Relationship of Cariprazine Plasma Concentration to Efficacy and Safety in Patients With Schizophrenia or Bipolar Mania

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ABSTRACT

Introduction: Population exposure-response analysis was undertaken to describe the relationship of drug concentrations to measures of clinical efficacy and safety in patients with schizophrenia or bipolar mania.

Methods: Data were obtained from >800 patients with bipolar mania who were randomized to cariprazine (3–12 mg/d) or placebo in two 3-week, double-blind, placebo-controlled Phase 3 studies. Data were obtained from >1700 patients with schizophrenia who were administered cariprazine (1.5–21 mg/d) or placebo in two Phase 1b and five Phase 2/3 studies (3–6-week, double-blind, placebo-controlled studies). Exposure metrics based on total cariprazine [nM] (defined as the molar sum of cariprazine and its two major metabolites of similar pharmacological activity, desmethyl-cariprazine [DCAR] and didesmethyl-cariprazine [DDCAR]) were explored for potential relationships with efficacy and safety endpoints. Modeling was performed with NONMEM, a nonlinear mixed-effects modeling software package, utilizing standard pharmacometric techniques.

Results: Bipolar mania: Exposure to average total cariprazine was found to relate to reductions in YMRS total scores via a saturable E_{max}-type relationship, with 50% of overall potential reduction reached at concentrations associated with typical values achieved with steady-state 4.5 mg/d dosing. Time-weighted total C_{ave} was found to have a statistically significant relationship with the probabilities of adverse events (akathisia, EPS without akathisia/restlessness, nausea and/or vomiting, and parkinsonism cluster). These analyses demonstrated an increase in efficacy with increasing dose in the range of 1.5–12 mg/d and supported 3 mg/d as the lowest efficacious dose. Dose uptitration from 3 to 12 mg/d was associated with a tradeoff between an increase in efficacy and increase in adverse events. Schizophrenia: Exposure to average total cariprazine was found to relate to reductions in PANSS total scores via a saturable E_{max}-type relationship, with 50% of overall potential reduction reached at concentrations associated with typical values achieved with steady-state 3 mg/d dosing. Time-weighted total C_{ave} was found to have a statistically significant relationship with the probabilities of adverse events (similar events to bipolar mania). These analyses demonstrated an increase in efficacy with increasing dose in the range of 1.5–12 mg/d. Dose uptitration from 1.5 to 12 mg/d was associated with a tradeoff between an increase in efficacy and increase in adverse events.

Conclusions: These population exposure-response analyses support the efficacy and safety of FDA-approved dose ranges of 3–6 mg/d for treatment of bipolar mania and 1.5–6 mg/d for treatment of schizophrenia.

INTRODUCTION

Cariprazine (CAR) is an orally active and potent dopamine D_3/D_2 receptor partial agonist, approved in the US in 2015 for the treatment of both schizophrenia and bipolar I disorder. Cariprazine binds with significantly higher affinity to D_3 than D_2 receptors and has a low affinity at other receptor sites, such as the 5-HT_{2C}, histamine H_1, and adrenergic receptor sites, thus suggesting a lower potential for side effects, such as extrapyramidal symptoms and body weight gain. In rodent models, cariprazine displayed potent antipsychotic-, antidepressant- and anxiolytic-like as well as procognitive activity. Clinical trials completed to date have demonstrated the tolerability, efficacy, and safety of oral cariprazine in patients with schizophrenia and bipolar mania.

OBJECTIVES

- Develop a PK/PD model characterizing the time-course and exposure-response relationships between cariprazine and metabolite exposures and the Positive and Negative Syndrome Scale (PANSS) total score, PANSS positive score, and PANSS negative score in patients with schizophrenia
- Develop a PK/PD model characterizing the time-course and exposure-response relationships between cariprazine and metabolite exposures and Young Mania Rating Scale (YMRS) total score in patients with bipolar mania
- For each indication, develop exposure-response models for the occurrence of select treatment-emergent adverse events (TEAEs) using logistic regression models
- Support dose selection and dose justification based on the trade-offs identified in the respective exposure-response models

DATA FOR ANALYSIS

Bipolar Mania

Data were obtained from >800 patients with bipolar mania who were randomized to cariprazine (3–12 mg/d) or placebo in two 3-week, double-blind, placebo-controlled Phase 3 studies.

Table 1. Studies Included in the Pharmacokinetic/Pharmacodynamic Analyses of Cariprazine (RGH-188) for Bipolar Mania

Study Number	Phase	Study Title	Planned Patients	Duration of Trial	Dosing Regimens
RGH-MD-32	3	A double-blind, placebo controlled evaluation of the safety and efficacy of cariprazine in patients with acute mania associated with bipolar I disorder	320 male and female patients with a diagnosis of bipolar mania[a] 18 to 65 years old	39 to 42 days total 3 weeks of double-blind treatment	3 weeks of oral dosing 2 dosing groups (1:1 allocation) 1. cariprazine 2. placebo cariprazine titrated from 3 to 12 mg/d based on clinical response and adverse events
RGH-MD-33	3	A double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with acute mania associated with bipolar I disorder	495 male and female patients with a diagnosis of bipolar mania[a] 18 to 65 years old	39 to 42 days total 3 weeks of double-blind treatment	3 weeks of oral dosing 3 dosing groups (1:1:1 allocation) 1. cariprazine 3-6 mg/d 2. cariprazine 6-12 mg/d 3. placebo cariprazine titrated based on clinical response and adverse events

[a]Meeting DSM-IV-TR criteria for bipolar I disorder, acute manic or mixed episode, and having a Young Mania Rating Scale (YMRS) total score ≥20 and a score of at least 4 on 2 of the following YMRS items: irritability, speech, content, and disruptive/aggressive behavior.

Schizophrenia

Data were obtained from >1700 patients with schizophrenia who were administered cariprazine (1.5–21 mg/d) or placebo in two Phase 1b and five Phase 2/3 studies (3–6-week, double-blind, placebo-controlled studies).

Table 2. Studies Included in the Pharmacokinetic/Pharmacodynamic Analysis of Cariprazine (RGH-188) for Schizophrenia

Study Number	Phase	Study Title	Study Population	Duration of Trial	Used in Analysis
RGH-MD-01	1b	A double-blind, randomized, placebo-controlled trial of the safety, tolerability and pharmacokinetics following escalating, multiple, oral doses of RGH-188 in patients with schizophrenia	56 men with schizophrenia 18 to 55 years old	33 to 43 days total 22 days of double-blind treatment	Safety analysis
RGH-MD-02	2b	Evaluation of the effects of sequential multiple-dose regimens of cariprazine on cardiac repolarization in patients with schizophrenia	100 men and women with schizophrenia or schizoaffective disorder 18 to 45 years old	9 weeks total 35 days of double-blind treatment	Safety analysis
RGH-MD-03	2	A double-blind, placebo-controlled evaluation of the safety and efficacy of RGH-188 in the acute exacerbation of schizophrenia	375 male and female patients with schizophrenia 18 to 65 years old	11 weeks total 6 weeks of double-blind treatment	Efficacy model; safety analysis
RGH-MD-04	3	A double-blind, placebo- and active-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia	600 male and female patients with schizophrenia 18 to 60 years old	9 weeks total 6 weeks of double-blind treatment	Efficacy model; safety analysis
RGH-MD-05	3	A double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia	450 male and female patients with schizophrenia 18 to 60 years old	9 weeks total 6 weeks of double-blind treatment	Efficacy model; safety analysis
RGH-MD-16	2b	Evaluation of the safety and efficacy of RGH-188 in the acute exacerbation of schizophrenia	675 male and female patients with schizophrenia 18 to 60 years old	9 weeks total 6 weeks of double-blind treatment	Efficacy model; safety analysis
RGH-MD-18	1b	A randomized, double-blind, placebo-controlled study of the safety, tolerability, and pharmacokinetics of cariprazine following escalating, multiple, oral doses in patients with schizophrenia	36 male and female patients with schizophrenia or schizoaffective disorder 18 to 55 years old	9 weeks total 4 weeks of double-blind treatment	Safety analysis

All above studies were used in the safety analyses, but only RGH-MD-03, RGH-MD-04, RGH-MD-05, and RGH-MD-16 were used in the efficacy analyses

METHODS

- Exposure metrics based on total cariprazine [nM] (defined as the molar sum of cariprazine and its two major metabolites of similar pharmacological activity, desmethylcariprazine [DCAR] and didesmethylcariprazine [DDCAR]) were explored for potential relationships with efficacy and safety endpoints. Modeling was performed with NONMEM, a nonlinear mixed effects modeling software package, utilizing standard pharmacometric techniques.

Pharmacokinetic/pharmacodynamic models were developed to characterize the time-course of efficacy endpoint scores in the absence of treatment and the exposure-response relationships for total average plasma concentration (C_{ave}). After the time-course of efficacy endpoint scores in patients treated with placebo was characterized by a model of the drug-free data, and after covariate effects were introduced to explain interindividual variability (IIV) in the placebo response, the effect of cariprazine exposure was added as an additional component to the base structural model for patients receiving treatment with cariprazine. Covariate analyses exploring the influence of selected demographic and clinical status indicators on drug effect model parameters were performed following development of the base PK/PD model that included both the time-course of response (placebo effect) and the relationship with drug exposure.

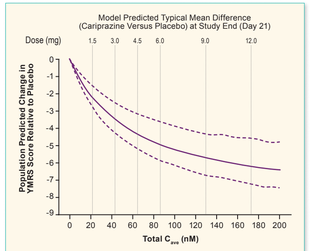
Logistic regression analysis was used to develop exposure-safety models that related the risk of experiencing akathisia, EPS without akathisia or restlessness, nausea and/or vomiting, and parkinsonism cluster to individual measures of exposure defined as the total C_{ave} and time-weighted total C_{ave} for the dosing regimen of the patient on the date of the first occurrence of the AEs. The exploratory empirical logit plots for each of the covariates were evaluated for observable trends and were used to help determine the functional form of the relationship between the estimated logit parameter and the covariate. The Hosmer-Lemeshow goodness-of-fit test and the area under the receiver operating characteristic curve were used for model evaluation.

RESULTS

Bipolar Mania

Exposure to average total cariprazine was found to relate to reductions in YMRS total scores via a saturable E_{max} type relationship, with 50% of overall potential reduction reached at concentrations associated with typical values achieved with steady-state 4.5 mg/d dosing. Time-weighted total C_{ave} was found to have a statistically significant relationship with the probabilities of adverse events (akathisia, EPS without akathisia/restlessness, nausea and/or vomiting, and parkinsonism cluster). These analyses demonstrated an increase in efficacy with increasing dose in the range of 1.5–12 mg/d and supported 3 mg/d as the lowest efficacious dose. Dose uptitration from 3 to 12 mg/d was associated with a tradeoff between an increase in efficacy and an increase in adverse events.

Figure 1. Model-Based Population Mean Placebo-Corrected Change From Baseline in YMRS Total Score



Dashed lines represent 90% confidence intervals.

Figure 2. Benefit-Risk for YMRS Total Scores and Treatment-Emergent Adverse Events in Bipolar Patients

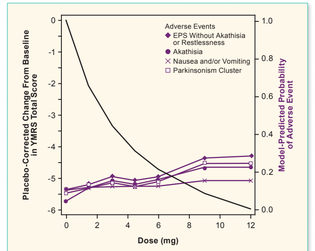


Table 3. Typical Incremental Improvement in YMRS Scores and Predicted Probabilities of Selected Adverse Events With Increases in Cariprazine Dose

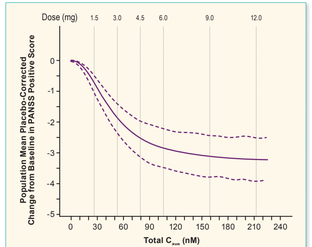
Cariprazine Dose[a] (mg/d)	Typical Predicted Placebo-Corrected Changes From Baseline in YMRS Scores After 3 Weeks of Therapy	Incremental Improvements in YMRS Scores (%)	Placebo-Adjusted Model-Predicted Probability of Akathisia	Placebo-Adjusted Model-Predicted Probability of EPS Without Akathisia or Restlessness	Placebo-Adjusted Model-Predicted Probability of Nausea and/or Vomiting	Placebo-Adjusted Model-Predicted Probability of Parkinsonism Cluster
1.5	-2.10	-	0.08	0.03	0.01	0.03
3.0	-3.34	59	0.11	0.07	0.02	0.06
4.5	-4.16	25	0.09	0.05	0.02	0.04
6.0	-4.74	14	0.11	0.07	0.02	0.06
9.0	-5.51	16	0.18	0.17	0.05	0.16
12.0	-6.00	9	0.18	0.18	0.05	0.16

[a]The doses for the YMRS analysis correspond to the mean total C_{ave} at each dose level predicted by the population pharmacokinetic model, while dose for akathisia, EPS without akathisia or restlessness, nausea and/or vomiting, and parkinsonism cluster corresponds to the median observed time-scaled exposures across each dose level.
C_{ave}, average plasma concentration; EPS, extrapyramidal symptoms; total C_{ave}, combined C_{ave} for cariprazine, desmethyl-cariprazine, and didesmethyl-cariprazine; YMRS, Young Mania Rating Scale.

Schizophrenia

Exposure to average total cariprazine was found to relate to reductions in PANSS total scores via a saturable E_{max} type relationship, with 50% of overall potential reduction reached at concentrations associated with typical values achieved with steady-state 3 mg/d dosing. Time-weighted total C_{ave} was found to have a statistically significant relationship with the probabilities of adverse events (similar events to bipolar mania). These analyses demonstrated an increase in efficacy with increasing dose in the range of 1.5–12 mg/d. Dose uptitration from 1.5 to 12 mg/d was associated with a tradeoff between an increase in efficacy and increase in adverse events.

Figure 3. Model-Based Population Mean (90% Confidence Interval) Placebo-Corrected Change From Baseline in PANSS Positive Score Versus Total C_{ave}



Dashed lines represent 90% confidence intervals.

Figure 4. Benefit-Risk for PANSS Total Scores and Treatment-Emergent Adverse Events in Patients With Schizophrenia

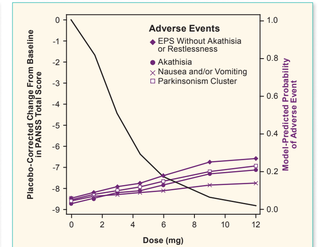


Table 4. Typical Incremental Changes in PANSS Total Scores and Adverse Event Probability With Increases in Cariprazine Dose in Schizophrenia

Cariprazine Dose (mg/d)	Typical Predicted Placebo-Corrected Changes From Baseline in PANSS Scores After 3 Weeks of Therapy	Incremental Improvements in PANSS Scores Relative to Previous Dose	Placebo-Adjusted Model-Predicted Probability of Akathisia	Placebo-Adjusted Model-Predicted Probability of EPS Without Akathisia or Restlessness	Placebo-Adjusted Model-Predicted Probability of Nausea and/or Vomiting	Placebo-Adjusted Model-Predicted Probability of Parkinsonism Cluster
1.5	-1.65	-	0.03	0.03	0.01	0.03
3.0	-4.49	172%	0.06	0.06	0.02	0.05
4.5	-6.39	42%	0.07	0.08	0.03	0.07
6.0	-7.46	17%	0.10	0.12	0.04	0.10
9.0	-8.42	13%	0.16	0.19	0.07	0.15
12.0	-8.81	5%	0.18	0.21	0.08	0.18

EPS, extrapyramidal symptoms; PANSS, Positive and Negative Syndrome Scale

CONCLUSIONS

- Modeling of exposures of total cariprazine found statistically significant relationships between exposure to total cariprazine and changes in the primary Phase 3 efficacy endpoints for both schizophrenia and bipolar I mania
- Time-weighted total C_{ave} was found to have a statistically significant relationship with the probabilities of adverse events (akathisia, EPS without akathisia/restlessness, nausea and/or vomiting, and parkinsonism cluster)
- These population exposure response analyses support the efficacy and safety of FDA approved dose ranges of 3–6 mg/d for treatment of bipolar mania and 1.5–6 mg/d for treatment of schizophrenia

DISCLOSURES

Timothy Carrothers, Antonia Periclou, Parviz Ghahramani, Suresh Durgam, Willie Earley, and Tatiana Khariton are or were employees of Forest Research Institute Inc., an Allergan affiliate, at the time of the study. Margit Kapás is an employee of Gedeon Richter Plc. Susan Willavize, David Jaworowicz, and Julie Passarell have nothing to disclose. Writing and editorial assistance was provided to the authors by Prescott Medical Communications Group (Chicago, IL) and funded by Allergan, Inc. (Irvine, CA). All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

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