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Characterization of Population Pharmacokinetics of Cariprazine and Its Major Metabolites

Antonia Periclou, PhD[1] Luann Phillips, MS[2] Sébastien Bihorel, PharmD, PhD[2] Parviz Ghahramani, PhD[3] Margit Kapás, PhD[4] Timothy Carrothers, ScD[1] Tatiana Khariton, PhD[3]
[1]*Allergan, Inc., Jersey City, NJ, USA;* [2]*Cognigen Corporation, Buffalo, NY, USA;* [3]*Inncelerex, Jersey City, NJ, USA;* [4]*Gedeon Richter Plc, Budapest, Hungary*

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ABSTRACT

Background: Population pharmacokinetic (PK) analysis was undertaken to describe the concentration-time profiles of cariprazine and its 2 major metabolites of similar pharmacological activity, desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR), and to assess the potential impact of demographic covariates, creatinine clearance, and metabolizer status.

Methods: Data were obtained from 3 Phase 1 and 10 Phase 2/3 studies in adult patients (18–65 y) with schizophrenia or bipolar mania. The combined dataset consisted of 13,227 cariprazine, 12,462 DCAR, and 12,092 DDCAR samples from 2199, 2180, and 2140 patients, respectively. Patients (66% male; mean weight 79 kg; mean age 39 y) were administered once-daily doses of 0.5–12.5 mg (various titrations). In 4 studies, serial sampling was performed over 24 hours following the first dose, and over 24, 168, or 2016 hours following the final dose (depending on study). In remaining studies, 4–9 non-serial blood samples were drawn at various times during the studies. Population PK modeling was performed using NONMEM, a nonlinear mixed-effects modeling software package. Compartmental modeling was performed sequentially, wherein the elimination rate of cariprazine served as the formation rate of DCAR, and the elimination rate of DCAR, with a delay, served as the formation rate for DDCAR. Standard pharmacometric practices for population model development and evaluation of covariates were utilized.

Results: Cariprazine PK were described by a 3-compartment model with zero-order input of the dose to a depot compartment followed by first-order absorption and first-order elimination. DCAR and DDCAR PK were described by 2-compartment models with linear elimination. Based on predicted steady-state AUC values, DDCAR was the most prominent moiety (64.2% of Total CAR [molar sum of cariprazine, DCAR and DDCAR] exposures), while cariprazine and DCAR represented 28.1% and 7.7% of Total CAR, respectively. Weight, gender, and race were statistically significant predictors of PK parameters. However, the resulting differences in exposures were not large enough to require dosage adjustment. CYP2D6 metabolizer status was not a statistically significant predictor of PK parameters, and mean exposure for the CYP2D6 poor metabolizers was within 10% of that of extensive metabolizers. Covariate analysis showed no statistically significant effect of creatinine clearance on cariprazine, DCAR, or DDCAR clearance. The median time to 90% of steady state was 5, 5, 21, and 18 days for cariprazine, DCAR, DDCAR, and Total CAR, respectively. The median functional effective half-life (time to reach 90% steady-state/3.32) was 1.5, 1.5, 6.3, and 5.4 days for cariprazine, DCAR, DDCAR, and Total CAR, respectively.

Conclusions: Population PK modeling provided a quantitative description of the concentration time profile of cariprazine and its metabolites.

BACKGROUND

Cariprazine (CAR) is an orally active, potent dopamine D_2/D_3 receptor partial agonist with preferential binding to D_3 receptors and partial agonism at serotonin 5-hydroxytryptamine $(5HT)_{1A}$ receptors, approved in the US in 2015 both for the treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder.

Cariprazine is extensively metabolized. CYP3A4 and, to a lesser extent, CYP2D6 are involved in the metabolism of cariprazine and its metabolites. The pharmacokinetic (PK) properties of cariprazine are characterized by relatively slow absorption, multi-exponential disposition, and slow elimination. Cariprazine is converted to several metabolites, two of which (desmethyl-cariprazine [DCAR] and didesmethyl-cariprazine [DDCAR]) possess similar pharmacological activity to the parent drug.

Cariprazine and its major active metabolites did not induce CYP1A2, CYP2B6 and CYP3A4 enzymes and did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5 enzymes *in vitro*.

OBJECTIVES

- To describe the concentration time profiles of cariprazine and its 2 major metabolites of similar pharmacological activity, DCAR and DDCAR
- To assess the potential impact of demographic covariates, creatinine clearance (CrCL), and metabolizer status on key PK parameters and exposure measures for each moiety
- To characterize the median time to 90% of steady state, terminal half-life, and functional (effective) half-life (time to reach 90% steady state/3.32) for each moiety

DATA FOR ANALYSIS

Clinical trials completed to date have demonstrated the tolerability, efficacy, and safety of oral cariprazine in patients with schizophrenia and bipolar I disorder. In the 3 Phase 1 and 10 Phase 2/3 studies in adult patients (18–65 y) with schizophrenia or bipolar mania included in the population pharmacokinetic (PK) analysis (**Table 1**), blood samples were collected for measurement of cariprazine DCAR, and DDCAR (Studies RGH-MD-11 and RGH-MD-17 were used for model validation and were excluded from the estimation step of the analysis). The combined dataset consisted of 13,227 cariprazine, 12,462 DCAR, and 12,092 DDCAR samples from 2199, 2180, and 2140 patients, respectively.

Patients (See **Table 2** for full demographic summary: 66% male; mean weight 79 kg; mean age 39 y) were administered once daily doses of 0.5–12.5 mg. There were 868 patients classified as extensive metabolizers (defined as ultra, extensive, and intermediate metabolizers) and 40 patients classified as poor metabolizers. All patients were titrated to their assigned dose using a variety of titration schemes. Titration was complete by Day 20 of active dosing for all patients. The final dose levels were 1.5, 2, 3, 4, 4.5, 5, 6, 9, 12, and 12.5 mg/d (data from doses of 15 mg/d or greater were excluded for purposes of model simplification on the grounds that the maximum proposed clinical dose would be 6 mg/d).

In Study RGH-MD-01, RGH-MD-02, RGH-MD-18, and A002-A11, serial blood samples were drawn for PK measurements for a 24-hour period following the first dose. Additional serial blood samples were collected for up to 168 and 2016 hours after the last dose for Studies RGH-MD-01 (22 or 30 doses) and A002-A11 (12 weeks), respectively. In Studies RGH-MD-02 and RGH-MD1-8, an additional 24-hour profile was collected following multiple doses (ranging from 2 to 29 doses). In all remaining studies, 4 to 9 non-serial blood samples were drawn from each patient for PK measurements.

METHODS

Population PK modeling was performed using NONMEM 7.1, a nonlinear mixed effects modeling software package. Exploratory data analyses and data visualization techniques were used to understand the informational content of the data, search for extreme values and potential outliers, and assess possible trends in the data. Compartmental modeling was performed sequentially, wherein the elimination rate of cariprazine served as the formation rate of DCAR, and the elimination rate of DCAR, with a delay, served as the formation rate for DDCAR (**Figure 1**). Standard pharmacometric practices for population model development and evaluation of covariates were utilized.[1]

- Base Structural Model Development with Serial Sampling Studies
- Finalize Base Structural Models with All Data
- Fit Full Multivariable Model to All Data
  - Prior Population PK analyses[2] of a subset of the current data (excluding A002-A11) showed ideal body weight (IBW), race, gender and age to be statistically significant predictors of PK parameters in the CAR, DCAR, or DDCAR models
  - Fit of full-multivariable model replacing IBW with weight
- Backward Elimination of Covariates (alpha = 0.001)
- Model refinement and evaluation
  - Additional univariate analysis of CrCL on the CL of CAR, DCAR, and DDCAR

The final PK models for cariprazine, DCAR, and DDCAR were used to compute area under the curve $(AUC)_{0\text{-}24}$, C_{max}, and C_{min} at steady state for each individual using the Bayesian parameter estimates. The Total CAR exposures were also calculated as the sum of cariprazine, DCAR, and DDCAR, corrected for differences in molecular weight. The exposures were calculated for each individual following hypothetical steady-state dosing of 6 mg. The Bayesian parameter estimates and exposures were used to assess the clinical significance of the covariates and to assess the impact of CYP2D6 Metabolizer Status.

Table 1. Studies Included in the Population Pharmacokinetic Analysis of Cariprazine, DCAR, and DDCAR

Study Number	Phase of Development	Study Population	Planned Number of Patients Receiving Cariprazine	Planned Doses (mg) at Time of Pharmacokinetic Sample Collection	Planned Duration of Active Treatment (Days)	Other
RGH-MD-01	1	Schizophrenia	48 (6 per cohort)	0.5, 1, 1.5, 2, 3, 3.5, 4, 5, 5.5, 7, 7.5, 9.5, 12.5	22 30 for Cohort G	Hospitalized
RGH-MD-02	1b	Schizophrenia	50	1.5, 9, 18	35	Hospitalized
RGH-MD-03	2	Schizophrenia	250 (125 per group)	4.5, 12	42	Hospitalized minimum of first 21 days of treatment
RGH-MD-04	3	Schizophrenia	300 (150 per group)	3, 6	42	Hospitalized minimum of first 28 days of treatment
RGH-MD-05	3	Schizophrenia	300	4.5, 6, 7.5, 9	42	Hospitalized minimum of first 28 days of treatment
RGH-MD-11	3	Schizophrenia (open label)	600	3, 6, 9	336	Hospitalized first week of treatment New patients and patients from Study RGH-MD-04 and Study RGH-MD-05
RGH-MD-16	2b	Schizophrenia	405 (135 per group)	1.5, 3.0, 4.5	42	Hospitalized minimum of first 28 days of treatment
RGH-MD-17	2b	Schizophrenia (open label)	250	1.5, 3.0, 4.5	336	Hospitalized first week of treatment Patients from Study RGH-MD-16
RGH-MD-18	1b	Schizophrenia	24 (6 per cohort)	1.5, 3, 6, 9, 12, 15, 18, 21, 24	28	Hospitalized
RGH-MD-32	3	Bipolar Mania	160	3, 6, 9, 12	21	Hospitalized minimum of first 14 days of treatment
RGH-MD-33	3	Bipolar Mania	330	3, 4.5, 6, 9, 12	21	Hospitalized minimum of first 14 days of treatment
RGH-MD-36	3	Bipolar Mania (open label)	400	1.5, 3, 6, 9	112	Hospitalized minimum of first 14 days of treatment
A002-A11[a]	2/3	Schizophrenia (open label)	30	3, 6, 9	84	Outpatient

[a]An oral tablet formulation was used for Study A002-A11. All other studies used an oral capsule formulation.

Table 2. Summary Statistics of Patient Descriptors

Patient Characteristic	Statistic	Phase I Studies	Phase 2/3 Studies	Combined Phase 1-3 Model Development Dataset	Model Exploration Dataset
Age (y)	Mean (SD)	40.6 (9.9)	39.1 (10.9)	39.2 (10.8)	38.3 (10.8)
	Median	41.0	39.0	40.0	37.0
	Min, Max	21, 64	18, 65	18, 65	18, 63
	N	163	2036	2199	645
Creatinine clearance (mL/min)	Mean (SD)	121.54 (31.21)	119.75 (36.30)	119.88 (35.95)	1 13.32 (31.78)
	Median	117.50	113.40	113.50	108.60
	Min, Max	62.6, 244.6	31.4, 360.5	31.4, 360.5	54.2, 253.5
	N	163	2036	2199	645
Ideal body weight (kg)	Mean (SD)	65.29 (8.55)	63.66 (8.32)	63.79 (8.35)	63.99 (8.20)
	Median	67.40	64.30	64.50	64.50
	Min, Max	43.5, 83.0	36.1, 89.2	36.1, 89.2	39.3, 87.0
	N	163	2036	2199	645
Weight (kg)	Mean (SD)	80.46 (16.55)	78.76 (18.87)	78.89 (18.71)	78.80 (19.97)
	Median	81.00	77.35	77.70	76.66
	Min, Max	39.8, 129.7	33.1, 155.1	33.1, 155.1	36.6, 140.6
	N	163	2036	2199	645
Race, N (%)	Caucasian	42 (25.8)	961 (47.2)	1003 (45.6)	285 (44.2)
	Black	78 (47.9)	689 (33.8)	767 (34.9)	231 (35.8)
	Asian[a]	2 (1.2)	312 (15.3)	314 (14.3)	94 (14.6)
	Japanese[a]	37 (22.7)	0 (0.0)	37 (1.7)	0 (0.0)
	Other	4 (2.5)	74 (3.6)	78 (3.5)	35 (5.4)
Renal function category, N (%)	Normal[b]	139 (85.3)	1663 (81.7)	1802 (81.9)	498 (77.2)
	Mild impairment[b]	24 (14.7)	353 (17.3)	377 (17. 1)	143 (22.2)
	Moderate impairment[b]	0 (0.0)	20 (1.0)	20 (0.9)	4 (0.6)
Age category, N (%)	18-49 y	132 (81.0)	1653 (81.2)	1785 (81.2)	523 (81.1)
	50-65 y	31 (19.0)	383 (18.8)	414 (18.8)	122 (18.9)
Sex, N (%)	Male	124 (76.1)	1337 (65.7)	1461 (66.4)	450 (69.8)
	Female	39 (23.9)	699 (34.3)	738 (33.6)	195 (30.2)

[a]Asian patients were mainly from studies conducted in India, and Japanese patients were from Study A002-A11 only.
[b]Renal function category: Normal (CrCL ≥90 mL/min), Mild (60≤ CrCL ≤89 mL/min), Moderate (30≤ CrCL ≤59 mL/min), and Severe (15≤ CrCL ≤29 mL/min).
Abbreviations: CrCL, creatinine clearance; N, number of patients; Max, maximum; Min, minimum; SD, standard deviation.

RESULTS

The PK of cariprazine, DCAR, and DDCAR demonstrated linear elimination over a dose range of 0.5–12.5 mg/d. The disposition of cariprazine was well described by a 3-compartment model with zero-order input of the dose followed by first-order absorption and first-order elimination. With the elimination of cariprazine acting as the formation rate of DCAR, a 2-compartment model with first-order elimination described the disposition of DCAR. With the elimination of DCAR acting as the formation rate of DDCAR to a transit compartment with first-order transfer to the central compartment, a 2-compartment model with first-order elimination described the disposition of DDCAR. While weight in kg (WTKG), race, and sex explained some of the variability between patients, the PK parameters of the models for all 3 analytes exhibited a moderate to high degree of inter-individual variability (IIV). Cariprazine showed the smallest amount of IIV for apparent CL (<32% CV), although the IIV for absorption rate and apparent central volume were high (118% and 109%, respectively).

Weight, race, and sex were statistically significant predictors of PK parameters. However, the differences in Total CAR exposures were within 36% of the relevant comparator groups (**Figures 2-3**).

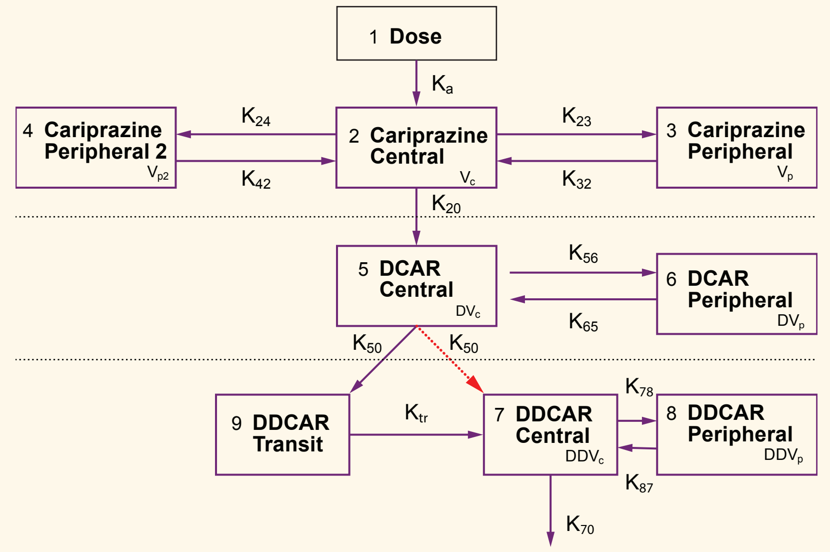
Additional univariate covariate analysis showed that CrCL was not a statistically significant predictor of cariprazine, DCAR, or DDCAR clearance, which is consistent with the minimal contribution of the renal pathway in the elimination of cariprazine, DCAR, and DDCAR.

There was not a statistically significant difference in the $AUC_{0\text{-}24}$ of cariprazine, DCAR, DDCAR, or Total CAR for patients classified as CYP2D6 poor metabolizers as compared to patients classified as CYP2D6 extensive metabolizers. The mean difference in exposure for the CYP2D6 poor metabolizers was within ±10% of the CYP2D6 extensive metabolizers.

Simulations of the final models for a typical patient (79 kg Caucasian adult male) were conducted to illustrate model results, to calculate time to steady state and effective half-life and to depict the decline in plasma concentration after the last dose. **Figure 4** and **Figure 5** display concentrations for a typical patient given 6 mg. **Figure 4** displays Day 1 plasma exposures; **Figure 5** displays the profile for a subject following the last 6 mg dose at steady state over the 24-hour dosing interval as well as the decline in concentration after the last dose over a period of 4 weeks. **Figure 6** displays one hypothetical titration scheme, with daily exposure expressed as AUC. These simulations showed that:

- Cariprazine is the prominent active moiety after the first dose on Day 1 while DDCAR is the prominent moiety at steady state
- The median time to 90% of steady state was 5, 5, 21, and 18 days for cariprazine, DCAR, DDCAR, and Total CAR, respectively; this translated into a median effective half-life of 1.5, 1.5, 6.3, and 5.4 days for cariprazine, DCAR, DDCAR, and Total CAR, respectively
- Plasma exposure declined by 50% after the last dose in about 1 day for cariprazine and DCAR and 1 week for DDCAR. A 90% decline in exposure occurred in about 1 week for cariprazine and DCAR and 4 weeks for DDCAR

Figure 1. Schematic of the Base Structural Cariprazine, DCAR, and DDCAR Pharmacokinetic Models for Evaluation



Abbreviations: DCAR, desmethyl-cariprazine; DDCAR, didesmethyl-cariprazine; K_{20}, elimination rate of cariprazine/formation rate of DCAR; K_{50}, elimination rate of DCAR/formation rate of DDCAR; K_{70}, elimination rate of DDCAR; K_{23}, K_{24}, K_{56}, K_{78}, rate of transfer from the central to the peripheral compartments for the respective moiety; K_{32}, K_{42}, K_{65}, K_{87}, rate of transfer from the peripheral to the central compartments for the respective moiety; K_a, first-order absorption rate constant; K_{tr}, rate of transfer from DDCAR transit compartment to central compartment; V_c, central volume of distribution of the respective moiety; V_p, peripheral volume of distribution of the respective moiety.

Black dashed lines indicate which components of the model are estimated for each moiety.

Red dashed line and parameter indicate the initial base model. The corresponding solid black line and parameter indicate the final base model.

Figure 2. Geometric Mean Ratios and 90% Confidence Intervals of 6 mg Steady-State Total CAR $AUC_{0\text{-}24}$ for the Phase 1-3 Analysis Dataset, by Covariate Comparison

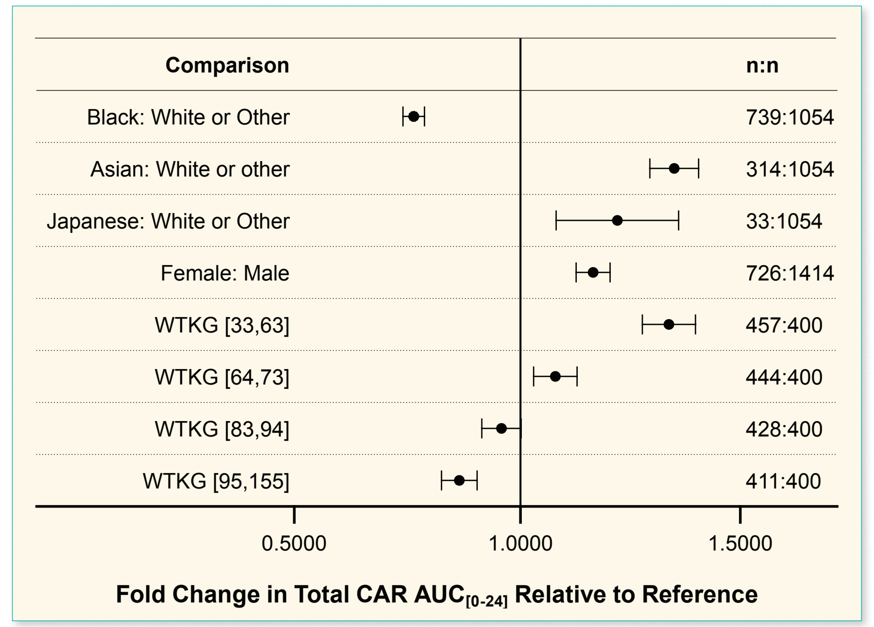


Figure 3. Geometric Mean Ratios and 90% Confidence Intervals of 6 mg Steady-State Total CAR C_{max} for the Phase 1-3 Analysis Dataset, by Covariate Comparison

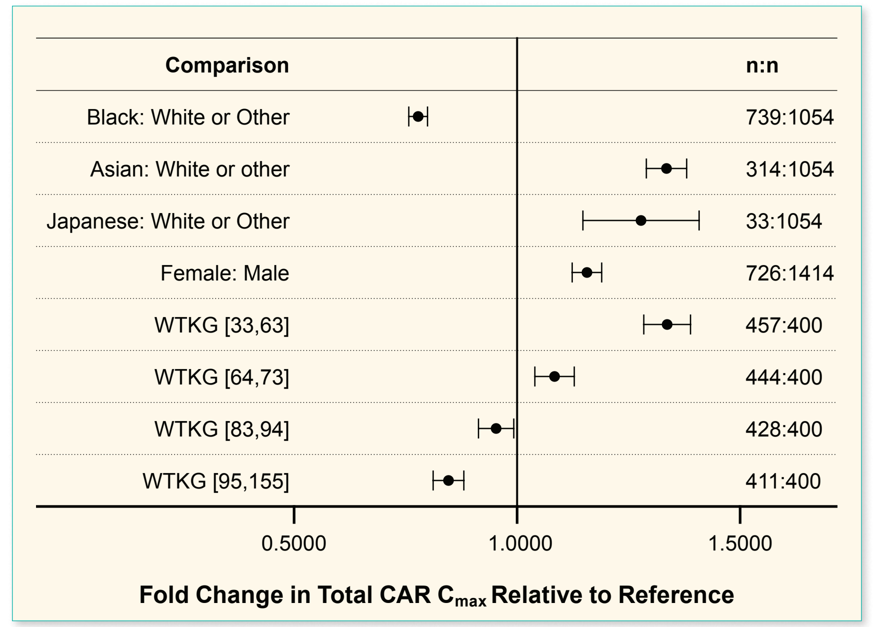


Figure 4. Day 1 Concentrations for a Typical Subject Following a Single 6 mg Dose

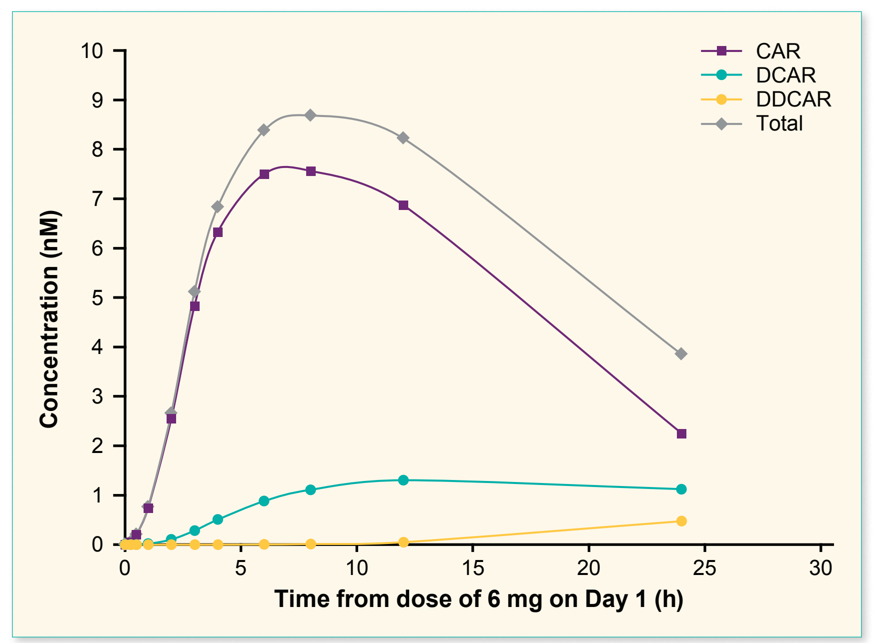


Figure 5. Plasma Concentrations for a Typical Subject Following Administration of the Last 6 mg Once-Daily Dose at Steady State

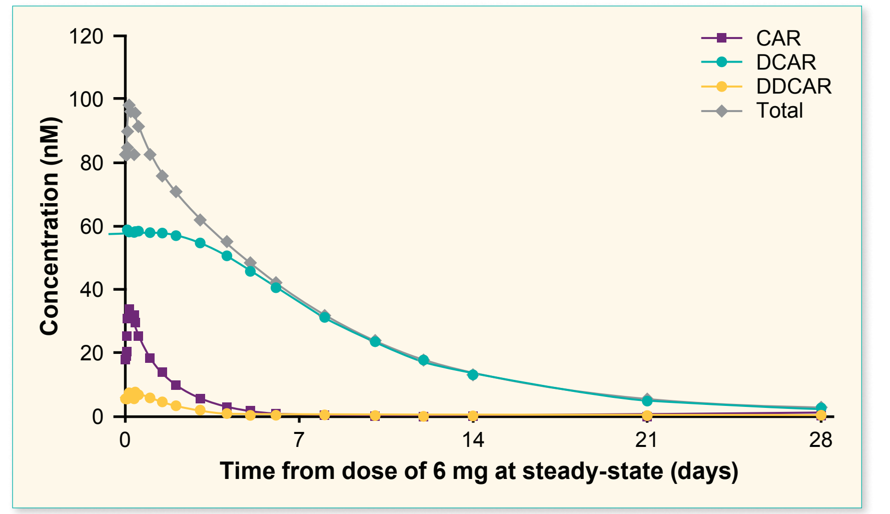
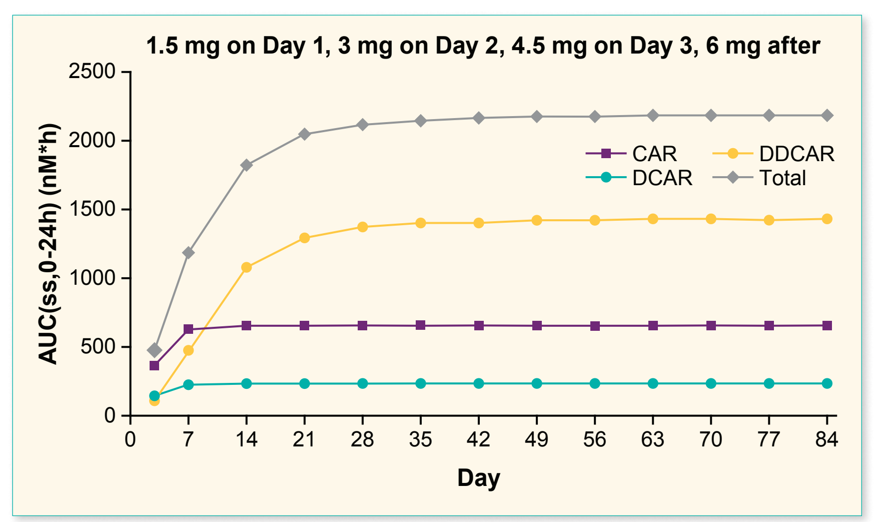


Figure 6. Simulations for a Typical Patient on a Dose of 6 mg/d (With Uptitration to 6 mg by Day 4)



CONCLUSIONS

- Based on predicted steady-state AUC values, DDCAR was the most prominent moiety (64% of Total CAR [molar sum of cariprazine, DCAR and DDCAR] exposures), while cariprazine and DCAR represented 28% and 8% of Total CAR, respectively.
- No covariates impacted exposures to the level of requiring dose adjustment.
- The median time to 90% of steady state was 5, 5, 21, and 18 days for cariprazine, DCAR, DDCAR, and Total CAR, respectively.
- The median effective half life (time to reach 90% steady state/3.32) was 1.5, 1.5, 6.3, and 5.4 days for cariprazine, DCAR, DDCAR, and Total CAR, respectively.
- Mean plasma DDCAR concentrations decreased by ≈50% at 1 week after the last dose and mean cariprazine and DCAR concentrations dropped by 50% in about 1 day. There was an approximate 90% decline in plasma exposure within 1 week for cariprazine and DCAR and within 4 weeks for DDCAR.

REFERENCES

1. Food and Drug Administration. Guidance for Industry - Population Pharmacokinetics. 1999.
2. Khariton et al. "A Population PK Model for Cariprazine and the Metabolites." ACoP 2013.

DISCLOSURES

Antonia Periclou and Timothy Carrothers are employees of Allergan, Inc. Parviz Ghahramani and Tatiana Khariton 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. Luann Phillips and Sébastien Bihorel 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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