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Population Pharmacokinetics of Cariprazine and its Major Metabolites

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SUPPLEMENTAL EQUATIONS

SUPPLEMENTAL EQUATION SET 1: DIFFERENTIAL EQUATIONS DESCRIBING THE BASE MODEL Of THE UPDATED DATASETS

$$\frac{dA_1}{dt} = -K_a \times A_1(t) \text{ ; with an initial condition of Dose/DUR} \quad \textbf{(1)}$$

$$\frac{dA_2}{dt} = -K_a \times A_1(t) - \left(\frac{{}^{Q_3}/_F}{{}^{V_c}/_F} + \frac{{}^{Q_4}/_F}{{}^{V_c}/_F} + \frac{{}^{CL}/_F}{{}^{V_c}/_F}\right) \times A_2(t) + \left(\frac{{}^{Q_3}/_F}{{}^{V_{P1}}/_F}\right) \times A_3(t) + \left(\frac{{}^{Q_4}/_F}{{}^{V_{P2}}/_F}\right) \times A_4(t) \quad \textbf{(2)}$$

$$\frac{dA_3}{dt} = \left(\frac{{}^{Q_3}/_F}{{}^{V_c}/_F}\right) \times A_2(t) - \left(\frac{{}^{Q_3}/_F}{{}^{V_{P1}}/_F}\right) \times A_3(t) \quad \textbf{(3)}$$

$$\frac{dA_4}{dt} = \left(\frac{{}^{Q_4}/_F}{{}^{V_c}/_F}\right) \times A_2(t) - \left(\frac{{}^{Q_4}/_F}{{}^{V_{P2}}/_F}\right) \times A_4(t) \quad \textbf{(4)}$$

$$\frac{dA_5}{dt} = \left(\frac{{}^{CL}/_F}{{}^{V_c}/_F}\right) \times A_2(t) - \left(\frac{{}^{DQ}/_F}{{}^{DV_c}/_F} + \frac{{}^{DCL}/_F}{{}^{DV_c}/_F}\right) \times A_5(t) + \left(\frac{{}^{DQ}/_F}{{}^{DV_P}/_F}\right) \times A_6(t) \quad \textbf{(5)}$$

$$\frac{dA_6}{dt} = \left(\frac{{}^{DQ}/_F}{{}^{DV_c}/_F}\right) \times A_5(t) - \left(\frac{{}^{DQ}/_F}{{}^{DV_P}/_F}\right) \times A_6(t) \quad \textbf{(6)}$$

$$\frac{dA_7}{dt} = DDK_{tr} \times A_9(t) - \left(\frac{{}^{DDQ}/_F}{{}^{DDV_c}/_F} + \frac{{}^{DDCL}/_F}{{}^{DDV_c}/_F}\right) \times A_7(t) + \left(\frac{{}^{DDQ}/_F}{{}^{DDV_P}/_F}\right) \times A_8(t) \quad \textbf{(7)}$$

$$\frac{dA_8}{dt} = \left(\frac{{}^{DDQ}/_F}{{}^{DDV_c}/_F}\right) \times A_7(t) - \left(\frac{{}^{DDQ}/_F}{{}^{DDV_P}/_F}\right) \times A_8(t) \quad \textbf{(8)}$$

$$\frac{dA_9}{dt} = \left(\frac{{}^{DCL}/_F}{{}^{DV_c}/_F}\right) \times A_5(t) - DDK_{tr} \times A_9(t) \quad \textbf{(9)}$$

Where:

$A_1(t)$ is the amount of cariprazine in the depot compartment (compartment 1)

$A_2(t)$ is the amount of cariprazine in the cariprazine central compartment (compartment 2)

$A_3(t)$ is the amount of cariprazine in the first cariprazine peripheral compartment (compartment 3)

$A_4(t)$ is the amount of cariprazine in the 2nd cariprazine peripheral compartment (compartment 4)

$A_5(t)$ is the amount of DCAR in the DCAR central compartment (compartment 5)

$A_6(t)$ is the amount of DCAR in the DCAR peripheral compartment (compartment 6)

$A_7(t)$ is the amount of DDCAR in the DDCAR central compartment (compartment 7)

$A_8(t)$ is the amount of DDCAR in the DDCAR peripheral compartment (compartment 8)

$A_9(t)$ is the amount of DDCAR in the DDCAR transit compartment (compartment 9), which acts to delay the transfer of DCAR to the DDCAR central compartment.

DUR is the duration of the zero-order input of the dose into the depot compartment;

K_a is the rate constant describing the transfer of cariprazine to cariprazine central compartment

CL/F is the cariprazine apparent clearance;

V_C/F is the cariprazine apparent central volume of distribution;

$Q3/F$ is the cariprazine apparent intercompartmental clearance for the first peripheral compartment;

V_{P1}/F is the cariprazine apparent volume of distribution for the first peripheral compartment;

$Q4/F$ is the cariprazine apparent intercompartmental clearance for the 2nd peripheral compartment;

V_{P2}/F is the cariprazine apparent volume of distribution for the 2nd peripheral compartment;

DCL/F is the DCAR apparent clearance;

DV_C/F is the DCAR apparent central volume of distribution;

DQ/F is the DCAR apparent intercompartmental clearance for the DCAR peripheral compartment;

DV_P/F is the DCAR apparent peripheral volume of distribution;

$DDCL/F$ is the DDCAR apparent clearance; and

DDV_C/F is the DDCAR apparent central volume of distribution;

DDQ/F is the DDCAR apparent intercompartmental clearance for the DDCAR peripheral compartment;

DDK_{tr} is the rate constant describing the transfer of DDCAR from a transit compartment to the central compartment for DDCAR;

SUPPLEMENTAL EQUATION SET 2: PARAMETER EQUATIONS DESCRIBING THE FINAL INITIAL DATASET MODELS

$$\frac{CL}{F}(L/h) = 22.8 + 0.183 \times (IBW - 64.5) - 1.76 \times Black - 4.01 \times Asian \quad \textbf{(A1)}$$

$$\frac{V_c}{F}(L) = (454 + 8.55 \times [IBW - 64.5]) \times (1 + 1.47 \times SD) \quad \textbf{(A2)}$$

$$\frac{DCL}{F}(L/h) = 70.9 + 1.33 \times (IBW - 64.5) + 24.4 \times Black + 2.03 \times Female \quad \textbf{(A3)}$$

$$\frac{DV_c}{F}(L) = 176 \times \left(\frac{IBW}{64.5}\right)^{3.16} \quad \textbf{(A4)}$$

$$\frac{DDCL}{F}(L/h) = 6.74 \times \left(\frac{IBW}{64.5}\right)^{1.12} + 4.23 \times Black \quad \textbf{(A5)}$$

$$\frac{DDV_c}{F}(L) = 2220 + 27.4 \times (Age - 40) + 39.7 \times (IBW - 64.5) \times (1180 \times Black) \quad \textbf{(A6)}$$

Where:

CL/F is the cariprazine apparent clearance;

V_C/F is the cariprazine apparent central volume of distribution;

IBW is ideal body weight;

Black is 1 for black or African-American patients and is 0 otherwise;

Asian is 1 for Asian patients and is 0 otherwise;

SD is 1 for concentrations following the first dose and is 0 otherwise;

DC/F *L* is the DCAR apparent clearance;

Female is 1 for female patients and is 0 otherwise;

DV_C/F is the DCAR apparent central volume of distribution;

DDCL/F is the DDCAR apparent clearance; and

DDV_C/F is the DDCAR apparent central volume of distribution.

SUPPLEMENTAL EQUATION SET 3: PARAMETER EQUATIONS FOR THE FINAL UPDATED MODELS

$$\frac{CL}{F} = 21.5 \times (1 - 0.0907 \times Black) \times (1 - 0.178 \times Asian) \times (1 - 0.111 \times Japanese) \times \left(\frac{WTKG}{79}\right)^{0.0946} \quad \textbf{(10)}$$

$$\frac{V_c}{F} = 266 \times \left(\frac{WTKG}{79}\right)^{1.66} \times (1 + 2.84 \times FD) \quad \textbf{(11)}$$

$$\frac{Q3}{\mathrm{F}} = 0.431 \times (1 + 39.4 \times FD) \quad \textbf{(12)}$$

$$\frac{V_{P1}}{F} = 149 \times (1 + 2.61 \times FD) \quad \textbf{(13)}$$

$$\frac{DCL}{F} = 77.3 \times (1 + 0.249 \times Black) \times (1 - 0.0861 \times Asian) \times (1 - 0.145 \times Japanese) \times (1 - 0.160 \times Female) \times \left(\frac{WTKG}{79}\right)^{0.578} \quad \textbf{(14)}$$

$$\frac{DV_c}{F} = 128 \times \left(\frac{WTKG}{79}\right)^{1.18} \times (1 + 1.27 \times FD) \quad \textbf{(15)}$$

$$\frac{DV_P}{F} = 347 \times (1 + 0.535 \times FD) \quad \textbf{(16)}$$

$$\frac{DDCL}{F} = 9.24 \times (1 + 0.547 \times Black) \times (1 - 0.194 \times Asian) \times (1 - 0.156 \times Japanese) \times \left(\frac{WTKG}{79}\right)^{0.427} \quad \textbf{(17)}$$

$$\frac{DDV_c}{F} = 1310 \times (1 + 0.676 \times Black) \times (1 - 0.240 \times Asian) \times (1 + 0.0888 \times Japanese) \times \left(\frac{WTKG}{79}\right)^{0.881} \quad \textbf{(18)}$$

Where:

WTKG is total body weight;

Black is 1 for black or African-American patients and is 0 otherwise;

Asian is 1 for Asian patients (mainly patients from studies conducted in India) and is 0 otherwise;

Japanese is 1 for Japanese patients (Study A002-A11 only) and is 0 otherwise;

FD is 1 for concentrations following the first dose and is 0 otherwise;

Female is 1 for female patients and is 0 otherwise.

SUPPLEMENTAL TABLES

Supplemental Table 1. Model Development Process

Process		**Initial Model**	**Updated Model**
1. Exploratory data analysis		Used to understand informational content of the data, search for extreme values and potential outliers, assess possible data trends, and determine if any errors were made.	Plots including the new study were generated and all summary statistics were re-generated.
2. Base structural model development	a. Phase 1	Initial dataset: full PK profiles from Studies RGH-MD-01, RGH-MD-02, and RGH-MD-18. Final dataset: analysis of the initial phase 1 datasets and excluding samples following a first dose <1.5 mg, samples following doses of 21 mg, samples collected >25 hr postdose, and DDCAR samples following the first dose.	Added Study A002-A11 Re-included data collected >25 hr postdose for all previous phase 1 studies. Phase 1 structural models were updated because the additional data from Study A002-A11 allowed estimation of parameters for additional compartments. Data obtained from doses ≥15 mg were excluded.
	b. Phase 1-3	Phase 1-3 datasets for samples collected within 25 hr of dosing and following doses <21 mg for all studies except RGH-MD-11 and RGH-MD-17.	Phase 1-3 models were updated based upon the revised phase 1 models. Updated dataset also included samples collected >25 hr postdose.
3. Evaluation of covariate effects		Covariate analysis was performed to explore measurable sources of variability in cariprazine, DCAR, and DDCAR.	Statistically significant covariates from the original model were added (race was modified to include Asian-Japanese and IBW was changed to WTKG) to define the full multivariate model.
4. Model refinement		The resultant model was evaluated for further refinement (eg, detect inadequacies or biases in covariate models, assure no trends remained).	After backward elimination, an additional univariate evaluation of the effect of CrCL on the CL parameters was performed ($\alpha = 0.001$).

5. Model evaluation	Assuming that uncertainty in the final model parameters was small relative to other sources of variability, the adequacy of the final models was evaluated using a simulation-based prediction-corrected VPC (PCVPC) method [21].	Performed using the updated final models under the same assumptions.
6. Post-Modeling Assessments	Further model validation: each of the final models was applied (with all parameters fixed) to the data from long-term Studies RGH-MD-11 and RGH-MD-17 to obtain population predictions and individual predictions of concentrations. Assessment of clinical relevance of statistically significant covariates: clinical significance was addressed through the summarization and graphical representation of the computed individual patient exposure measures following a 12-mg steady-state dose. For each covariate, geometric mean ratios and 90% CIs of the individual exposure measures at steady state ($C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-24,ss}$) were calculated and the percent change in relevant PK exposures was used to assess for clinical significance. Assessment of CYP2D6 metabolizer status: an analysis of variance was performed to test the statistical significance of CYP2D6 metabolizer status (poor versus extensive) in patients with a known CYPD6 genotype on the model-predicted PK exposure of cariprazine, DCAR, and DDCAR where PK exposure was defined as dose-normalized $C_{min,ss}$, $C_{max,ss}$, $AUC_{0-24,ss}$, and clearance at steady state.	Performed using the updated final models under the same assumptions, unless otherwise stated below. Assessment of clinical relevance of statistically significant covariates: a 6-mg steady-state dose was used for the final updated models.

$AUC_{0-24,ss}$, area under the plasma concentration-time curve over a 24-hr period at steady state; *CI*, confidence interval; *CL*, apparent clearance; *$C_{max,ss}$*, maximum plasma concentration; *$C_{min,ss}$*, minimum plasma concentration; *CrCL*, creatinine clearance; *CYP2D6*, cytochrome P450 2D6; *DCAR*, desmethyl-cariprazine; *DDCAR*, didesmethyl-cariprazine; *IBW*, ideal body weight; *PK*, pharmacokinetic; *Total CAR*, sum of cariprazine and major metabolites (DCAR and DDCAR); *VPC*, visual predictive check; *WTKG*, body weight.

Supplemental Table 2. Summary Statistics of Patient Descriptors for the Updated Dataset

Patient Characteristic	Statistic	Phase 1 Studies Dataset	Phase 2/3 Studies Dataset	Combined Phase 1-3 Model Dataset	Model Validation Dataset[a]
Age, years	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
Age category, n (%)	18-49 years	132 (81.2)	1653 (81.7)	1785 (81.2)	523 (81.1)
	50-65 years	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)
Race, n (%)	White/Caucasian	42 (25.8)	961 (47.2)	1003 (45.6)	285 (44.2)
	Black/African-American	78 (47.9)	689 (33.8)	767 (34.9)	231 (35.8)
	Asian[b]	2 (1.2)	312 (15.3)	314 (14.3)	94 (14.6)
	Japanese[b]	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)
Body weight (WTKG), kg	Mean (SD)	80.5 (16.6)	78.8 (18.9)	78.9 (18.7)	78.8 (20.0)
	Median	81.0	77.4	77.7	76.7
	Min, max	39.8, 129.7	33.1, 155.1	33.1, 155.1	36.6, 140.6
	N	163	2036	2199	645
Ideal body weight (IBW), kg	Mean (SD)	65.3 (8.6)	63.7 (8.3)	63.8 (8.4)	64.0 (8.2)
	Median	67.4	64.3	64.5	64.5
	Min, max	43.5, 83.0	36.1, 89.2	36.1, 89.2	39.3, 87.0
	N	163	2036	2199	645
Creatinine clearance (CrCL), mL/min	Mean (SD)	121.5 (31.2)	119.8 (36.3)	119.9 (36.0)	113.3 (31.8)
	Median	117.5	113.4	113.5	108.6
	Min, max	62.6, 244.6	31.4, 360.5	31.4, 360.5	54.2, 253.5
	N	163	2036	2199	645
Renal function, n (%) category	Normal	139 (85.3)	1663 (81.7)	1802 (81.9)	498 (77.2)
	Mild impairment[c]	24 (14.7)	353 (17.3)	377 (17.1)	143 (22.2)
	Moderate impairment[c]	0 (0.0)	20 (1.0)	20 (0.9)	4 (0.6)

SD, standard deviation.

[a] The Model Validation Dataset included Studies RGH-MD-11 and RGH-MD-17 only.

[b] Asian patients were mainly from studies in India; Japanese patients were from Study A002-A11 only.

[c] Renal function categories: normal (CrCL ≥90 mL/min); mild (60≤ CrCL ≤89 mL/min); moderate (30≤ CrCL ≤59 mL/min).

Supplemental Table 3. Pharmacokinetic Parameter Estimates and Standard Errors for the Final Models of the Initial Datasets

Parameter	Description/Factors (Units)	Estimate (90% CI)[a]	RSE%	IIV (90% CI)[a]
Cariprazine				
DUR	Duration of zero-order process (h)	3.14 (2.93, 3.38)	4.67	NE
K_a	First-order absorption rate constant (1/h)	0.578 (0.501, 0.683)	8.28	96.5 %CV (86.7, 107)
CL/F	Apparent central clearance[b] (L/h)	22.8 (22.3, 23.3)	1.25	34.2 %CV (32.8, 35.8)
	Linear effect of IBW (L/h/kg)	0.183 (0.143, 0.221)	12.8	
	Additional shift in black patients (L/h)	-1.76 (-2.47, -1.08)	24.3	
	Additional shift in Asian patients (L/h)	-4.01 (-4.87, -3.25)	11.8	
V_C/F	Central volume of distribution[c] (L)	454 (397, 515)	5.05	44.0 %CV (37.9, 51.2)
	Proportional shift in V_c for first dose	1.47	FIXED[d]	
	Linear effect of IBW (L/kg)	8.55 (6.29, 10.6)	14.5	
Q/F	Intercompartmental clearance (L/h)	92.3 (66.5, 126)	12.1	NE
V_P/F	Peripheral volume of distribution (L)	415 (334, 490)	7.02	NE
DCAR				
DCL/F	Apparent DCAR clearance[e] (L/h)	70.9 (69.0, 72.7)	1.59	45.4 %CV (43.8, 47.0)
	Linear effect of IBW (L/h/kg)	1.33 (1.11, 1.52)	9.82	
	Additional shift in black patients (L/h)	24.4 (20.9, 28.2)	8.39	
	Additional shift in female patients (L/h)	2.03 (-1.77, 5.87)	114	
DV_C/F	Apparent DCAR central volume of distribution (L)	176 (159, 198)	6.88	106 %CV (98.1, 112)
	Power effect of IBW	3.16 (1.95, 3.93)	18.0	
DDCAR				
DDCL/F	Apparent DDCAR clearance[f] (L/h)	6.74 (6.46, 7.04)	2.54	68.9 %CV (65.0, 73.4)
	Power effect of IBW	1.12 (0.813, 1.42)	15.7	
	Additional shift in black patients (L/h)	4.23 (3.45, 5.01)	10.9	
DDV_C/F	Apparent DDCAR central volume of distribution[g] (L)	2220 (2120, 2316)	2.49	70.3 %CV (65.4, 74.1)
	Linear effect of Age (L/y)	27.4 (20.3, 33.4)	14.2	
	Linear effect of IBW (L/kg)	39.7 (32.2, 47.3)	11.3	
	Additional shift in black patients (L)	1180 (975, 1412)	10.5	

CI, confidence interval; *CV*, coefficient of variance; *DCAR*, desmethyl-cariprazine; *DDCAR*, didesmethyl-cariprazine; *IBW*, ideal body weight; *IIV*, interindividual variability; *NE*, not estimated; *RSE*, relative standard error.

[a] The 5th to 95th percentile of the estimates from fitting the model to 500 bootstrap datasets. Minimization was successful for 91.2% (456), 55.6% (278), and 94.4% (478) of the datasets for cariprazine, DCAR, and DDCAR, respectively.

[b] In white, 64.5-kg IBW patients.

[c] In 64.5-kg IBW patients.

[d] Due to differences in sampling designs, additional models were tested that considered various combinations of the absorption parameters and the peripheral compartment parameters fixed to the values from the phase 1 model.

[e] In non-black, male, 64.5-kg IBW patients.

[f] In non-black, 64.5-kg IBW patients.

[g] In non-black, 40-year old, 64.5-kg IBW patients.

Supplemental Table 4. Mean (SD) Model-Predicted PK Exposures of Cariprazine, DCAR, and DDCAR Following Steady-State Dosing of Cariprazine at 6 mg/d for All Patients in the Population PK Analysis Compared to Non-Compartmental PK Exposures Following Multiple Dose Administration of Cariprazine for Japanese Patients in Study A002-A11.

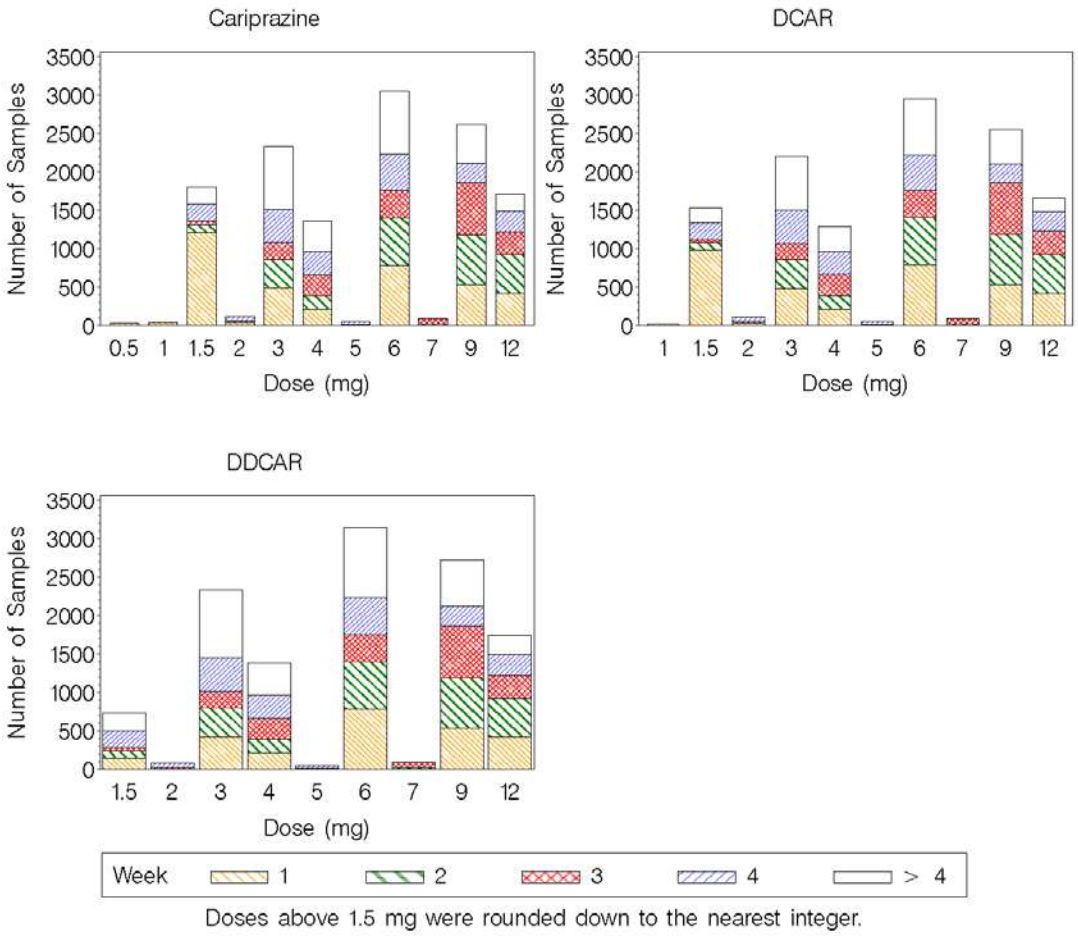
		C_{max} (ng/mL)			$AUC_{0–24}$ (ng·h/mL)		
		Cariprazine	DCAR	DDCAR	Cariprazine	DCAR	DDCAR
PopPK Model Prediction: All Subjects	Mean (SD)	16.1 (5.8)	3.65 (1.69)	26.2 (42.6)	295 (134)	78.0 (39)	629 (1022)
	N	2599	2580	2539	2599	2580	2539
PopPK Model Prediction: Japanese Patients	Mean (SD)	20.1 (4.9)	5.04 (1.8)	32.7 (12.8)	306 (95.4)	105 (41)	784 (308)
	N	37	37	33	37	37	33
Nakamura et al 2016: Japanese Patients[a]	Mean SD	22.7 (4.18)	5.96 (1.59)	35.9 (8)	358 (85.2)	115 (23.5)	800 (207)
	N	8	8	8	8	8	8

AUC_{0-24}, area under the plasma concentration-time curve over a 24-hr period; C_{max}, maximum plasma concentration; *DCAR*, desmethyl-cariprazine; *DDCAR*, didesmethyl-cariprazine; *PK*, pharmacokinetic; *SD*, standard deviation.

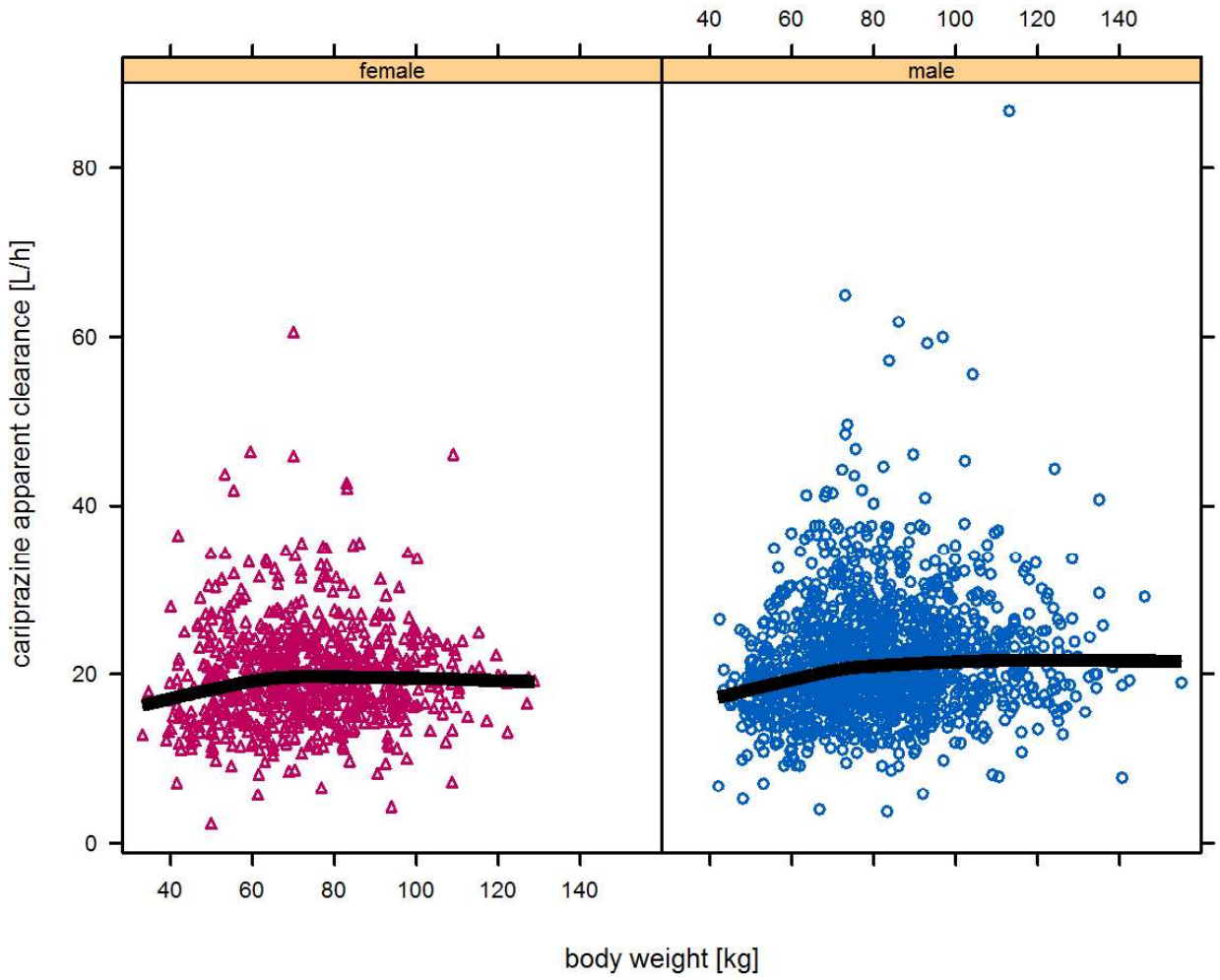
[a] Data from Table 3 of Nakamura et al. [11].

SUPPLEMENTAL FIGURES

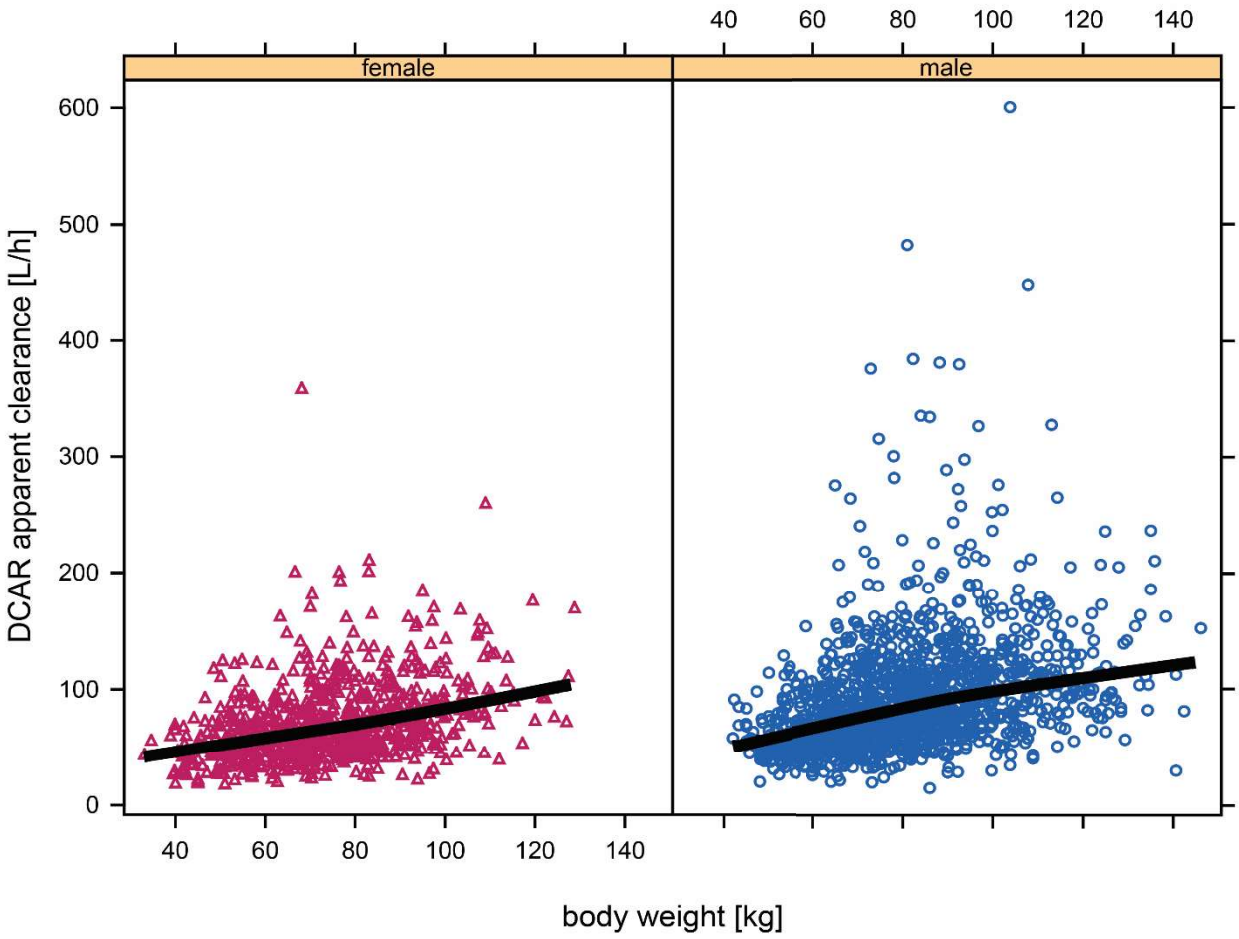
Supplemental Figure 1. Histogram of the Number of Samples Stratified by Dose and Week. *DCAR*, desmethyl-cariprazine; *DDCAR*, didesmethyl-cariprazine.



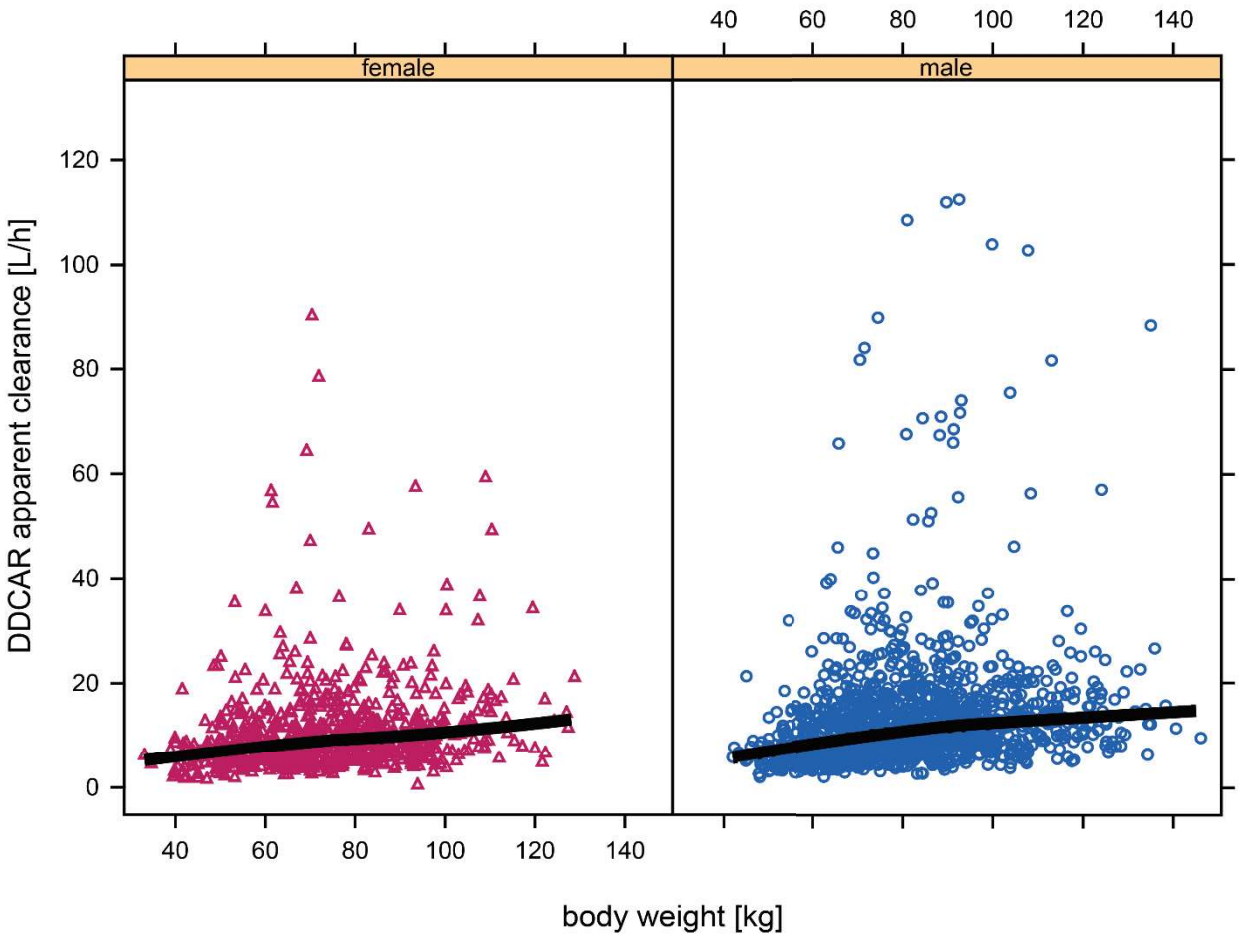
Supplemental Figure 2. Effects of Body Weight by Sex on Cariprazine Apparent Clearance. Scatter plot showing the relationship between cariprazine apparent clearance and body weight. Individual patients are represented by pink triangles (female) and blue circles (male), and the black lines represent locally estimated scatterplot smoothing (LOESS).



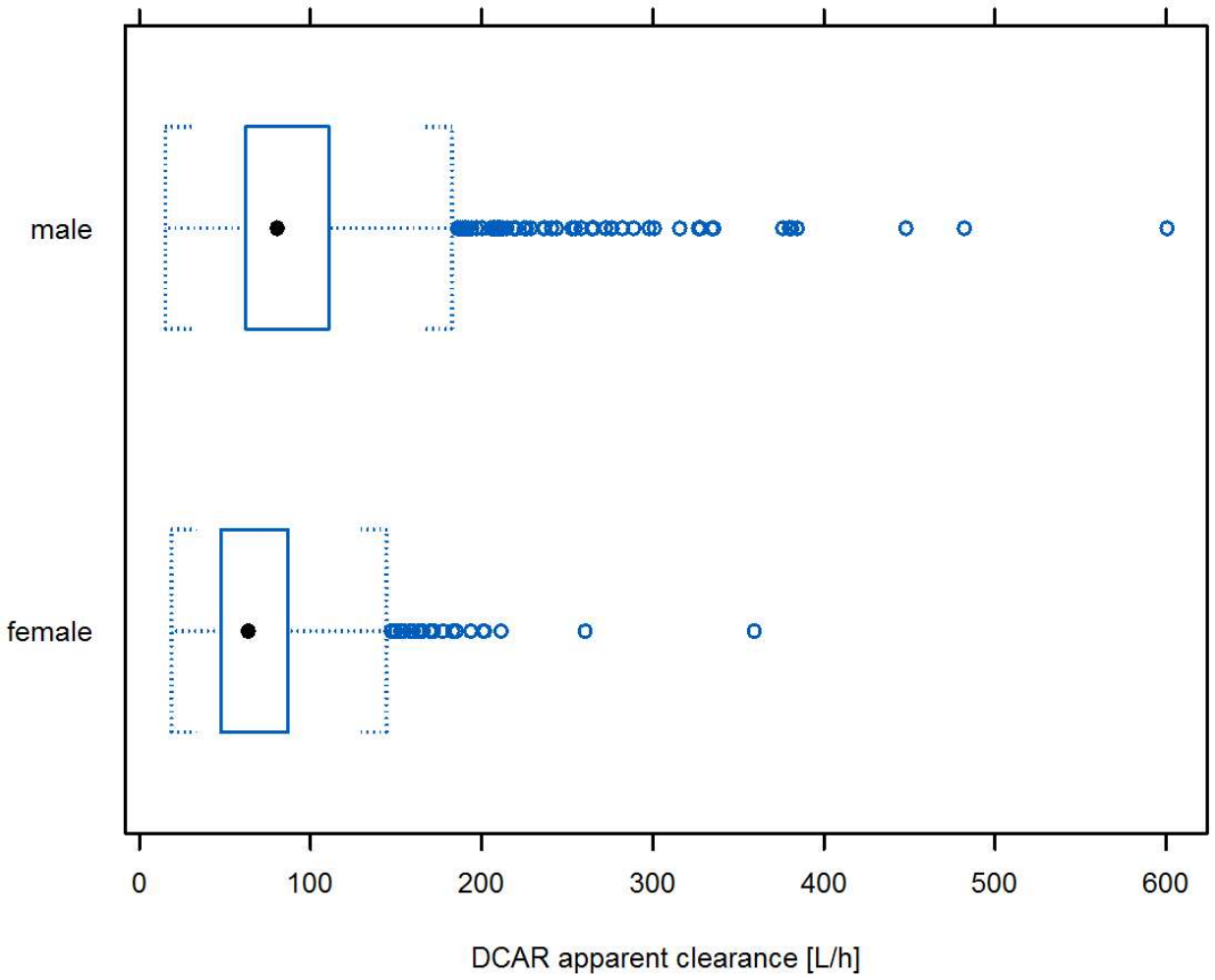
Supplemental Figure 3. Effects of Body Weight by Sex on Desmethyl-Cariprazine (DCAR) Apparent Clearance. Scatter plot showing the relationship between desmethyl-cariprazine apparent clearance and body weight. Individual patients are represented by pink triangles (female) and blue circles (male), and the dashed lines illustrate locally estimated scatterplot smoothing (LOESS).



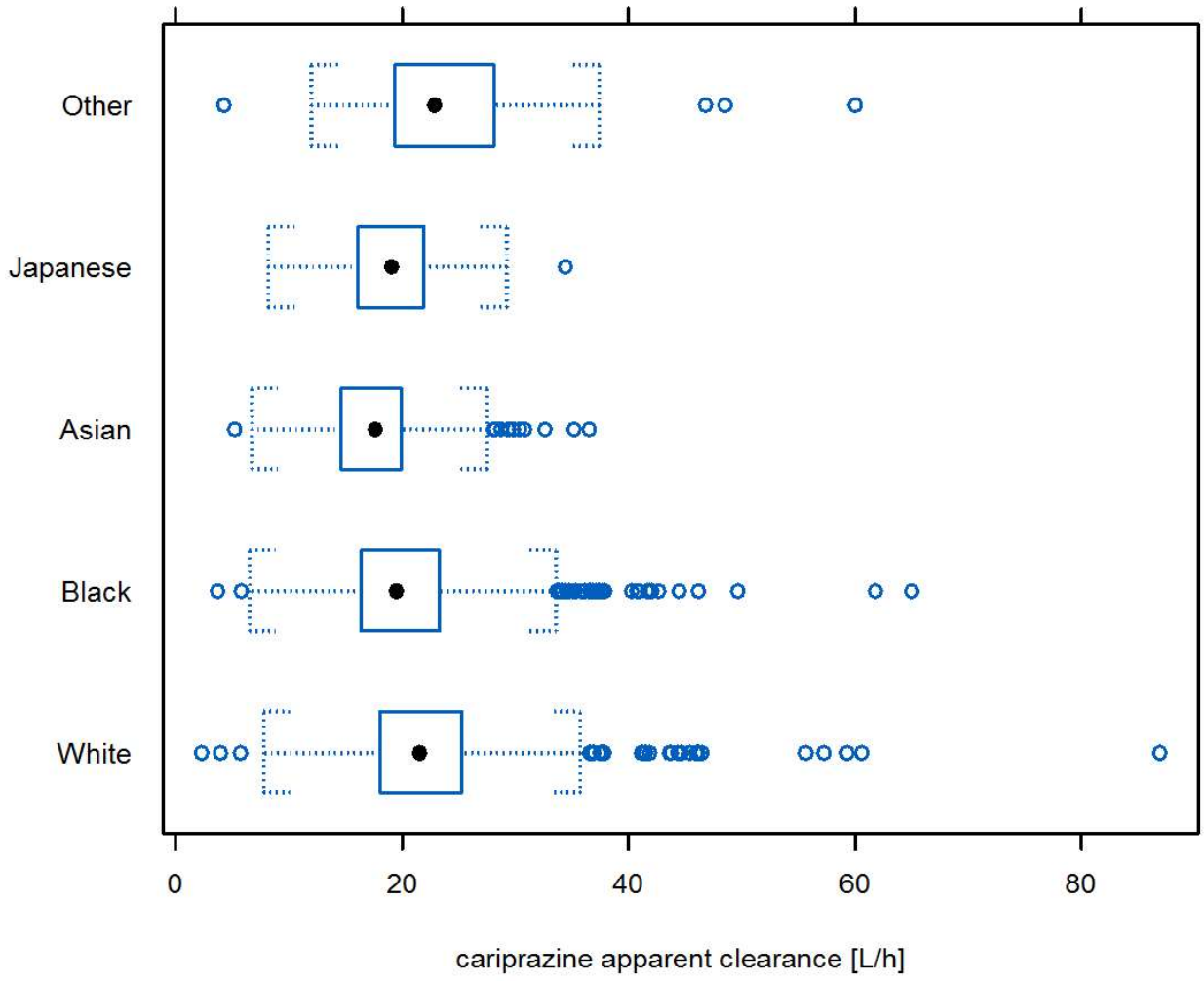
Supplemental Figure 4. Effects of Body Weight by Sex on Didesmethyl-Cariprazine (DDCAR) Apparent Clearance. Scatter plot showing the relationship between didesmethyl-cariprazine apparent clearance and body weight. Individual patients are represented by pink triangles (female) and blue circles (male), and the dashed lines illustrate locally estimated scatterplot smoothing (LOESS).



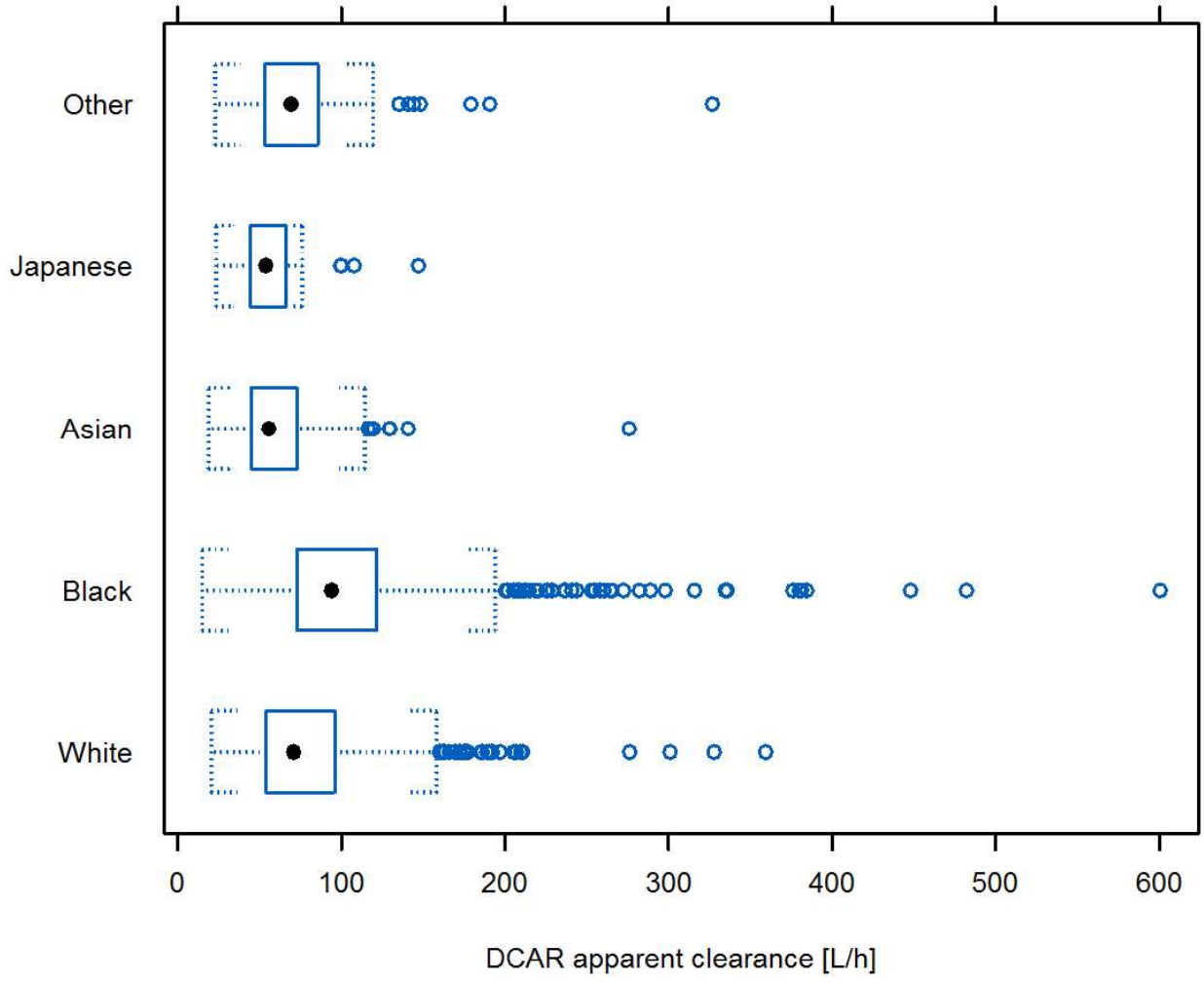
Supplemental Figure 5. Effects of Sex on Desmethyl-Cariprazine (DCAR) Apparent Clearance. Box and whisker plots showing the distribution of desmethyl-cariprazine apparent clearance by sex. Individual patients with values outside the upper and lower quartile are represented by blue circles.



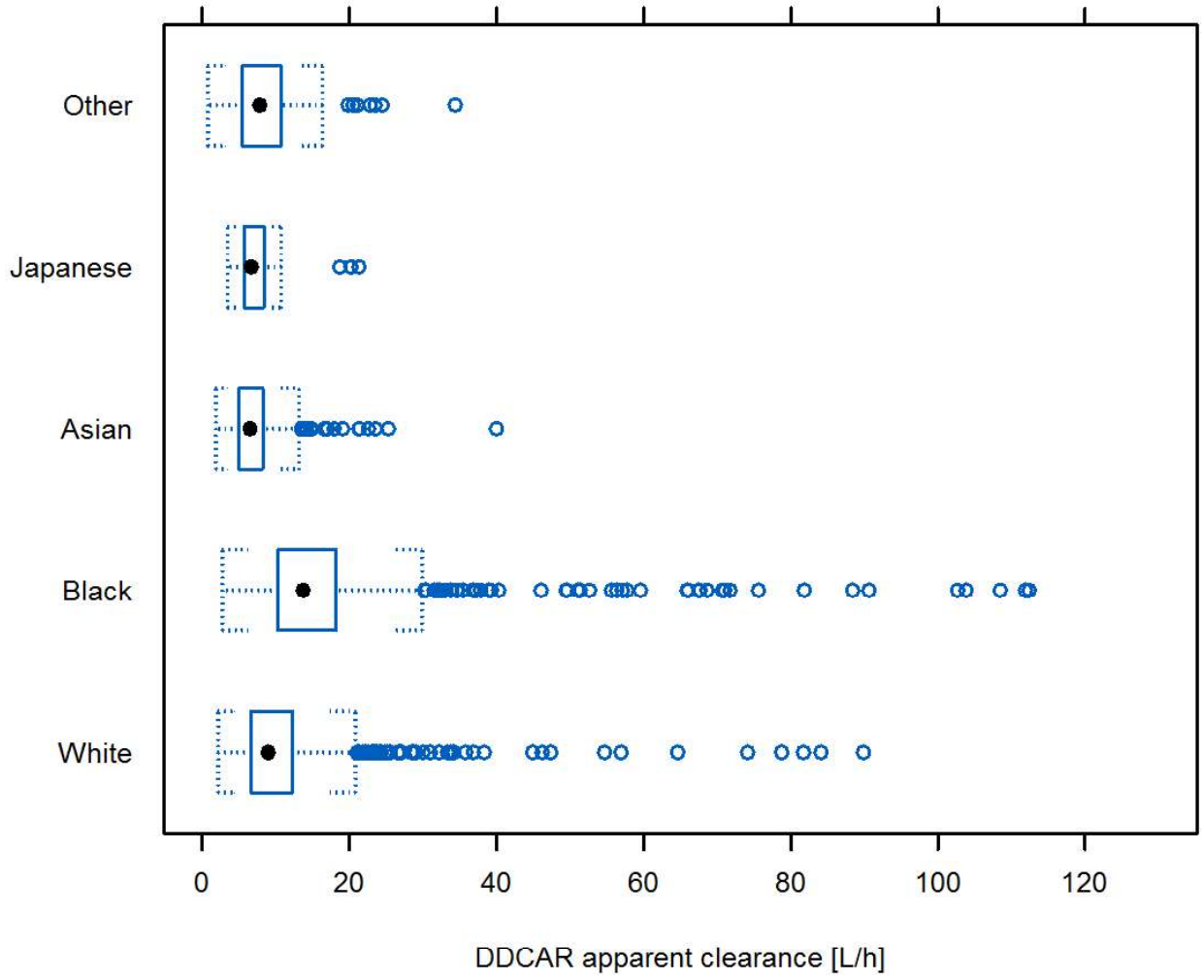
Supplemental Figure 6. Effects of Race on Cariprazine Apparent Clearance. Box and whisker plots showing the distribution of cariprazine apparent clearance by race. Individual patients with values outside the upper and lower quartile are represented by blue circles.



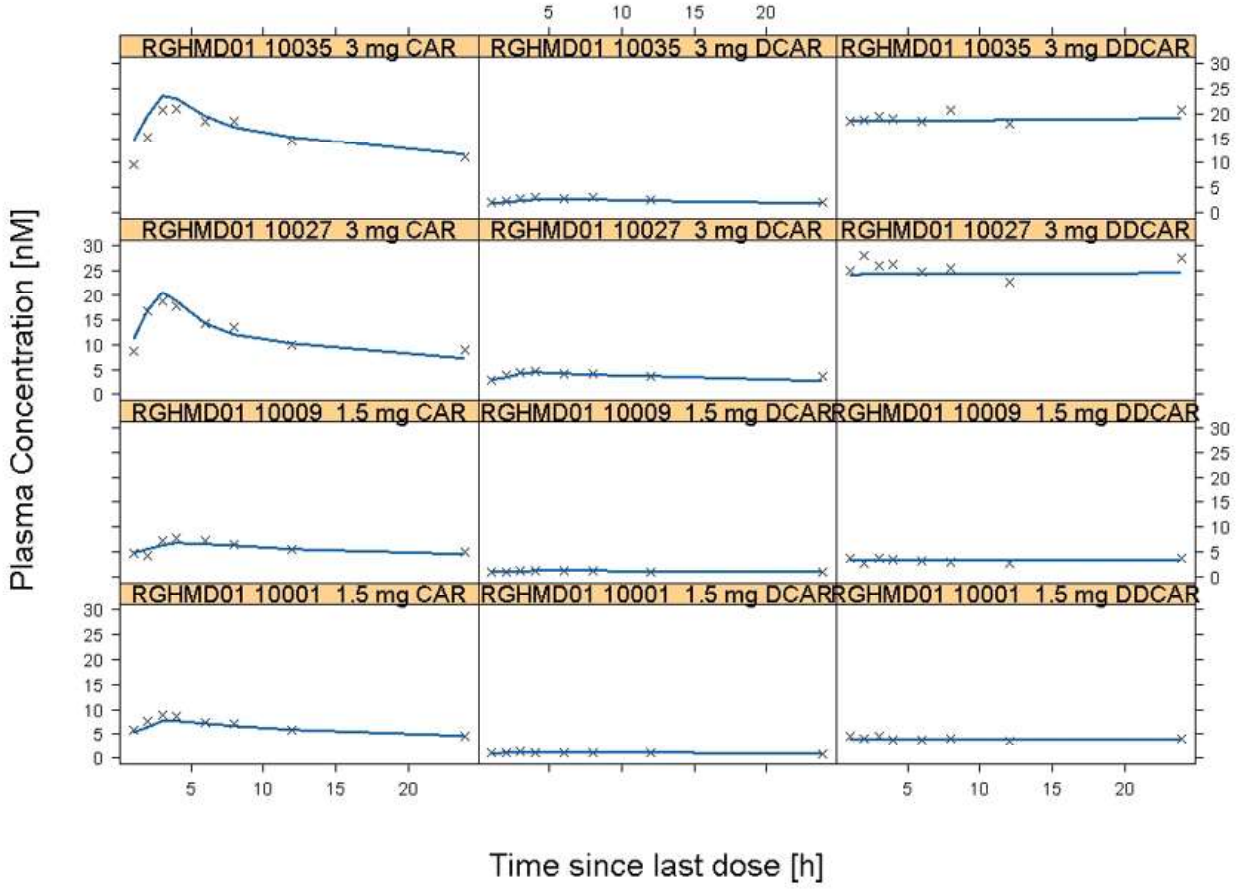
Supplemental Figure 7. Effects of Race on Desmethyl-Cariprazine (DCAR) Apparent Clearance. Box and whisker plots showing the distribution of desmethyl-cariprazine apparent clearance by race. Individual patients with values outside the upper and lower quartile are represented by blue circles.



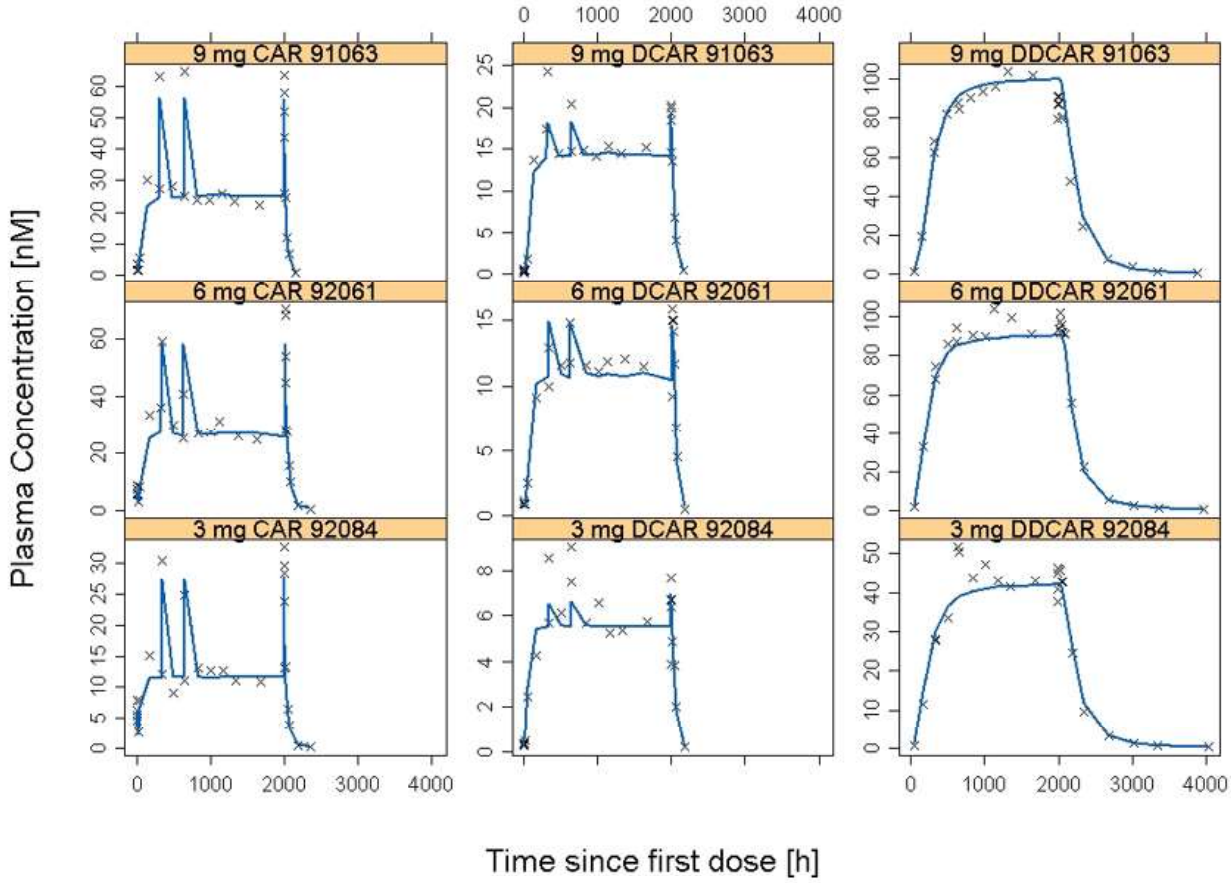
Supplemental Figure 8. Effects of Race on Didesmethyl-Cariprazine (DDCAR) Apparent Clearance. Box and whisker plots showing the distribution of didesmethyl-cariprazine apparent clearance by race. Individual patients with values outside the upper and lower quartile are represented by blue circles.



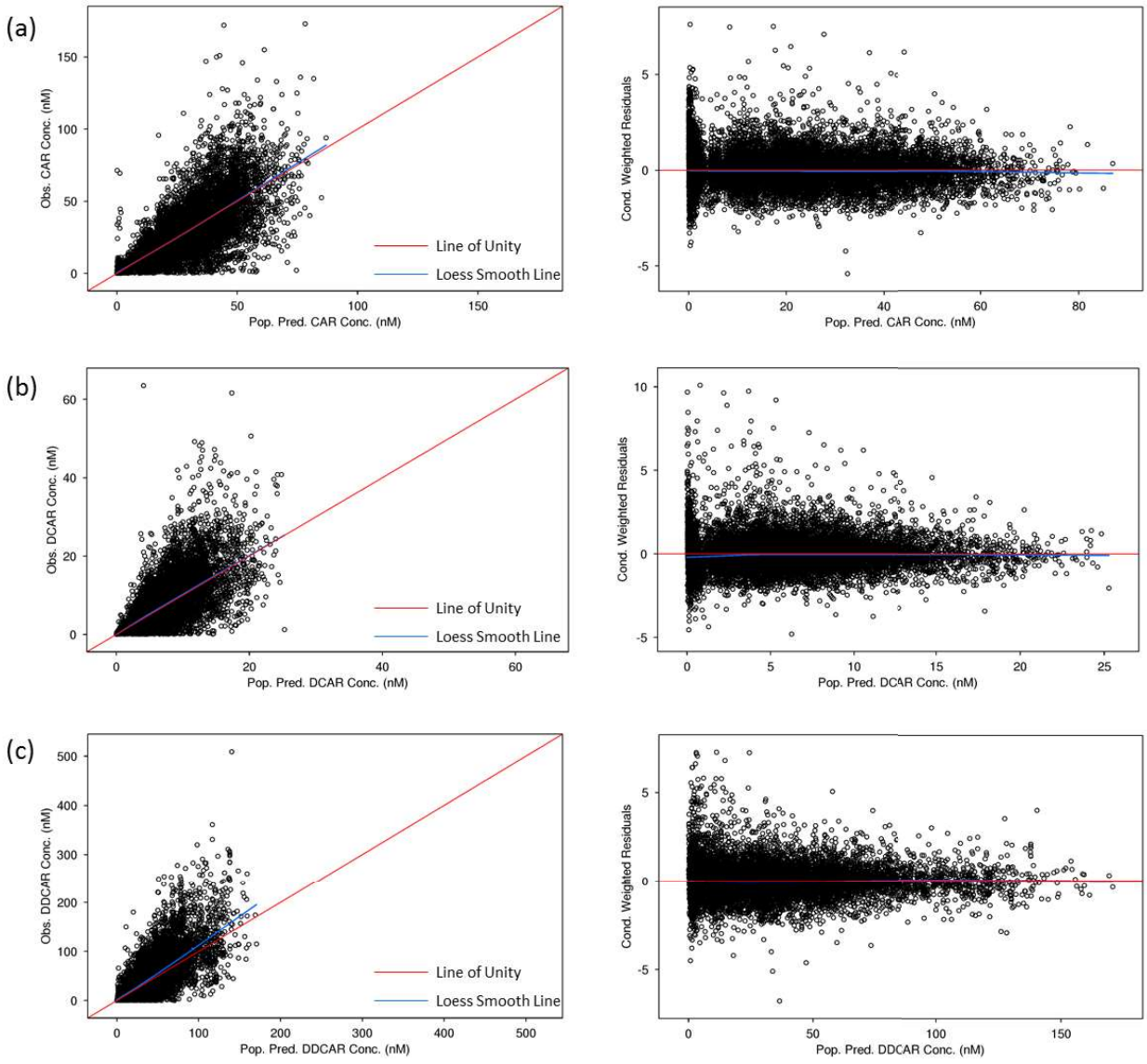
Supplemental Figure 9. Measured Plasma Exposures of Cariprazine (CAR), Desmethyl-Cariprazine (DCAR), and Didesmethyl-Cariprazine (DDCAR) For Representative Individual Subjects in Study RGH-MD-01. Plasma concentrations of cariprazine, DCAR, and DDCAR in 2 patients treated with 3 mg cariprazine and in 2 patients treated with 1.5 mg cariprazine measured after 3 cariprazine doses. X's represent blood collection timepoints, and the individual fit is represented by a blue line.



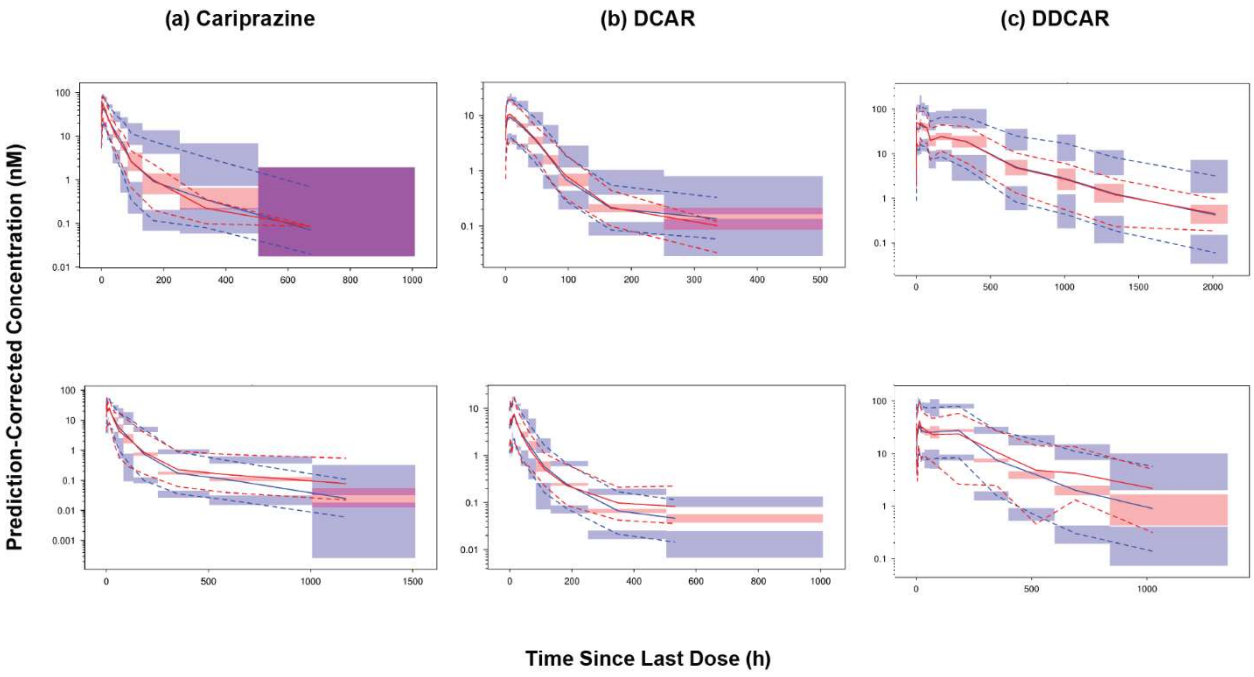
Supplemental Figure 10. Measured Plasma Exposures of Cariprazine (CAR), Desmethyl-cariprazine (DCAR), and Didesmethyl-cariprazine (DDCAR) For Representative Individual Subjects in Study A002-A11. Plasma concentrations of cariprazine, DCAR, and DDCAR in 3 patients treated with 3 mg, 6 mg, or 9 mg cariprazine, measured after 3 cariprazine doses. X's represent blood collection timepoints, and the best fit is represented by a blue line.



Supplemental Figure 11. Goodness-of-Fit Plots of the Final Updated Models. Goodness-of-fit plots for **a** cariprazine, **b** DCAR, and **c** DDCAR showing observed concentrations (left) or conditional weighted residuals (right) versus population-predicted concentrations. Red lines represent the line of unity (panels on the left) and a horizontal reference line at the value of zero (panels on the right). *Conc*., concentration; *DCAR*, desmethyl-cariprazine; *DDCAR*, didesmethyl-cariprazine; *Obs*., observed; *Pop*., population; *Pred*., predicted



Supplemental Figure 12. Predicted-Corrected Visual Prediction Check (PCVPC) of the Final Updated Models for the Complete Range of Time Since Last Dose. Visual predictive check of final models for the complete time profile since last dose for **a** cariprazine, **b** DCAR, and **c** DDCAR. PCVPC plots of phase 1 studies (top, multiple dose) and phase 3 studies (bottom, multiple dose) are shown separately. Red and blue lines denote observed data and predictions, respectively; solid lines denote median, dashed lines represent 5th and 95th percentiles; shaded areas represent 95% CI of prediction percentiles, purple boxes represent areas where 95% CI of observed and predicted data overlap. *CI*, confidence interval; *DCAR*, desmethyl-cariprazine; *DDCAR*, didesmethyl-cariprazine.



Supplemental Figure 13. Prediction-Corrected Visual Prediction Check (PCVPC) of the Final Updated Models in the Model Validation Dataset. Up to 50 hours (top) and for complete range of time (bottom) since last dose for: **a** cariprazine, **b** DCAR, and **c** DDCAR, respectively. Red and blue lines denote observed data and predictions, respectively; solid lines denote median, dashed lines represent 5th and 95th percentiles; shaded areas represent 95% CI of prediction percentiles. *CI*, confidence interval; *DCAR*, desmethyl-cariprazine; *DDCAR*, didesmethyl-cariprazine.