Citation: Clin Transl Sci (2020) 13, 362–371; doi:10.1111/cts.12720

ARTICLE

Relationship Between Plasma Concentrations and Clinical Effects of Cariprazine in Patients With Schizophrenia or Bipolar Mania

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Population pharmacokinetic/pharmacodynamic modeling (via NONMEM) was used to describe longitudinal exposure-response relationships for total cariprazine (sum of cariprazine and its major active metabolites) in 2,558 patients with schizophrenia or bipolar mania. Drug exposure metrics were explored for potential relationships with efficacy and safety end points. Total cariprazine exposures were significantly related to reductions in Positive and Negative Syndrome Scale (PANSS) or Young Mania Rating Scale (YMRS) total scores in schizophrenia or bipolar mania, respectively, via a maximum effect (E_{max})-type relationship. Typical steady-state plasma concentrations after 3 and 4.5 mg/day were associated with 50% of maximum typical reductions in PANSS and YMRS total scores, respectively. Time-weighted cariprazine exposures had significant relationships with the probability of common adverse events (AEs). Dose increase was associated with increased efficacy but was also associated with an increase in AEs. Results of these pharmacokinetic/pharmacodynamic analyses support that the recommended dose range (1.5–6 mg/day for schizophrenia and 3–6 mg/day for bipolar mania) provides an appropriate benefit-risk balance between cariprazine efficacy and safety.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Cariprazine has demonstrated efficacy for the treatment of schizophrenia and bipolar mania based on phase II/III, double-blind, randomized, placebo-controlled, short-term studies.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This population pharmacokinetic/pharmacodynamic study investigated the relationship between drug exposures and efficacy/safety within patients enrolled in the cariprazine clinical development program for schizophrenia and bipolar mania. Efficacy-exposure and safety-exposure models were used to quantify the risk-benefit tradeoffs associated with increases in dose and exposure.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The analyses revealed that doses ≤ 6 mg/d have a favorable benefit-risk balance, with increases in efficacy that are coupled with less pronounced increases in the probability of adverse events compared with doses > 6 mg/d. These results support the recommended clinical dose ranges of 1.5–6 mg/d for schizophrenia and 3–6 mg/d for bipolar mania, respectively.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ These risk-benefit assessments support the ongoing clinical development of cariprazine in the treatment of schizophrenia and bipolar disorder (both mania and depression).

Identifying the appropriate efficacious dose for an antipsychotic is often confounded by placebo response and high dropout rate in psychiatric clinical trials.[1,2] Population pharmacokinetic/pharmacodynamic (PK/PD) modeling, in which data from several studies can be analyzed simultaneously,[3] is a useful tool for clarifying exposure-response relationships and can assess the cumulative data to support optimal clinical dose. Model-based analysis also increases the power to detect differences in clinical trials.[4]

Cariprazine is an orally active and potent dopamine D_3-preferring D_3/D_2 receptor partial agonist and a serotonin 5-HT_{1A} receptor partial agonist.[5] Cariprazine also acts as an antagonist at 5-HT_{2B} receptors, with lower affinity for 5-HT_{2A}, 5-HT_{2C}, histamine H_1, and adrenergic α_1 receptors and negligible affinity for other receptors (e.g., cholinergic muscarinic receptors).[5] Two major metabolites, desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR), are formed from cariprazine, and both DCAR and

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Received: June 27, 2019; accepted: October 3, 2019. doi:10.1111/cts.12720

DDCAR are pharmacologically equipotent to cariprazine.[6] Steady-state levels of cariprazine and DCAR can be reached within 1–2 weeks and reached for DDCAR within 4 weeks. Steady-state exposure for DDCAR is 2–3 times higher than cariprazine, whereas DCAR is 30–40% of carprazine exposure.[6]

Cariprazine is approved for the treatment of adult patients with schizophrenia (United States and Europe; recommended dose range: 1.5–6 mg/day) and manic or mixed episodes associated with bipolar I disorder (United States; recommended dose range: 3–6 mg/day). Clinical trials included in the development programs for schizophrenia and bipolar mania have demonstrated the efficacy, safety, or tolerability of cariprazine in adult patients[7–16]; in these studies, blood samples were collected for the measurement of plasma concentrations of cariprazine and its major metabolites.

Population PK models were used to predict the systemic exposure of cariprazine, DCAR, and DDCAR in patients with schizophrenia and bipolar mania (A. Periclou, L. Phillips, P. Ghahramani, M. Kapás, T. Carrothers, and T. Khariton, unpublished data). The objectives were to develop PK/PD models characterizing the time-course and exposure-response relationships for efficacy associated with cariprazine treatment and to develop exposure-response models for the occurrence of treatment-emergent adverse events (TEAEs) using logistic regression models for each indication. The efficacy measures evaluated were the Positive and Negative Syndrome Scale (PANSS)[17] total, positive subscale, and negative subscale score for patients with schizophrenia and the Young Mania Rating Scale (YMRS)[18] total score for patients with manic or mixed episodes of bipolar I disorder. The overall objective of the PK/PD analyses was to describe the trade-off between the adverse events (AEs) and efficacy of cariprazine with increases in dose when administered to patients with schizophrenia or bipolar mania and to support the recommended clinical doses for cariprazine.

METHODS

Studies

A summary of the studies used for PK/PD analyses is presented in **Table S1**. The studies were approved by institutional review boards or ethical committees at each trial site and written informed consent was obtained from all patients before enrollment. The key inclusion and exclusion criteria were shared across studies for the treatment of schizophrenia or bipolar mania. Patients were randomly assigned to treatment groups in a double-blind fashion; demographics and baseline efficacy scores were balanced and similar between treatment groups within each study.[7–10,12,14,15] All patients included in the PK/PD analysis population had a baseline measurement and ≥ 1 documented post-first dose efficacy end point measurement.

Schizophrenia. Data from patients who had received cariprazine or placebo during the four double-blind, multisite, placebo-controlled studies (United States only: RGH-MD-03; Global: RGH-MD-04, RGH-MD-05, and RGH-MD-16) were used for efficacy analyses (PANSS models), and data from patients who received cariprazine or placebo from all seven studies (additionally RGH-MD-01, RGH-MD-02, and RGH-MD-18) were used for safety analyses. Sparse PK samples (≤ 12 per patient) were collected in each study, with serial PK samples collected in selected studies; PANSS total, positive subscale, and negative subscale scores were collected weekly for a maximum of ~ 6 weeks following initiation of study treatment, with the measured PANSS total scores modeled as the primary efficacy end point.

Bipolar I disorder. Data from patients who had received cariprazine or placebo during the two double-blind, international, placebo-controlled studies (RGH-MD-32 and RGH-MD-33) were used for both the efficacy (YMRS models) and safety analyses. Sparse PK samples (≤ 8 per patient) were collected in each study, YMRS total scores were collected weekly for a maximum of 3 weeks following initiation of study treatment, and the measured YMRS total score was modeled as the primary efficacy end point.

Modeling

The model development process is described in **Figure S1**; briefly, the steps were: exploratory data analysis, base structural model development, evaluation of covariate effects (covariates evaluated are listed in **Table 1**), model refinement, and model evaluation. The first-order conditional estimation method with interaction was used to estimate model parameters for the efficacy models, and Laplacian estimation was used for safety modeling. Exploratory data and statistical analyses were performed using SAS version 9.2 and KIWI version 1.1,[19,20] population modeling was performed using NONMEM version 7.1.2,[21] and bootstrap and visual predictive check procedures were performed using PsN version 3.12.[22]

Table 1 Covariates explored in efficacy and safety models

	Schizophrenia		Bipolar	
Variable	Efficacy (PANSS)	Safety	Efficacy (YMRS)	Safety
Age, years	X	X	X	X
Race[a]	X	X	X	X
Sex[b]	X	X	X	X
Disease severity[c]	X		X	
Hospitalization status[d]	X		X	
Duration of disease, years	X		X	
Region[e]	X	X	X	
Smoking status[f]	X		X	X
Study indicator	X			
Rescue medications for EPS or akathisia				X

EPS, extrapyramidal symptoms; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.
[a]Race: 1 = White, 2 = Black or African-American, 3 = Asian, 4 = American-Indian or Alaska Native, 5 = Native Hawaiian or other Pacific Islander, 99 = Other. [b]Sex: 0 = male, 1 = female. [c]Disease severity corresponds to baseline PANSS or YMRS total score for patients with schizophrenia or bipolar disorder, respectively. [d]Hospitalization status: 0 = outpatient, 1 = inpatient. [e]Region: 0 = United States, 1 = Asia (mostly patients from India), 2 = Eastern Europe, 3 = South America, 4 = Africa, 5 = Russia. [f]Smoking status: 0 = nonsmoker, 1 = smoker.

Efficacy model development. Population PK models (A. Periclou, L. Phillips, P. Ghahramani, M. Kapás, T. Carrothers, T. Khariton, unpublished data) were used to predict total cariprazine concentrations. The total cariprazine active moiety, including the DCAR and DDCAR metabolites (total CAR), was considered in the modeling due to the high exposure values of the metabolites and their equipotency with cariprazine. To derive the average total CAR concentration (C_{ave}), the total area under the plasma concentration-time curve was calculated within each inter-assessment time interval and then divided by the time span for the relevant interval. The primary efficacy parameter for patients with schizophrenia was the PANSS total score, although PANSS-positive ($PANSS_P$) and PANSS-negative ($PANSS_N$) subscale scores were also evaluated, and for patients with bipolar disorder was the YMRS total score.

Selection of the most appropriate model was based upon the minimum value of the objective function (minVOF), reductions in unexplained variability, precision in model parameter estimates, magnitude of residual variability (RV), and goodness-of-fit evaluations. Diagnostic goodness-of-fit plots were used between steps to assess validity of the base placebo and combined placebo plus cariprazine models. The placebo response models (including covariate selection) were fitted using the placebo data only. Functional forms for the time course of placebo response ($EFF_{placebo}$) were explored as appropriate, based on exploratory data analysis, including but not limited to, the Weibull function, and linear, maximum effect (E_{max}), and sigmoid E_{max} models. Then, using data from cariprazine-treated patients and pooled with placebo data, a base structural model was developed that included both the $EFF_{placebo}$ and the effects of drug exposure ($EFF_{cariprazine}$). The effects of cariprazine treatment were incorporated into the model as either being additive to baseline and placebo effects, proportional to the baseline and additive to the efficacy score as predicted by the placebo model, or proportional to both the baseline and efficacy score as predicted by the placebo model. Functional forms for $EFF_{cariprazine}$ were explored using linear, log-linear, E_{max}, sigmoid E_{max}, and power models, as appropriate, based on the data.

Additive and exponential interindividual variability (IIV) models, and additive and proportional RV models were explored and modeled as appropriate. Covariate analyses were performed following the development of the base model using a forward selection followed by backward elimination procedure to explore the influence of selected demographic and clinical status indicators on exposure-response parameters (**Table 1**). In the forward selection procedure, each covariate was individually added to the new base covariate model and tested for statistical significance; covariates that contributed a change of ≥ 6.63 in the minVOF (α = 0.01, 1 df) were included into the model and this process was repeated until there were no further covariates that produced statistically significant reductions in the minVOF. After forward selection and evaluation of the full multivariate model, univariate stepwise backward elimination proceeded, in which each covariate was removed from each parameter equation separately; statistically significant covariates were retained in the model (α = 0.001 for PANSS; α = 0.0005 for YMRS).

Model robustness was evaluated via prediction-corrected visual predictive checks (pcVPCs) and a nonparametric bootstrap procedure. The pcVPC procedure involved using NONMEM to simulate 1,000 replicates of the analysis data; the simulated data were overlaid on the observed data to visually assess concordance between the model-based simulations and observed data. In addition, a total of 1,000 bootstrap data sets were created by resampling with replacement from the analysis data set; the final population PK/PD efficacy model was then estimated for each of the bootstrap data sets, resulting in bootstrap distributions (including confidence intervals) for each of the estimated parameters.

AE model development. Logistic regression analysis was used to develop a base model that related the probability of the event to a measure of drug exposure (e.g., TC_{ave}). Only TEAEs with ≥ 5% incidence were evaluated. Population PK models (A. Periclou, L. Phillips, P. Ghahramani, M. Kapás, T. Carrothers, T. Khariton, unpublished data) were used to predict C_{ave} on the day of the first incidence of each TEAE for patients who experienced a TEAE or the highest predicted C_{ave} over the course of the treatment period for patients who did not experience a TEAE. To calculate TC_{ave}, the relevant C_{ave} value was divided by the number of days from the start of dosing to the event (for patients who experienced the event) or the number of days from the start of dosing to the highest exposure (for patients who did not experience the event).

The logistic regression model used to predict the probability (*P*) of the end point for a specified predicted drug exposure is shown here:

$$P(Y=1)=\frac{e^{\text{Logit}(P)}}{1+e^{\text{Logit}(P)}}, \quad (3.1)$$

$$P(Y=0)=\frac{1}{1+e^{\text{Logit}(P)}}, \quad (3.2)$$

where *Y* is the dichotomous end point variable (0 = not experiencing a TEAE, 1 = experiencing the TEAE). Logit is the predicted log-odds of the end point occurring (a TEAE), which was determined empirically for a specified TEAE during the exploratory data analysis step by fitting to the following equation:

$$\text{Logit}(P)=\theta_{\text{placebo}}+\theta_{\text{cariprazine}}(\text{Exposure})^{\theta_{\text{pon}}}, \quad (3.3)$$

where $\theta_{placebo}$ is the population placebo effect; $\theta_{cariprazine}$ is the population drug effect; exposure is the TC_{ave} on the day of the event or on the day associated with the highest exposure; and θ_{pon} is the power of drug exposure. Typical plots of residuals were not used because the end point is a dichotomous variable; therefore, the population-predicted response was compared with the observed proportion of patients experiencing the end point. In addition, IIV and RV were not estimated because the data set for analysis consisted of only one record per patient (e.g., the first incidence of AE was included in the model for the patients who experienced an AE).

A univariate analysis of each covariate was performed by testing for significance via the likelihood ratio test; covariates contributing ≥ 3.84 change in the minVOF (α = 0.05, 1 df) were considered significant. The covariate contributing to the most significant change in the minVOF (or smallest *P* value) was included in the base covariate logistic regression model, which was then used to generate a predicted logit function for each patient. Two methods of model evaluation were performed: Hosmer-Lemeshow goodness-of-fit[23] and the area under the receiver operating characteristic (ROC) curve.[24]

RESULTS

Schizophrenia

PANSS model. A total of 10,327 observations from 1,756 patients were included in the PK/PD efficacy analysis data set (**Table S1**). Of these patients, the mean age (SD) was 38 years (11 years), 71.4% were men, 42.7% were white, 34.8% were black, and 17.3% were Asian. First, the PANSS total score placebo response ($PANSS_{placebo}$) model was built using placebo data alone and covariates (**Table 1**) were evaluated. $PANSS_{placebo}$ was found to be proportional to the baseline estimate of PANSS total score ($PANSS_0$):

$$PANSS_{placebo} = PANSS_0 \left(1 - EFF_{placebo}\right), \quad (1.1)$$

where placebo effect ($EFF_{placebo}$) was best described by a Weibull function:

$$EFF_{placebo} = PL_{max}\left(1 - e^{-\left(\frac{TIME}{TD}\right)^{WPOW}}\right), \quad (1.2)$$

where PL_{max} is the maximum placebo effect, TIME is time since baseline (days), TD is the time denominator, and WPOW is the power parameter in the Weibull function. The $PANSS_{placebo}$ model included additive IIV terms for $PANSS_0$ and PL_{max} and exponential IIV terms for TD and WPOW; and RV was described using an additive model. Statistically significant covariates were added to the $PANSS_{placebo}$ model, which included the influence of study RGH-MD-03 on both $PANSS_0$ and WPOW terms, and the influence of baseline disease severity. This allowed for the characterization of any significant response differences observed in study RGH-MD-03, as overall efficacy results from this study did not meet statistical significance and were inconsistent with the other studies included in this modeling analysis.

Following the development of the $PANSS_{placebo}$ model, active treatment data were added to the analysis data set and a second covariate analysis was performed (**Table 1**); the combined placebo plus cariprazine PANSS response ($PANSS_{combined}$) was found to be proportional to $EFF_{placebo}$ (Eq. 1.2) and the cariprazine effect ($EFF_{cariprazine}$):

$$PANSS_{combined} = PANSS_0 \left(1 - EFF_{placebo}\right)\left(1 - EFF_{cariprazine}\right), \quad (1.3)$$

where $EFF_{cariprazine}$ was best described by a sigmoidal E_{max} function:

$$EFF_{cariprazine} = \frac{E_{max} C_{ave}^{\gamma}}{\left(C_{ave}^{\gamma} + EC_{50}^{\gamma}\right)}, \quad (1.4)$$

where E_{max} is the maximum drug effect due to C_{ave}; EC_{50} is the C_{ave} corresponding to 50% of E_{max} (EC_{50} values represent total active moiety; i.e., sum of cariprazine, DCAR, and DDCAR); and γ is the Hill coefficient describing the steepness of the exposure-response relationship. C_{ave} is the predicted total plasma concentration of cariprazine, DCAR, and DDCAR averaged over the time interval between two consecutive PANSS assessment visits. In addition to IIV terms already incorporated into the $PANSS_{placebo}$ model, the $PANSS_{combined}$ model included IIV terms for E_{max} (additive) and EC_{50} (exponential); and RV was described using an additive error model. Further, the only covariate describing a statistically significant and clinically relevant modification to the $PANSS_{combined}$ model was an additive shift for Study RGH-MD-03 on E_{max}.

All fixed and random effect parameters were estimated with reasonable precision (SEM < 44%; **Table 2**); this was also supported by the goodness-of-fit plots (**Figure 1a,b**) and bootstrap analyses (**Table 2**). The pcVPC plots showed that the central tendency of the data was accurately described by the model, although an overprediction bias for the median of PANSS total scores occurred at the latest time points, which may be due to dropouts at the later time points (**Figure 1c,d** and **Figure S2**). The population-predicted change in PANSS total score relative to placebo after 6 weeks of cariprazine treatment is shown in **Figure 2**.

The population mean estimates for $PANSS_0$, WPOW, and E_{max} were estimated to be 96.4%, 1.14%, and 11.8%, and the equations to predict their typical values based on covariate values within specific individuals (denoted by subscript *i*) are presented below:

$$PANSS_{0,i} = 96.4 - 1.47\,(ST3), \quad (1.5)$$

$$WPOW_i = 1.14\left(DisSev_i/95\right)^{2.41} - 0.392\,(ST3), \quad (1.6)$$

$$E_{max,i} = 0.118 - 0.087\,(ST3), \quad (1.7)$$

where ST3 is 1 if the patient is from study RGH-MD-03 and 0 otherwise, DisSev is the baseline disease severity as indicated by the baseline PANSS total score, and E_{max} is the maximum drug effect due to C_{ave}.

The PANSS total score model also adequately described the $PANSS_P$ and $PANSS_N$ subscale scores. For $PANSS_P$ scores, the equations to predict the typical value of $PANSS_{P,0}$, $WPOW_P$, and $E_{max,P}$ are:

$$PANSS_{P,0,i} = 25.4 + 0.564\,(ST3), \quad (1.8a)$$

$$WPOW_{P,i} = 1.30\left(DisSev_i/26\right)^{1.35} - 0.481\,(ST3), \quad (1.8b)$$

$$E_{max,P,i} = 0.168 - 0.131\,(ST3). \quad (1.8c)$$

For $PANSS_N$ scores, the equations to predict the typical value of $PANSS_{N,0}$ and $WPOW_N$ are:

$$PANSS_{N,0,i} = 24.4 - 1.61\,(ST3), \quad (1.9a)$$

Table 2 Parameter estimates and SEs from the final population PK/PD efficacy models

Schizophrenia				Bipolar disorder			
Parameter	**Typical value**	**90% CI[a]**	**% SEM**	**Parameter**	**Typical value**	**90% CI[a]**	**% SEM**
$PANSS_0$	96.4	(95.9, 96.8)	0.265	$YMRS_0$	32.7	(32.3, 33.1)	0.603
AS: ST3	–1.47	(–2.48, –0.379)	44.0				
PL_{max}	0.263	(0.229, 0.326)	9.92	PL_{max}	0.433	(0.392, 0.474)	4.72
TD (days)	36.8	(30.6, 51.6)	15.2	TD (days)	8.41	(7.44, 9.39)	5.85
				AS: Asian	2.36	(0.446, 4.27)	39.7
				AS: DisSev	0.385	(0.213, 0.557)	21.6
WPOW	1.14	(1.03, 1.26)	5.87	WPOW	1.53	(1.40, 1.67)	4.21
AS: ST3	–0.392	(–0.545, –0.244)	22.2				
ES: DisSev	2.41	(1.74, 3.37)	18.1				
E_{max}	0.118	(0.090, 0.156)	16.5	E_{max}	0.250	(0.186, 0.315)	12.7
AS: ST3	–0.087	(–0.130, –0.048)	28.1				
EC_{50} (nM)	55.0	(47.2, 66.8)	10.4	EC_{50} (nM)	62.4	(42.6, 82.2)	15.6
γ	2.11	(1.80, 2.51)	10.1				
RV	36.7	(33.6, 39.8)	5.02	RV	13.8	(12.5, 15.1)	4.77

AS, additive shift (slope of listed term); Asian, indicator variable if patient is of Asian descent (1 if patient is Asian, 0 otherwise); CI, confidence interval; DisSev, baseline disease severity (as indicated by baseline score of the relevant efficacy measure); EC_{50}, average plasma concentration for 50% of exposure effect; E_{max}, maximum exposure effect; ES, exponential shift (power of listed term); γ, Hill coefficient; PANSS, Positive and Negative Syndrome Scale; $PANSS_0$, predicted PANSS total score at baseline (model intercept); PK/PD, pharmacokinetic/pharmacodynamic; PL_{max}, maximum placebo effect; RV, residual variability; TD, time denominator; ST3, indicator variable for enrollment in study RGH-MD-03 (1 if in study RGH-MD-03, 0 otherwise); YMRS, Young Mania Rating Scale; $YMRS_0$, predicted YMRS total score at baseline (model intercept); WPOW, Weibull power term.
[a]The 90% CI represents the 5th to 95th percentile of the estimates from fitting the model to 1,000 bootstrap data sets.

$$WPOW_{N,i} = 1.20\left(DisSev_i/24\right)^{1.23} - 0.456\,(ST3)\,. \quad (1.9b)$$

The assessment of the final PK/PD model of $PANSS_N$ score showed that there was no influence of study RGH-MD-03 on E_{max}. Parameter estimates and SEs for the $PANSS_P$ and $PANSS_N$ subscale models are presented in **Table S2**.

Modeling of TEAEs. The PK/PD safety analysis data set, including multiple occurrences of AEs, consisted of 7,548 AE records from 1,887 patients (**Table S1**). Occurrences of common TEAEs (≥ 5%; i.e., akathisia, extrapyramidal symptoms without akathisia or restlessness, nausea and/or vomiting, and parkinsonism cluster) were analyzed.

The probability of the first occurrence of each TEAE during the treatment period was modeled using logistic regression (see Methods section for the base structural models). There was a significant relationship between time-weighted TC_{ave} and the probability of each TEAE. The population PK models (A. Periclou, L. Phillips, P. Ghahramani, M. Kapás, T. Carrothers, T. Khariton, unpublished data) were used to estimate C_{ave} on the day of the first incidence of each TEAE for those patients who experienced a TEAE or the highest C_{ave} over the course of the treatment period if a patient did not experience a TEAE. Then, to obtain TC_{ave}, these exposures were divided by the number of days from the start of dosing to the event (for patients who experienced the event) or the number of days from the start of dosing to the highest exposure (for patients who did not experience the event).

The final models describing the logit transformation of the estimated probability for each TEAE (abbreviated as p_{TEAE} for the following TEAEs: akathisia (AKA), extrapyramidal symptoms (EPS) without akathisia or restlessness, nausea and/or vomiting (NAV), and parkinsonism cluster (PKC)) and their relationship to TC_{ave} are shown below:

$$\text{Logit}(P_{AKA_i}) = -3.64 + 1.25\left(\frac{TC_{ave_i}}{1.52}\right)^{0.477}, \quad (1.10)$$

$$\text{Logit}(P_{EPS_i}) = -2.78 + 0.787\left(\frac{TC_{ave_i}}{1.52}\right)^{0.626}, \quad (1.11)$$

$$\text{Logit}(P_{NAV_i}) = -2.73 + 0.164 TC_{ave_i}, \quad (1.12)$$

$$\text{Logit}(P_{PKC_i}) = -2.99 + 0.777\left(\frac{TC_{ave_i}}{1.54}\right)^{0.638}. \quad (1.13)$$

Hosmer-Lemeshow goodness-of-fit statistics and area under the ROC curve were calculated for each final logistic regression model; all models were found to provide adequate fit (**Table S3**). Model-predicted probabilities of each TEAE occurring at least once for patients with schizophrenia in relation to the median-observed TC_{ave} are presented in **Figure S3**.

Bipolar I disorder

YMRS model. A total of 4,862 observations from 802 patients were included in the PK/PD efficacy analysis data set (**Table S1**). Of these patients, the mean age (SD) was 40 years (12 years), 57.5% were men, 50.4% were white, 24.4% were black, and 23.7% were Asian. Using similar methodology and covariate analysis (**Table 1**) performed for the $PANSS_{placebo}$ model, the YMRS placebo response ($YMRS_{placebo}$) model was found to be proportional to the baseline estimate of the YMRS total score ($YMRS_0$):

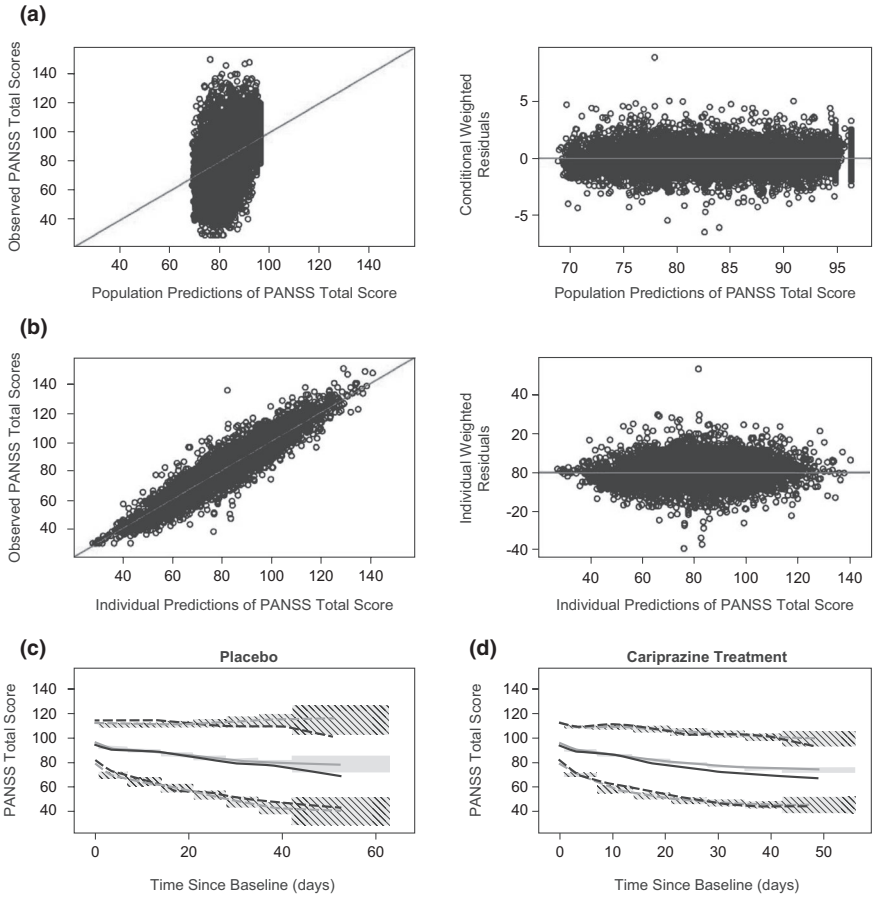

Figure 1 Goodness-of-fit plots and visual predictive checks of the pharmacokinetic/pharmacodynamic Positive and Negative Syndrome Scale (PANSS) model. Goodness-of-fit plots for (**a**) population and (**b**) individual predictions, and visual predictive check plots (VPCs) for patients on (**c**) placebo or (**d**) cariprazine treatment (1.5–12 mg/day). For the VPCs, black and gray lines denote observed data and predictions, respectively; solid lines denote median, dashed lines represent 5th and 95th percentiles; shaded areas represent 95% confidence interval of prediction percentiles; and medians and percentiles are plotted at the mean time since baseline of the data observed within each time since baseline interval.

$$YMRS_{placebo} = YMRS_0\left(1 - EFF_{placebo}\right), \quad (2.1)$$

where $EFF_{placebo}$ for the YMRS model was also found to be best described by the Weibull function (Eq. 1.2). The $YMRS_{placebo}$ model included IIV terms for $YMRS_0$ and PL_{max} (additive), and for TD (exponential); and RV was described using an additive error model. Two covariates were added to the $YMRS_{placebo}$ model to include the influence of baseline disease severity and additive shifts for race (Asian compared with others) on TD.

Next, the cariprazine YMRS data were added to the analysis data set and a second covariate analysis was performed (**Table 1**) to obtain the combined placebo plus cariprazine YMRS response ($YMRS_{combined}$) model:

$$YMRS_{combined} = YMRS_0\left(1 - EFF_{placebo} - EFF_{cariprazine}\right), \quad (2.2)$$

where $EFF_{cariprazine}$ for the YMRS model was found to be best described by an E_{max} function:

$$EFF_{cariprazine} = \frac{E_{max}C_{ave}}{\left(C_{ave} + EC_{50}\right)}. \quad (2.3)$$

The $YMRS_{combined}$ model included IIV terms for E_{max} (additive) and EC_{50} (exponential); and RV was described using an additive error model. In addition to the covariates already incorporated into the $YMRS_{placebo}$ model, none were found to be statistically significant for the $YMRS_{combined}$ model.

All fixed and random effect parameters were estimated with reasonable precision (SEM < 39.7%; **Table 2**); this was further supported by the goodness-of-fit plots (**Figure 3a,b**) and bootstrap analyses (**Table 2**). The pcVPC plots indicated that the YMRS models adequately characterized the observed data, with only a minor bias in the variability and median YMRS total score (**Figures 3c,d and 4**). The population-predicted change in YMRS total score relative to placebo after 3 weeks of cariprazine treatment is shown in **Figure 4**.

The population mean estimate for TD was 8.41, and the equation to predict its typical value is:

$$TD_i = 8.41 + 0.385\left(DisSev_i - 32\right) + 2.36Asian_i, \quad (2.4)$$

where DisSev is indicated by the baseline YMRS total score, and Asian is 1 for Asian race and 0 otherwise.

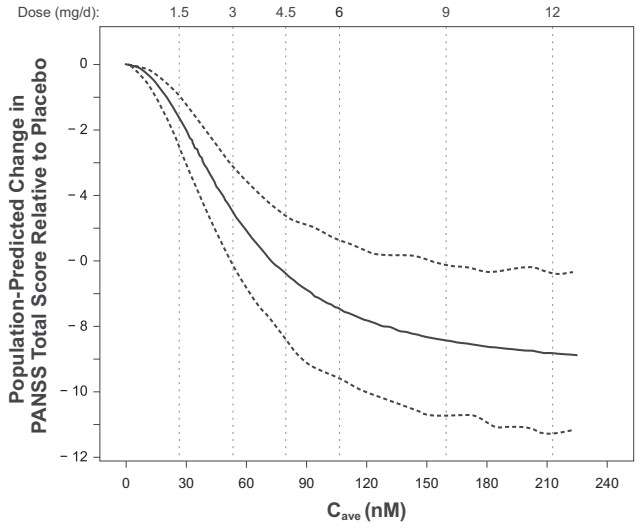

Figure 2 Predicted change in Positive and Negative Syndrome Scale (PANSS) total score for cariprazine relative to placebo. The black dashed lines represent 90% confidence interval; the vertical reference (gray dashed) lines correspond to the mean average total cariprazine concentration (C_{ave}) at each maintenance dose level as predicted by the population pharmacokinetic model.

Modeling of TEAEs. The PK/PD safety analysis data set, including multiple occurrences of AEs, consisted of 3,379 AE records from 806 patients. The four common TEAEs in this data set were the same as those previously described, and similar analyses were performed. There was a significant relationship between TC_{ave} and the probability of each TEAE, and covariate analysis (**Table 1**) found that there was also a significant relationship between the age of the patient (age) and the probability of nausea and/or vomiting.

The final probability models for each TEAE in relation to TC_{ave} (and age) are:

$$\text{Logit}\left(P_{\text{AKA}_i}\right) = -3.21 + 1.36\left(\frac{\text{TC}_{\text{ave}_i}}{3.42}\right)^{0.381}, \quad (2.5)$$

$$\text{Logit}\left(P_{\text{EPS}_i}\right) = -2.24 + 0.144\text{TC}_{\text{ave}_i}, \quad (2.6)$$

$$\text{Logit}(P_{\text{NAV}_i}) = -2.25 - 0.036(\text{Age}_i - 40) + 0.049\text{TC}_{\text{ave}_i}, \quad (2.7)$$

$$\text{Logit}(P_{\text{PKC}_i}) = -2.47 + 0.150\text{TC}_{\text{ave}_i}. \quad (2.8)$$

Hosmer-Lemeshow goodness-of-fit statistics and area under the ROC curve were calculated for each final logistic regression model; all models were found to provide adequate fits

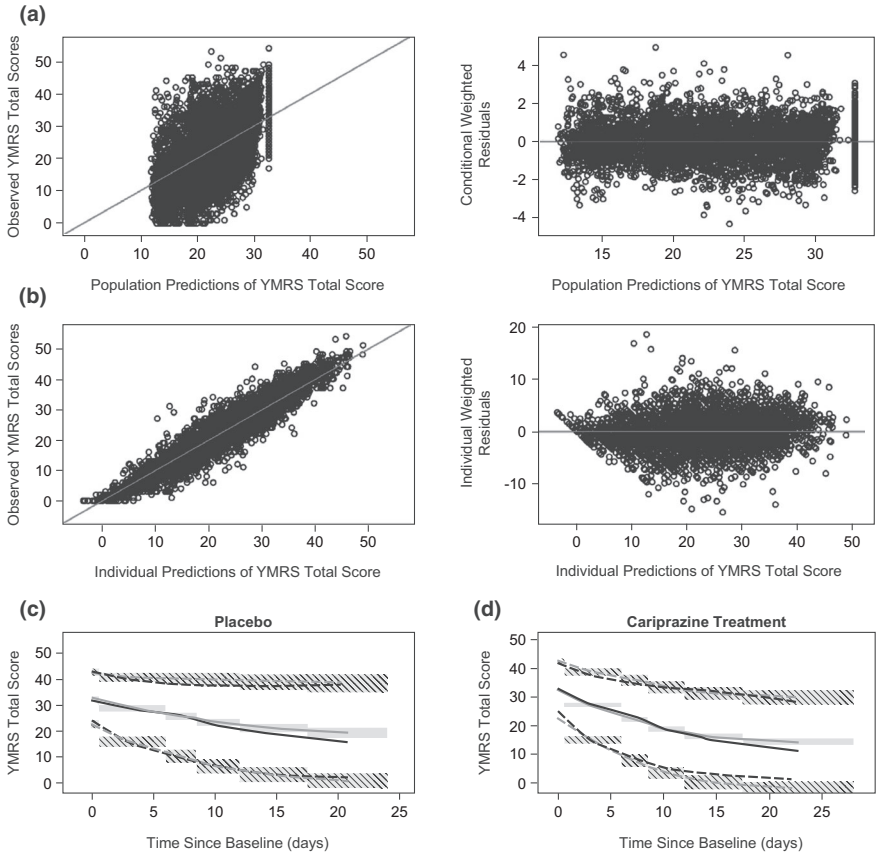

Figure 3 Goodness-of-fit plots and visual predictive checks of the pharmacokinetic/pharmacodynamic Young Mania Rating Scale (YMRS) model. Goodness-of-fit plots for (**a**) population and (**b**) individual predictions, and visual predictive check plots (VPCs) for patients on (**c**) placebo or (**d**) cariprazine treatment (3–12 mg/day). For the VPCs, black and gray lines denote observed data and predictions, respectively; solid lines denote median, dashed lines represent 5th and 95th percentiles; shaded areas represent 95% confidence interval of prediction percentiles; and medians and percentiles are plotted at the mean time since baseline of the data observed within each time since baseline interval.

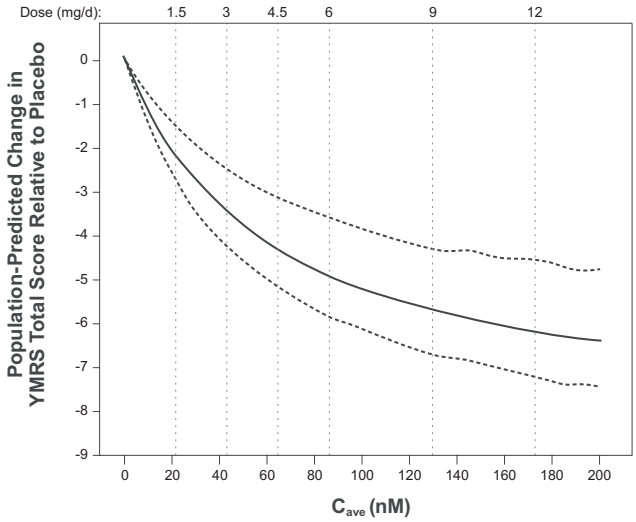

Figure 4 Predicted change in Young Mania Rating Scale (YMRS) total score for cariprazine relative to placebo. The black dashed lines represent 90% confidence interval; the vertical reference (gray dashed) lines correspond to the mean total plasma concentration of cariprazine and its metabolites (C_{ave}) at each maintenance dose level as predicted by the population pharmacokinetic model.

(**Table S4**). Model-predicted probabilities of each TEAE occurring at least once for patients with bipolar mania in relation to the median-observed TC_{ave} values are presented in **Figure S5**.

DISCUSSION

Schizophrenia

The time-course of PANSS total scores following cariprazine treatment was well-characterized by the $PANSS_{combined}$ model (**Figure 1**), and the model indicated that treatment effects over time were due to cariprazine exposures. The time-course of the placebo effect for the PANSS models was best described by the Weibull function, which captured the initial improvement in PANSS scores and subsequent plateau and also accounted for the flat placebo response exhibited by a subset of patients. The main subpopulation effect was for patients in study RGH-MD-03, a study that failed to demonstrate overall statistical significance for cariprazine treatment vs. placebo, and the diminished drug effect in this study was inconsistent with the other studies (MD-04, MD-05, and MD-16). The reasons for this discrepancy are unknown; however, it should be noted that study RGH-MD-03 only enrolled patients from US centers, whereas the other studies were multinational.[8] The cariprazine treatment effect was included in the $PANSS_{combined}$ model as a proportional effect on the baseline PANSS total score; this aligns with previous models for the effects of asenapine, another atypical antipsychotic, on baseline PANSS total scores in patients with schizophrenia.[25]

Based on population mean estimates and assuming a cariprazine dose of 3 mg/day (or C_{ave} near the EC_{50} of 55 nM), a typical patient (i.e., baseline PANSS total score of 95, not enrolled in study RGH-MD-03) will have an approximate reduction of 22.9% in PANSS total score due to the combined cariprazine and placebo effects at the end of 6 weeks of treatment; note that of the 22-point reduction in PANSS total score, ~ 5 points are attributed to cariprazine exposure alone and the remaining 17 points are associated with the placebo effect. E_{max} was an 11.8% reduction in PANSS total score for patients receiving cariprazine in studies RGH-MD-04, RGH-MD-05, and RGH-MD-16, and 3.11% in patients from study RGH-MD-03 (**Table 2**). The Hill coefficient (γ) was 2.11;

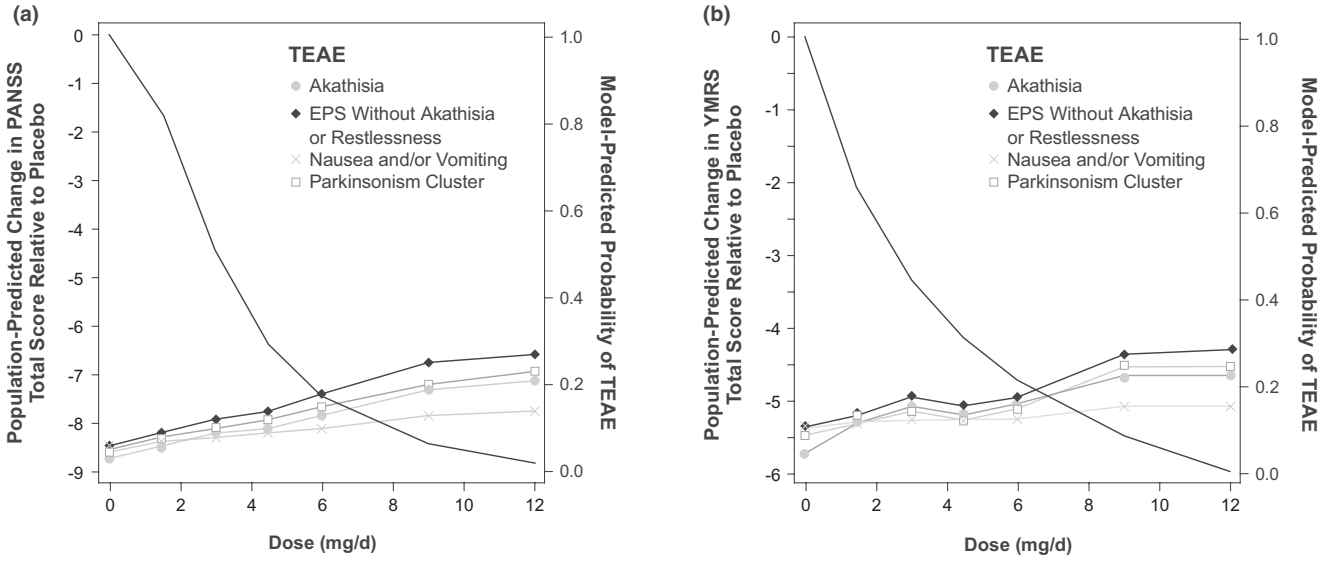

Figure 5 Risk-benefit analysis for cariprazine treatment in patients with schizophrenia (**a**) or bipolar disorder (**b**). The doses for each efficacy analysis correspond to the mean total plasma concentration of cariprazine and its metabolites (C_{ave}) at each dose level predicted by the population pharmacokinetic models, whereas the doses for akathisia, extrapyramidal symptoms (EPS) without akathisia or restlessness, nausea and/or vomiting, and parkinsonism cluster correspond to the median observed time-scaled exposures across each dose level. PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.

most of the reduction in PANSS total score was predicted to occur by 6 mg/day and only minor incremental reductions in PANSS total score were predicted at higher exposures (> 9 mg/day; **Figure 2**).

$PANSS_P$ and $PANSS_N$ subscale scores could also be adequately described using the structure of the developed models; however, study RGH-MD-03 was not included as a covariate in the modeling of $PANSS_N$ scores. One reason could be because, in study RGH-MD-03, patients on cariprazine treatment (1.5–4.5 mg/day) exhibited significant improvement over the placebo group in $PANSS_N$ scores.[8] A typical patient with a baseline $PANSS_P$ score of 26 or $PANSS_N$ score of 24 can have a maximum reduction of ~ 28% or 18% in their respective scores, assuming a C_{ave} exposure of 47 or 73.4 nM, which can be achieved with a dose of 3 or 4.5 mg/day, respectively.

The relationships between the probability of TEAEs and TC_{ave} were well-described by logistic regression models. Risk-benefit assessment showed that increasing dose from 1.5 to 12 mg/day is associated with a trade-off between efficacy and safety (**Figure 5a**). For example, lower doses (≤ 6 mg/day) have larger increases in efficacy with more moderate increases in probability of TEAEs, whereas higher doses (> 6 mg/day; unapproved dose range) have minor increases in efficacy with higher increases in the probability of TEAEs (**Table S5**). Therefore, this population exposure-response analysis supports the efficacy and safety of the recommended dose range of 1.5–6 mg/day for treatment of schizophrenia.

Bipolar I disorder

The time-course of total YMRS scores following cariprazine treatment was well-characterized by the $YMRS_{combined}$ model (**Figure 3**), and the model indicated that treatment effects over time were due to cariprazine exposures. The overall placebo effect for the YMRS model was best described by the Weibull function. Subpopulations of Asian vs. non-Asian patients and high vs. low disease severity in patients exhibited different placebo responses. A placebo patient starting at a YMRS total score of 54 would decline to an average score of 42 (reduction of 22%) in 16 days for Asians and 14 days for non-Asians. Comparatively, a patient with lessened baseline disease severity, starting at a YMRS total score of 16, would decline to an average score of 13 (reduction of 19%) in 3 days for Asians and 2 days for non-Asians. The cariprazine effect was included in the $YMRS_{combined}$ model as an additive effect on baseline YMRS total score, which differed from the proportional effect previously reported for modeling the effects of cariprazine (this paper) and asenapine on baseline PANSS total scores in patients with schizophrenia.[25]

Based on population mean parameter estimates and assuming a cariprazine dose of 4.5 mg/day (or C_{ave} near the EC_{50} of 62.4 nM), a typical patient (i.e., a baseline YMRS total score of 32, non-Asian) on cariprazine treatment will have an approximate total reduction in YMRS total score of 55.8% due to the combined cariprazine and placebo effects after 3 weeks of treatment. Note that of the 18-point reduction in YMRS total score, ~ 4 points are associated with cariprazine and the remaining 14 points are attributed to the placebo effect. E_{max} was estimated as a 25% reduction in the placebo-corrected YMRS total score for patients receiving cariprazine (**Table 2**).

The relationships between the probability of TEAEs and TC_{ave} were also well-described by logistic regression models. Risk-benefit assessment showed that increasing dose from 1.5 to 12 mg/day is associated with a trade-off between efficacy and safety (**Figure 5b**); however, results pertaining to the 1.5 mg/day dose are extrapolations because the dose range in the 2 phase III studies of bipolar mania was 3–12 mg/day. Lower doses (≤ 6 mg/day) have larger increases in efficacy with more moderate increases in probability of TEAEs compared with higher doses (> 6 mg/day; unapproved dose range), although relative increases in efficacy are still fairly substantial in comparison to smaller increases in probabilities of TEAEs (**Table S6**). Therefore, this population exposure-response analysis supports the efficacy and safety of the recommended dose range of 3–6 mg/day for treatment of bipolar mania.

Limitations of PK/PD analyses

Because the PK/PD efficacy models were developed using data from acute studies with short treatment durations (e.g., 6 weeks for schizophrenia, 3 weeks for bipolar mania), these models may not be generalizable to patients undergoing long-term treatment as such analyses would require model extrapolation. For example, the predictive efficacy values may be more pronounced with long-term treatment as some patients require longer treatment times to exhibit an adequate drug response.[26] Additionally, placebo effect in the assessment of efficacy end points in schizophrenia trials has been reported and confirmed by several studies. This effect has been increasing in magnitude over the last 2 decades.[1] In contrast, there does not seem to be similar phenomenon in regard to side effects. This may be explained by the fact that patients do not desire negative effects, so in the absence of any real pharmacological effect (i.e., placebo), patients do not have an expectation bias for side effects, unlike their desire for improvement in efficacy assessments.

In addition, some patient demographic characteristics included in the studies analyzed were not all inclusive. For example, patients enrolled were primarily from three geographic regions (United States, Asia, and Eastern Europe). As such, the additive shift for the Asian race in the YMRS models was obtained from studies conducted in India and may not be reflective of patients from other geographic regions in Asia. Race did not seem to have a substantial effect on PK.[6,27] Subgroup analyses from clinical efficacy studies did not distinguish any efficacy difference based on race or geographic region.[28]

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Figure S1. Model development process.
Figure S2. Visual predictive checks of the PK/PD PANSS model with observed data overlaid.
Figure S3. Probability of TEAEs in patients with schizophrenia after 6 weeks of treatment with cariprazine.

Figure S4. Visual predictive checks of the PK/PD YMRS model with observed data overlaid.
Figure S5. Probability of TEAEs in patients with bipolar disorder after 3 weeks of treatment with cariprazine.
Table S1. Summary of studies included in the analyses.
Table S2. Parameter estimates and standard errors from the final population PANSS positive and negative subscale score models.
Table S3. Parameter estimates and standard errors from the probability models of the first occurrence of TEAEs in patients with schizophrenia.
Table S4. Parameter estimates and standard errors from the probability models of the first occurrence of TEAEs in patients with bipolar disorder.
Table S5. Risk-benefit summary in patients with schizophrenia administered cariprazine.
Table S6. Risk-benefit summary in patients with bipolar disorder administered cariprazine.
Supplementary Material S1. Model code for PK/PD analysis.

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

Funding. Financial support for this work was provided by Forest Research Institute, Inc., an Allergan affiliate, Jersey City, NJ, USA.

Conflicts of Interest. T.C., A.P., P.G., S.D., W.E., and T.K. are or were employees of Forest Research Institute, Inc., an Allergan affiliate, at the time of the study. M.K. is an employee of Gedeon Richter Plc. S.W., D.J., and J.P. were or are employees of Cognigen, which was contracted by Forest Research Institute to perform the analysis herein.

Author Contributions. A.P., S.W., D.J., J.P., T.C., P.G., S.D., W.E., M.K., and T.K. wrote the manuscript. A.P., S.W., D.J., J.P., T.C., P.G., S.D., W.E., M.K., and T.K. designed the research. S.W., D.J., and J.P. performed the research (modeling). A.P., S.W., D.J., J.P., T.C., P.G., S.D., W.E., M.K., and T.K. analyzed the data.

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