manic or hypomanic episodes, Young Mania Rating Scale (YMRS) score ≥ 12, and imminent risk of injuring self or others or significant damage to property
- Inadequate response was defined as < 50% improvement with up to 3 antidepressant agents of adequate dose and duration, as measured by (modified) *Antidepressant Treatment Response Questionnaire* (ATRQ).
- Adequate dose was defined as a dose above the minimum labeled dose. Adequate duration was defined as continuous antidepressant therapy for at least 6 weeks, with at least 3 of the 6 weeks at a dose above the minimum labeled dose.

Study Protocol RGH-MD-75: *A Double-blind, Placebo-Controlled Study of Cariprazine (RGH-188) as Adjunctive Therapy in Major Depressive Disorder*

This randomized, double-blind, placebo-controlled study was conducted over two years (2011–13) in 819 subjects randomized at 76 CI sites in US, Sweden, Finland, Estonia, Ukraine, and Slovakia. The primary study objective was to evaluate the utility of cariprazine as an adjunctive agent in treating MDD that respond inadequately to ADT.

The study consisted of three periods: (1) 7-14 days of screening and washout of prohibited medications; (2) 8 weeks of blinded treatment; and (3) one-week safety follow-up. The *primary efficacy endpoint* was the change in MADRS score from baseline to Week 8. Subjects were randomized in equal ratio to 3 groups:

- Cariprazine 1.0 – 2.0 mg/day + ADT
- Cariprazine 2.0 - 4.5 mg/day+ ADT
- Placebo + ADT

Subjects were selected for age (18-65 years) and the diagnosis of MDD without psychotic features according to the criteria specified in *Diagnostic and Statistical Manual of Mental* Disorders*, Fourth Edition* (DSM-IV-TR criteria) as assessed at subject screening using *Structured Clinical interview*, AND:

- Current major depressive episode (8 weeks to 24 months in duration)
- Ongoing inadequate response to adequate ADT
- MADRS score ≥ 22 at screening and baseline (Visits 1 and 2)

Subjects were excluded for principal DSM-IV-TR diagnosis of an Axis I disorder other than MDD, or any Axis I disorder other than MDD treated within 6 months, OR:

- History of meeting DSM-IV-TR criteria for: any depressive episode with psychotic or catatonic features; any manic, hypomanic, or mixed episode; schizophrenia, schizoaffective, or other psychotic disorder; panic disorder; obsessive-compulsive disorder; eating disorders; or dementia, mental retardation, or other cognitive disorders
- History of meeting DSM-IV-TR criteria for MDD with seasonal pattern, if the anticipated season of remission coincides with the study

Reference ID: 5079068

- DSM-IV-TR–based diagnosis of borderline or antisocial personality disorder or other Axis II disorder of sufficient severity to interfere with participation in this study
- Suicide risk, as evidenced by: (a) suicide attempt within the past year; (b) significant risk, as judged by the Investigator, based on the psychiatric interview or information collected using *Columbia–Suicide Severity Rating Scale* (C-SSRS) at Visit 1 or Visit 2; or MADRS Item 10 score ≥ 5 at baseline or screening

III. INSPECTION RESULTS

1. Gary J. Booker, M.D.

851 Olive Street
Shreveport, LA 71104

Inspection dates: October 17 – 21, 2022

This CI site was closed; the CI and all site staff were unavailable, and the study records were maintained by the sponsor. The inspection was limited to records review at the sponsor's records storage facility (2525 Dupont Drive; Irvine, California 92612).

Study 3111-301-001, Site 40: 29 subjects were screened, 19 were enrolled, and 17 completed the study (1 withdrew consent, 1 lost to follow up). Subject case records for all enrolled subjects were reviewed, including detailed review for 10 subjects.

No significant GCP deficiencies were observed. Study files and subject case records were well maintained. The records review indicated adequate compliance with GCP principles and regulations. No unreported protocol deviations or adverse events (AEs) were discovered. Evidence of unblinding was not observed. The primary and the major secondary efficacy endpoints (as noted in the protocol summary above, Section II) were audited in detail and determined to be verifiable against the data reported in the sNDA, as were the audited AE data.

Note: The final Establishment Inspection Report (EIR) for this inspection has not been received at OSI. The inspectional findings reported in this Clinical Inspection Summary (CIS) are based on preliminary communication with the field investigator. If significant new findings are noted upon receipt and review of the EIR, an addendum to the CIS will be forwarded to the review division.

2. Mustafa Rawaf, D.O. (Jelena Kunovac, M.D.)

3012 West Charleston Boulevard, Suite 100
Las Vegas, NV 89102

Inspection dates: June 3 - 6, 2022

At time of inspection, Dr. Rawaf had succeeded Dr. Kunovac as the head of this clinical research site facility. Dr. Rawaf served as the primary CI for the entire study duration.

Reference ID: 5079068

Study 3111-301-001, Site 14: 40 subjects were screened, 26 were enrolled, and 24 completed the study (1 withdrawn, 1 lost to follow up). Subject 36 was withdrawn on Day 2 of cariprazine dosing (3.0 mg/day) for apparent treatment-related AE, after two episodes of syncope (reported in sNDA). Subject case records were reviewed for all subjects, including detailed review for 20 enrolled subjects.

GCP deficiency observations included: transient lapse in CGI rater certification for an otherwise qualified CGI rater; and occasional temperature record corrections (study medication storage log) noted in a way that made it difficult to read the original record, and without documenting who made the correction, when, and why. These observed deficiencies appeared minor, few or isolated, and unlikely to be significant.

GCP deficiencies were otherwise not observed. Study files and subject case records were adequately organized to facilitate review. The inspection confirmed adequate compliance with GCP principles and regulations. No significant unreported protocol deviations or AEs were discovered. Evidence of unblinding was not observed. The primary and the major secondary efficacy endpoint (as noted in the protocol summary above, Section II) were audited in detail and determined to be verifiable against the data reported in the sNDA, as were the audited AE data.

3. Alexander Horwitz, M.D.

702 Church Street, NE
Salem, OR 97301

Inspection dates: October 24 - 28, 2022

This CI site was closed; the CI and all site staff were unavailable, and the study records were maintained by the sponsor. The inspection was limited to records review at the sponsor's records storage facility (2525 Dupont Drive; Irvine, California 92612).

Study RGH-MD-75, Site 27: 27 subjects were screened, 23 were enrolled, and 18 completed the study (1 excluded, 3 withdrew consent, 1 lost to follow-up). Subject case records were reviewed in detail for all enrolled subjects.

No significant deficiencies were observed. Study files and subject case records were well maintained. The records review indicated adequate compliance with GCP principles and regulations. No unreported protocol deviations or AEs were discovered. Evidence of unblinding was not observed. The primary and the major secondary efficacy endpoints (as noted in the protocol summary above, Section II) were audited in detail and determined to be verifiable against the data reported in the sNDA, as were the audited AE data.

Note: The final EIR for this inspection has not been received at OSI. The inspectional findings reported in this CIS are based on preliminary communication with the field investigator. If significant new findings are noted upon receipt and review of the EIR, an addendum to the CIS will be forwarded to the review division.

Reference ID: 5079068

4. Thomas Shiovitz, M.D.

4835 Van Nuys Boulevard, Suite 104
Sherman Oaks, CA 91403

Inspection dates: May 17 - 20, 2022

Study RGH-MD-75, Site 66: 26 subjects were screened, 20 were enrolled, and 15 completed the study (2 withdrawn, 2 excluded, 1 withdrew consent). Subjects (b) (6) and (b) (6) (cariprazine 1.0 – 2.0 mg/day) were withdrawn for AEs of akathisia and fatigue, respectively (reported in sNDA). Subject case records were reviewed for all subjects, including detailed review for 18 enrolled subjects.

GCP deficiency observations consisted of: incorrect dates of laboratory report review (discrepant by one day) and occasionally illegible handwritten notes. The observed deficiencies appeared minor, few or isolated, and unlikely to be significant.

GCP deficiencies were otherwise not observed. Study files and subject case records were well organized. The inspection confirmed good compliance with GCP principles and regulations. No unreported protocol deviations or AEs were discovered. Evidence of unblinding was not observed. The primary and the major secondary efficacy endpoints (as noted in the protocol summary above, Section II) were audited in detail and determined to be verifiable against the data reported in the sNDA, as were the audited AE data.

Note: The EIR review for this inspection has not been completed at OSI. The inspectional findings reported in this CIS are based on the EIR, the sNDA, and on-going discussion with the field investigator. If new significant findings are discovered in discussing the EIR with the field investigator, an addendum to the CIS will be forwarded to the review division.

{See appended electronic signature page}

John Lee, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Reference ID: 5079068

CONCURRENCE: *{See appended electronic signature page}*

Jenn Sellers, M.D., Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DPP/Division Director/ Mitchell Mathis
DPP/Team Leader/Jean Kim
DPP/Clinical Reviewer/Nancy Dickinson
DPP/Regulatory Project Manager/Sarah Seung
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Acting Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Primary Reviewer/John Lee
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

Reference ID: 5079068

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