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APPLICATION NUMBER:

204370Orig1Orig2s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA/eCTD#	204,370/067
Submission Type	Resubmission
Proposed Brand Name	Vraylar
Generic Name	Cariprazine HCl
Dosage Form	Immediate-Release Hard Gelatin Capsule
Dosage Strength (mg)	1.5, 3, 4.5, 6
Indication	Schizophrenia and Bipolar Mania
Sponsor	Forest Lab
Review Type	Standard
Submission Date	December 17, 2014
OCP Review Team	Huixia Zhang, Atul Bhattaram, Kevin Krudys, Hao Zhu

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1 EXECUTIVE SUMMARY

NDA204370 for cariprazine was originally submitted on November 19, 2012 for approval in the treatment of (1) schizophrenia, and (2) manic and mixed episodes associated with bipolar I disorder in adult patients. A complete response letter was issued on November 19, 2013, indicating the [redacted] (b) (4) dose-related toxicity as the major deficiencies.

The original clinical pharmacology program provided adequate pharmacokinetic (PK) information on cariprazine (CAR) and one of its active metabolites, desmethyl cariprazine (DCAR). However, there was insufficient information on the accumulation of the major active metabolite didesmethyl cariprazine (DDCAR). The dedicated multiple-dose PK study (Study RHG188-002) was conducted with 1mg/day dose in healthy volunteers up to 21 days, by which

average DDCAR concentration was still rising. The maximum multiple-dose regimen evaluated in patients was 12.5 mg/day for 27 days (Study RGH-MD-01). However, predose samples were collected only in 3 consecutive days, which was not sufficiently long to help determine when steady state was reached for a drug with long half-life. In addition, sparse PK samples were collected in fixed-dose, Phase 2/3 trials in patients up to 6 weeks. Two subgroups of patients seemed to be presented based on the concentration time profiles between Week 4 and Week 6. In some individuals it was observed that DDCAR concentration dropped significantly between Week 4 and Week 6 (decrease in concentration level was greater than 20%, the allowed assay variability). The rest of the subjects demonstrated increased DDCAR concentration over the time course between Week 4 and Week 6 (Appendix 3.2).

In the current resubmission, Forest submitted observed PK data from a recently completed Study A002-A11, blinded PK data from an ongoing Study RGH-MD-06, and safety database reanalyzed by cariprazine modal daily dose. In addition, Forest proposed (b) (4) , based on the reassessment of the overall benefit/risk profile and the new safety analyses.

For this resubmission, the focus of Office of Clinical Pharmacology (OCP) review is the PK features of DDCAR, DCAR, and CAR (Section 2. Specific Issues) based on the results from Study A002-A11 and other pharmacokinetic information/data obtained from the original submission. Study A002-A11 evaluated the pharmacokinetics and safety of orally administered cariprazine tablets once a day for 12 weeks to Japanese schizophrenia patients, starting with an initial dose of 1.5 mg/day on Day 1, followed by gradual daily up-titration over 1 to 4 days to a fixed final dose of 3 mg/day, 6 mg/day, or 9 mg/day. PK of CAR, DCAR, and DDCAR were evaluated during the 12-week treatment period and the 12-week washout period.

Findings of Clinical Pharmacology are summarized below:

1.) Effective half-life, as proposed by the sponsor, does not appear to be appropriate for describing the pharmacokinetic features of CAR, DCAR, and DDCAR. For example, the proposed effective half-life does not project the observed accumulation for CAR.
2.) Approximately 18%, 50% and 37% of the enrolled subjects discontinued the treatment in the 3-mg, 6-mg and 9-mg dose groups, respectively, in Study A002-A11. Assuming there is no compliance issue, different patterns on DDCAR accumulation were observed in patients who completed the 12-week treatment (i.e., completers). For some patients, DDCAR concentration reached maximum at Week3/4 then dropped down to a lower level; for other patients, DDCAR concentration kept rising even by the end of the 12-week treatment, though at a smaller rate of rising after Week3/4. This finding appears to be consistent with the sparse PK data collected in Phase 2/3 trials. At present, we do not have explanations for the concentration decrease of DDCAR after Week 3/4 in some patients based on mechanisms or known changes in study conduct (e.g., comedications, or bioassay changes).
3.) Total cariprazine (CAR + DCAR + DDCAR), CAR, DCAR, and DDCAR plasma concentrations declined in a multi-exponential manner following discontinuation of cariprazine treatment. Mean CAR concentration dropped about 50% in about 1 day. Mean plasma concentrations of total cariprazine (CAR+DCAR+DDCAR) and DDCAR

decreased by about 50% one week after the last dose. About 90% decline in plasma exposure occurred within 1 week for cariprazine and DCAR, 3 weeks for total cariprazine (CAR+DCAR+DDCAR), and 4 weeks for DDCAR. The results are consistent with the findings in the Phase 2/3 trials from the original NDA submission. In addition, it is worth pointing out that, following a single dose of 1 mg of CAR administration, DDCAR was still detectable 8 weeks postdose (Study A002-A6 from the original submission).

1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP I) has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA (resubmission and original) to support a recommendation of approval of cariprazine. The acceptability of specific drug information in the label is pending satisfactory agreement with the Sponsor.

1.2 Post-Marketing Studies

Refer to original Clinical Pharmacology review (Clinical Pharmacology Review was signed off in DARRTS on 7/19/2013).

2 SPECIFIC ISSUES

2.1 Using Effective Half Life To Describe PK Features

The sponsor proposed to use effective half-life to describe the PK profiles of CAR, DCAR, and DDCAR. In general, effective half-life can be used to approximate drug accumulation following a relatively complicated pharmacokinetic process (e.g., a two-compartment model with first-order absorption and first-order elimination) by using a simple pharmacokinetic model, (e.g., a one-compartment model with i.v. bolus and first-order elimination process). However, the effective half-life, as the sponsor proposed, does not appear to be appropriate.

The approach the sponsor proposed to obtain effective half-life is based on time to steady state. Like all major pharmacokinetic parameters (e.g., Cmax and AUC) using two-stage approach, the time to steady state should be obtained on the basis of each individual. However, given the observed different patterns of DDCAR accumulation across different patients, as discussed in Section 2.2.2, it appears to be infeasible to derive robust estimates of time to steady state using individual pharmacokinetic profiles. Directly deriving time to steady state based on mean pharmacokinetic profile of DDCAR does not appear to be appropriate. Mean concentration level is obtained by averaging one group of observations which reached maximum level then followed a decrease, with another group of observations whose values kept rising over the entire observation period. The mean curve may be flattened at early time points, not adequately representing the profile in the true patient population.

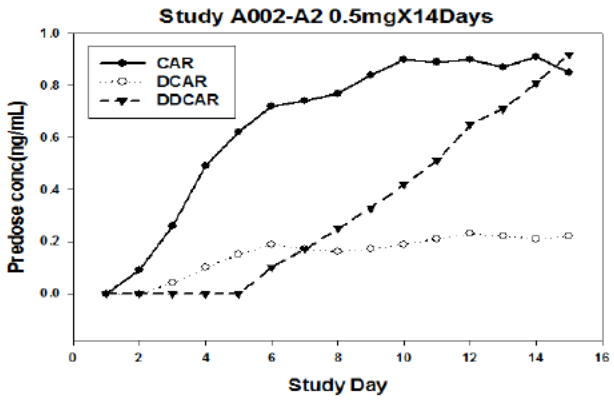
The sponsor used the half-life of initial decline phase to support the selected effective half-life. The sponsor proposed effective half-life for cariprazine is about 1 day, which is consistent with the half-life of the initial decline phase of the PK profile after cariprazine is discontinued. If effective half-life is 1 day, the anticipated accumulation of cariprazine following a once-daily dosing is 2 fold, while the observed accumulation was found to be 6-11 fold (Table 1). Moreover, a compound with an effective half-life of one day is anticipated to reach about 50%

and greater than 90% of its steady state level on Day 1 and Day 4, respectively. In reality, the accumulation rate following 0.5 mg once-daily dosing is much slower than the anticipated levels (Figure 1). Hence, the sponsor proposed effective half-life does not appear to project drug accumulation.

Table 1: Observed Accumulation for Cariprazine from Studies Submitted in Original Submission

Study	Dosing Regimen	Fold Accumulation
RGH-188-002	1mg x21 days	6.9x
A002-A2	1mg QD 14 days	6x
A002-A2	0.5mg QD 14 days	11x
RGH-PK-04	0.5mg x 14 days	7.9x

Figure 1: Accumulation of Cariprazine Following a Once-Daily Treatment of 0.5 mg for 14 Days



(Source: Study A002-A2)

2.2 Time To Steady State

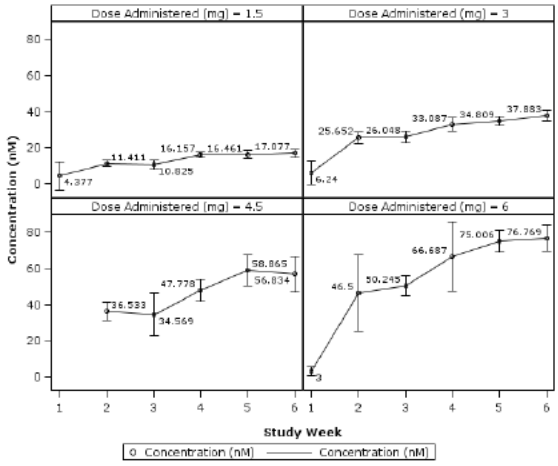
2.2.1 Phase 2/3 Trials in the Original Submission

Sparse pharmacokinetic samples obtained from Study RGH-MD-04 and RGH-MD-16 were assessed. For some individuals, DDCAR concentration appears to be decreased over the time interval between Week 4 to Week 6, where we have no apparent mechanistic explanations at this point of time.

To understand accumulation and time to reach steady state for DDCAR for the rest of the subjects, a sensitivity analysis was conducted. Percentage change in DDCAR concentrations relative to those measured at previous week was calculated in each patient. These calculations were done on data collected at Weeks 4, 5 and 6 in Study RGH-MD-04 and RGH-MD-16. Patients whose concentrations at Week 5 and/or Week 6 were less than 20% those observed at Week 4 were removed and the overall mean concentrations of DDCAR were calculated. The 20% cut off was determined based on the fact that a validated bioassay may allow at maximum 20% variation. A concentration decreased greater than 20% suggests that the concentration

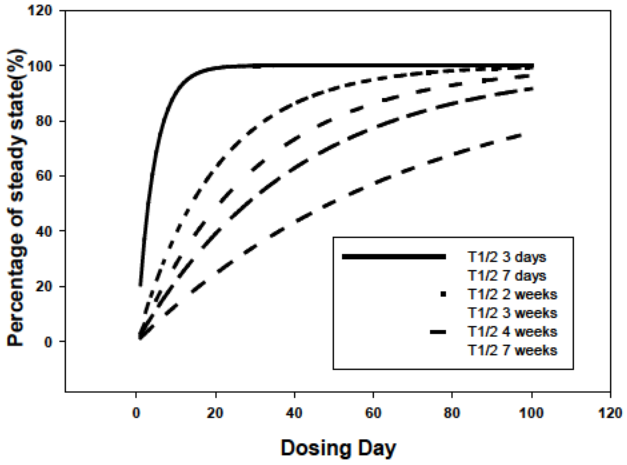
decrease may be real. Figure 2 shows the mean concentrations of DDCAR at various doses after removing patients who showed a drop in concentrations of 20% relative to previous visit. The results indicated that DDCAR concentrations were still on a rising phase from Week 4 to Week 6. The percentage of increase in the mean DDCAR concentration from Week 4 to Week 6 is about 14.5%, 19.0%, and 15.1%, for the 3mg, 4.5mg, and 6mg dose group, respectively.

Figure 2: Mean DDCAR Concentration (Mean ± 95%CI) in Study RGH-MD-04 and RGH-MD16.



A simulation was performed to understand the time to steady state for hypothetical compounds with different effective half-lives. This simulation assumes that the compounds have fast absorption as if doses are given intravenously and follow simple first-order elimination. Percentage to true steady state after multiple once daily dosing is depicted in Figure 3.

Figure 3: Percentage of Steady State after Multiple Once Daily Dosing for Compounds with Different Half Life Values



Comparing to Dosing Day 28, a 16.7% and 25% increase on Day 42 was observed for compounds with half-life value of 2 weeks and 3 weeks, respectively (Table 2). The results

suggest that for this subgroup of patients, DDCAR concentration appears to be still rising until Week 6.

Table 2: Percentage of Steady State on Dosing Day 28 and Day 42 for Compounds with Different Half-Life Values

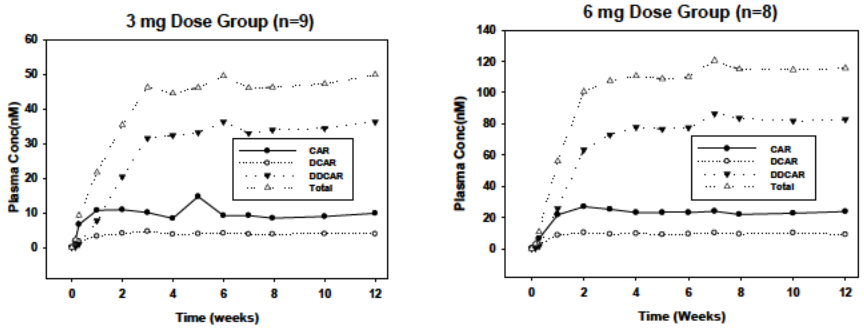
Dosing Day	**$T_{1/2}$ = 3days**	**$T_{1/2}$ = 7days**	**$T_{1/2}$= 2weeks**	**$T_{1/2}$ = 3 weeks**	**$T_{1/2}$= 4 weeks**	**$T_{1/2}$= 7 weeks**
28 (Week 4)	99.8	93.8	75	60.3	50	32.7
42 (Week 6)	100	98.4	87.5	75	64.7	44.8
% increase comparing Day 42 to Day 28	0.2	4.9	16.7	24.4	29.4	37.0

2.2.2 Study A002-A11

2.2.2.1 Mean Profile

The mean concentration time profile of cariprazine and its major active metabolites following 12-week treatment of cariprazine (3mg/day and 6mg/day) are shown in Figure 4. The mean profile indicated that CAR and DCAR concentration seemed to reach plateau at around Week 2, though by week 1, the curve started to level off. For the major active metabolite DDCAR, following a quick increase in the first 3 weeks after once daily dosing, the concentration seemed started to level off by Week 3, though a trend of small increase is evident till Week 12. Total cariprazine (CAR + DCAR + DDCAR), shares the similar profile as the DDCAR, which constitutes about 70% of the total moiety after Week 3.

Figure 4: Mean Plasma Concentration-Time Profile During and Following 12-weeks of Treatment with Cariprazine. Total is Total cariprazine (CAR + DCAR + DDCAR).

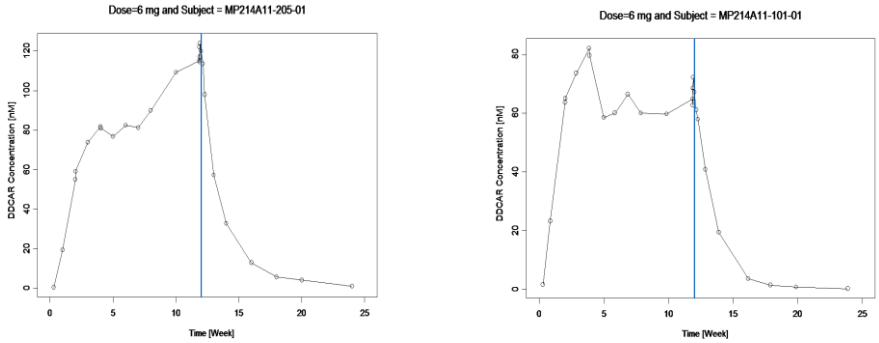


2.2.2.2 Individual Profile

Plasma concentration time profile was also assessed at individual level, and a large variability was observed. Two subgroups of patients seem to be present: for one group of patients, DDCAR concentration reached maximum at about Week3/4 then dropped down to a somewhat steady lower level, though mechanistically, the peak at Week 3/4 could not be explained. One

possible explanation is compliance. However, accurate dosing information is lacking. For other patients, DDCAR concentration kept rising even at Week12, though at a smaller slope after Week3/4. The concentration time profile of one representative individual for each subgroup is shown in Figure 5.

Figure 5: DDCAR concentration time profile for two typical individual subject in the 6 mg dose group of study A11.



Given the (1) dramatic difference in the mean and individual concentration time profiles of DDCAR, hence of the total cariprazine, and (2) significant drop out from the trial (37%-50% in 9-mg and 6-mg dose groups), it is challenging to draw a firm conclusion when steady state has been reached for the general patient population following once daily dosing of cariprazine.

2.2.3 Conclusion

Analysis from Phase 2/3 trials and Study A002-A11 are consistent with each other, both indicating that different patterns of DDCAR accumulation seemed to be present after Week3/4. It is hard to draw a firm conclusion when steady state has been reached for the general patient population following once daily dosing of cariprazine.

2.3 Extent Of Accumulation

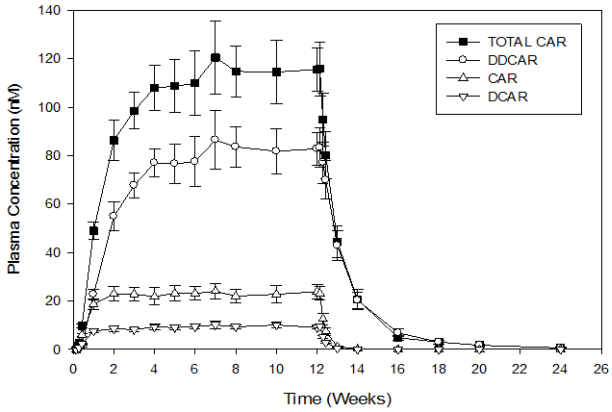
To calculate extent of accumulation, exposure data during dosing interval both on Day 1 and at steady state after the same dose administration need to be available for estimation. In Study A002-A11, patients received an up-titration regimen, i.e., 1.5 mg on Day 1, then up-titrated to the targeted doses. Thus no exposure data on Day 1 at therapeutic dose levels are available. Accumulation factor, therefore, cannot be estimated from this study.

In healthy volunteers, because of toxicity/tolerability issues, multiple dose study was only conducted at lower dose levels, i.e., 0.5 mg/day and 1 mg/day, with the longest duration of 3 weeks (most of them are 2 weeks long). Steady state is not reached yet for DDCAR by Week 3, but is for the parent compound cariprazine and DCAR (steady state seemed to be reached by Week 2). Therefore, extent of accumulation can only be calculated in healthy volunteers at low dose levels (Table 1) for the parent compound and DCAR. Since DCAR only has minor contribution to the total pharmacological effect (circulation level is <10% of total cariprazine) after multiple dosing, accumulation factor is not assessed for DCAR.

2.4 Decline In Plasma Concentration Over Time

Study A002-A11 followed the decline in plasma concentrations of cariprazine and both of its major active metabolites (DCAR and DDCAR) over a 12-week period. Total cariprazine, cariprazine, DCAR, and DDCAR plasma concentrations declined in a multi-exponential manner with small variability following discontinuation of cariprazine treatment (Figure 6). Mean plasma concentrations of total cariprazine and DDCAR decreased by about 50% one week after the last dose, and mean CAR concentration dropped about 50% in about 1 day. About 90% decline in plasma exposure occurred within 1 week for cariprazine and DCAR, 3 weeks for total cariprazine and 4 weeks for DDCAR.

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



a Trough concentrations shown during treatment with cariprazine 6 mg/day.
TOTAL CAR = Total cariprazine

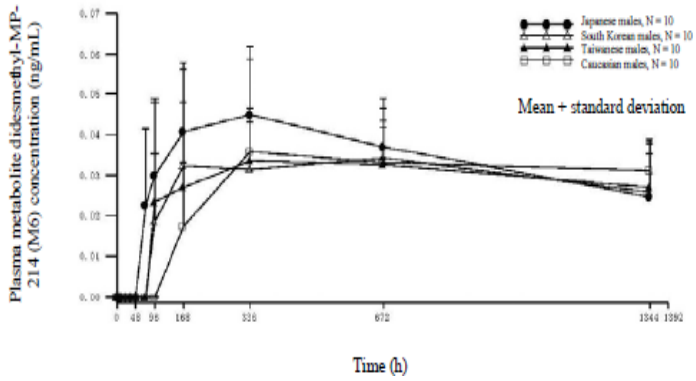
Table 3: Decline in Plasma Concentrations (nM) of Cariprazine Active Moieties Starting on Day 85 (Day 1 of the Follow-up Period)

Day	*Cariprazine*	*DCAR*	*DDCAR*	*Total Cariprazine*
		3 mg/day		
85	10.03	3.91	36.38	50.28
86	5.10	2.26	34.39	41.71
87	3.04	1.33	30.93	35.27
91	0.53	0.19	19.01	19.71
98	0.13	0.00	10.12	10.08
112	0.00	0.00	3.52	3.52
126	0.00	0.00	1.61	1.61
140	0.00	0.00	0.79	0.79
168	0.00	0.00	0.30	0.30
		6 mg/day		
85	23.05	9.54	83.33	115.82
86	12.50	5.27	77.13	94.81
87	7.44	2.87	69.91	80.14
91	1.15	0.38	42.88	44.38
98	0.19	0.00	20.27	20.60
112	0.00	0.00	6.82	4.83
126	0.00	0.00	3.02	3.02
140	0.00	0.00	1.71	1.71
168	0.00	0.00	0.62	0.62
		9 mg/day		
85	28.91	12.17	115.99	156.93
86	13.33	6.25	108.39	127.86
87	6.67	3.25	96.02	105.85
91	0.93	0.34	55.20	46.50
98	0.00	0.00	23.49	19.54
112	0.00	0.00	7.26	7.25
126	0.00	0.00	3.02	3.02
140	0.00	0.00	1.08	1.08
168	0.00	0.00	0.43	0.43

-Source: Table 3.1.4.1-1 Summary of Clinical Pharmacology Studies

Though a sharp decline in the plasma concentration was observed after cariprazine discontinuation, the terminal elimination phase for DDCAR is prolonged. In Study A002-A6, following 1 mg single dose administration of cariprazine, DDCAR concentration remained low and steady after T_{max}, which was still measurable even at two months post the single dose (Figure 7).

Figure 7: DDCAR Plasma Concentration Time Profile after 1 mg Single Dosing of Cariprazine to Healthy Volunteers.



2.5 Overall Conclusion

Overall speaking, the PK properties of cariprazine and its two active metabolites DCAR and DDCAR are rather complex. The terminal elimination phase for the three moieties, especially DDCAR, is long and variable. Steady state seemed to be reached for cariprazine and DCAR at Week 2 after once daily dosing of cariprazine. However, it is challenging to draw a firm conclusion about time to steady state for the major active metabolite DDCAR. In some patients, DDCAR concentration reached maximum at about Week3/4 then dropped down to a somewhat steady lower level; while for other patients, DDCAR concentration kept rising even at the end of Week 12 treatment, albeit at a much slower rate after Week 3/4.

SIGNATURES

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3 APPENDIX

3.1 Study A11

Multiple Ascending Dose - Schizophrenia Patients

Report # A002-A11 **Study Period**: 05/07/2012-08/23/2013
Title: Clinical Pharmacology Study of MP-214 in Japanese Patients with Schizophrenia (12-week Treatment)

- **Objectives:** 1) To administer MP-214 (cariprazine) orally in Japanese patients with schizophrenia, once daily, at the initial dosage of 1.5 mg/day followed by the dosage of either 3 mg/day, 6 mg/day or 9 mg/day for 12 weeks, 2) to evaluate pharmacokinetics of unchanged MP-214 and its metabolites, desmethyl cariprazine (M7, DCAR) and didesmethyl cariprazine (M6, DDCAR), 3) to evaluate safety and efficacy of MP-214.
- **Study Design:** This was a multicenter, randomized, open-label, parallel-group comparison, fixed-dose study in Japanese patients with schizophrenia. Patients were administered orally after breakfast with the assigned study drug for each group, once daily, 1 tablet on Day 1 and 2 tablets thereafter. Only for Day 1, the study drug was allowed to be administered any time before noon. MP-214 tablets were administered once daily after breakfast, starting at an initial dose of 1.5 mg/day, then orally administered for 12 weeks at a dose of 3 mg/day, 6 mg/day or 9 mg/day.

Table 1: Dosing Schedule for Each Dose Group

Study Period	3 mg dose	6 mg dose	9 mg dose
Day 1	1.5 mg	1.5 mg	1.5 mg
Day 2	3 mg	3 mg	3 mg
Day 3	3 mg	4.5 mg	4.5 mg
Day 4	3 mg	6 mg	6 mg
Day 5 - Day 84	3 mg	6 mg	9 mg

- **Blood Sampling:** predose on Day 1, 2, 7, 14, 21, 28, 35, 42, 49, 56, 70, and 84, Day 85, 86, 87, 91, 98, 112, 130 ,146, 168; two additional samples at 3-4hr postdose on Days 14 and 28; Serial sampling on Day 1 and Day 84 (3, 4, 6, and 8 hr post dose).
- **Analytical Method:** plasma samples were analyzed using LC-MS/MS.
  The performance of the analytical method is acceptable Yes ☑ No ☐
  Calibration curve range: 0.02-25.0 ng/mL for all three analytes (CAR, DCAR and DDCAR).
  Lower limit of quantification: 0.02 ng/mL for all three analytes.
- **Results:**

1. Study Population (Safety Analysis Population):

Table 2: Demographic Characteristics of Patients

Cariprazine Dosing Group	3mg	6mg	9mg
Randomized	11	16	11
Completed	9	8	7
Discontinued Due to AE	1	3	2
Withdrawal of Consent	1	4	2
Other Reason	0	1*	0
Age [Mean(SD)]	43.2 (13.2)	43.1 (10.7)	43.2 (13.3)
Male/Female	6/5	7/9	5/6
Race (Japanese/other)	11/0	16/0	11/0

* The patient is found to be clearly ineligible for the study (liver function test abnormal after Day 1 dosing)

Table 3: Adverse Events Causing Subject Discontinuation

Cariprazine Dosing Group	#Event	#Patients	AE Type
3 mg	1	1	schizophrenia
6mg	5	4	cataract, vomiting, schizophrenia, cold sweat and chills, liver function (test) abnormal
9mg	2	2	liver function (test) abnormal

2. Pharmacokinetics

Pharmacokinetics Parameters (mean (sd))for cariprazine, desmethylcariprazine, didesmethylcariprazine in plasma (follow up period from Day 84 of the treatment period)

-Cariprazine (RGH-188, MP-214)

Cariprazine Dose (mg)	AUC_{0-24} (hr. ng/mL)	C_{max} (ng/mL)	T_{max} (hr)*	Terminal $T_{1/2}$ (hr)
3.0 (n=9)	156 (72)	10.2 (4.7)	3.0 (2.9-4.1)	68.4 (46)
6.0 (n=8)	358(85)	22.7 (4.2)	3.0 (2.8-5.8)	44.3 (6.9)
9.0 (n=7)	466 (155)	28.78 (8.0)	3.0 (2.0-4.0)	31.6 (9.9)

*median(minimum-maximum); -source: Table 11.4-2 of CSR A002-A11

-Desmethyl Cariprazine (DCAR, M7)

Cariprazine Dose (mg)	AUC_{0-24} (hr. ng/mL)	C_{max} (ng/mL)	T_{max} (hr)*	Terminal $T_{1/2}$ (hr)
3.0 (n=9)	50.0 (31.2)	2.6 (1.5)	4.0 (3.0-6.1)	37.5 (6.7)
6.0 (n=8)	115.3 (23.5)	6.0 (1.6)	4.0	37.2(10.6)

			(2.8-8.0)	
9.0 (n=7)	163.3 (72.7)	8.6 (3.8)	6.0 (2.8-6.2)	29.7 (6.2)

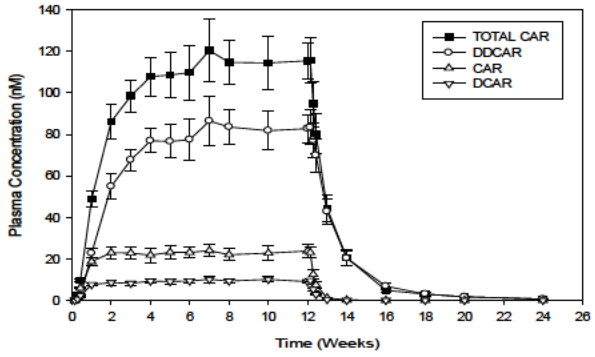
*median(minimum-maximum); -source: Table 11.4-5

-Didesmethyl Cariprazine (DDCAR, M6)

Cariprazine Dose (mg)	AUC_{0-24} (hr. ng/mL)	C_{max} (ng/mL)	T_{max} (hr)*	Terminal $T_{1/2}$(hr)
3.0 (n=9)	352.3 (252.8)	15.8 (10.9)	3.1 (0-23.6)	399.1 (84.7)
6.0 (n=8)	800.2 (206.7)	35.9 (8.0)	4.9 (2.8-23.5)	446 (113.4)
9.0 (n=7)	1140.4 (711.6)	51.8 (32.7)	6 (3.0-23.8)	313.6 (60.3)

*median(minimum-maximum); -source: Table 11.4-8

Figure 1: Mean Plasma Concentration-Time Profile in Completers (50% of the Total Subjects, n=8) During and Following 12-weeks of Treatment with Cariprazine 6 mg/day[a]



a Trough concentrations shown during treatment with cariprazine 6 mg/day.
Plasma concentrations presented as mean (standard error).
TOTAL CAR = Total cariprazine

- **Safety:** Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

- **Reviewer's Comments & Summary:**
  1) Time to steady state
     Mean concentration time profile indicated that cariprazine and DCAR concentration seemed to reach a steady level after Week 1/2. For DDCAR and total active moiety, though concentration time curve started to level off at Week 3/4, a trend of increase (though small) is still present till Week 12.
  2) Extent of accumulation
     Subjects were up-titrated to the targeted dose (i.e., 3 mg, 6 mg, and 9mg) when

initiating the dose: 1.5 mg (Day 1), Day 2 (3mg), Day 3 (4.5 mg), Day 4 (6mg) and Day 5 (9mg). The targeted fixed dose was 3 mg, 6 mg, and 9 mg. There was no Day 1 data on doses of 3, 6, and 9mg, so extent of accumulation at Week 12 could not be estimated from this study.

3) Terminal half-life (in days) of cariprazine and active metabolites

Moiety	**3 mg**	**6 mg**	**9 mg**
Cariprazine	2.9	1.8	1.3
DCAR	1.6	1.6	1.2
DDCAR	16.7	18.6	13.1

Summary: The terminal half-life of cariprazine and its two major active metabolites are rather consistent across the dose levels. It is about 1-3 days, 1.5 days, and 2-3 weeks for cariprazine, DCAR, and DDCAR, respectively.

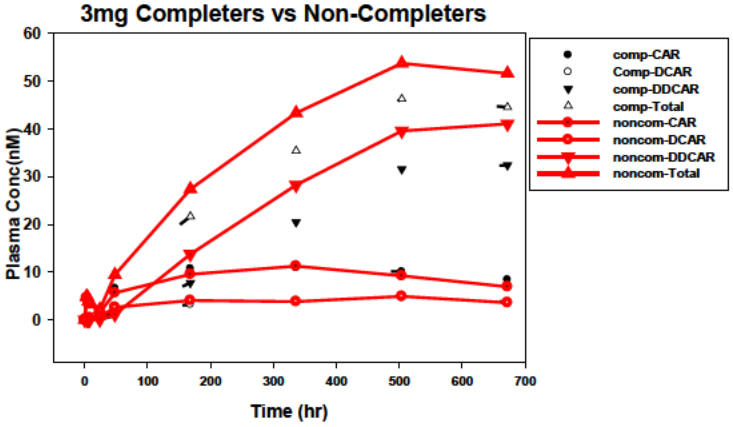
4) Dose proportionality evaluation using data on Day 84:

Dose-normalized mean PK parameters

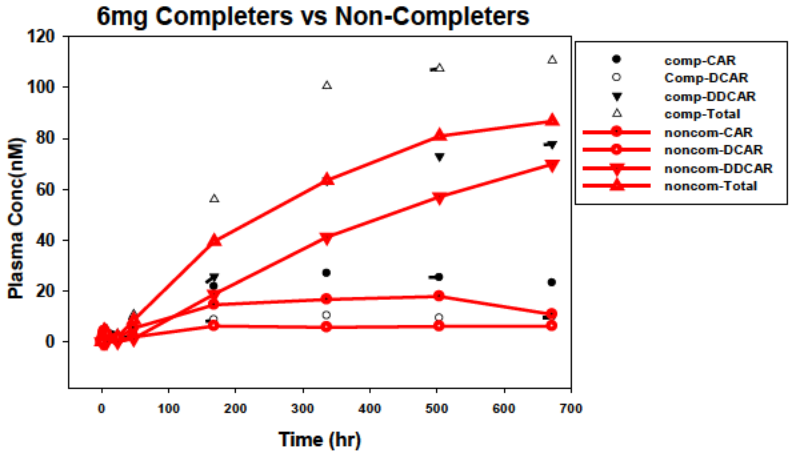
	3 mg	**6 mg**	**9 mg**
Cariprazine			
Cmax	3.3	3.8	3.2
AUC_{0-24}	52.0	59.7	51.8
DCAR			
Cmax	0.9	1.0	1.0
AUC_{0-24}	16.7	19.2	18.1
DDCAR			
Cmax	5.3	6.0	5.8
AUC_{0-24}	117.3	133.3	126.7

Summary: cariprazine and its major active metabolites exhibit approximately dose linearity in the proposed therapeutic dose range.

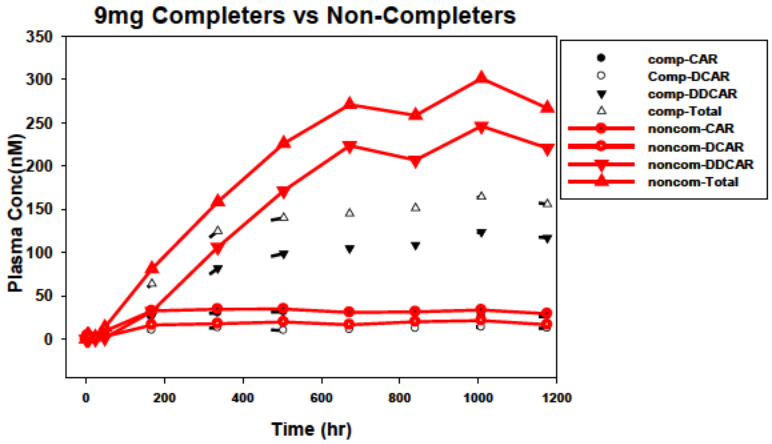
5) Comparison between Completers vs Non-Completers till the last time points when the last sample was obtained for the non-completer(s).
   a. 3mg dose group: there were 11 subjects who were randomized to the 3mg dosing group. Nine of the subjects finished the trial and two subjects discontinued. For those two subjects, the first subjects discontinued after week 3, and the second subject discontinued after week 4. Mean exposure comparison was performed up to 4 weeks (692hr) after 1st dosing.



b. 6mg dose group: there were 16 subjects who were randomized to the 6mg dosing group. Eight of the subjects finished the trial and the other eight discontinued. The last subject discontinued after week 4. Mean exposure comparison was performed up to 4 weeks (692 hr) after 1st dosing.



c. 9mg dose group: there were 11 subjects who were randomized to the 9mg dosing group. Seven of the subjects finished the trial and four of them discontinued. The last subject discontinued after week 7. Mean exposure comparison was performed up to 7 weeks (1176 hr) after 1st dosing.



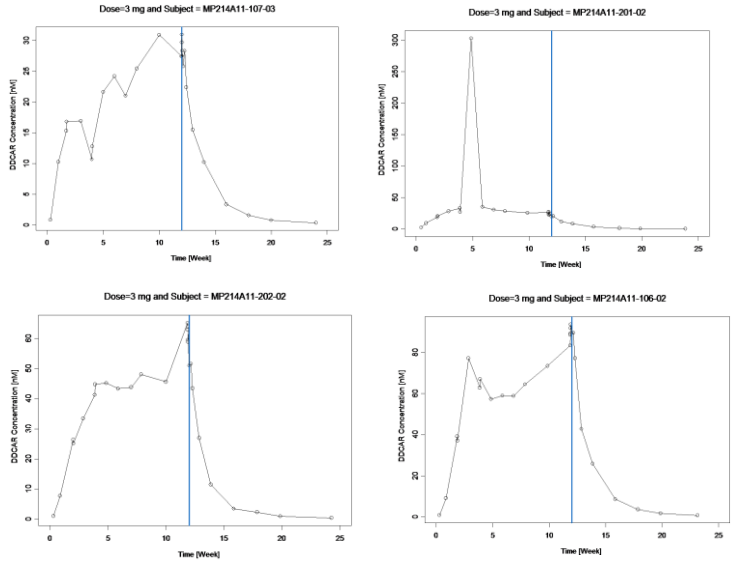
Summary of the exposure comparison analysis:

I. *There is no clear dose-dependent trend of the relative mean exposure between completers and non-completers. The mean exposure of the non-completers was higher compared to the completers in the same dose group for the 3mg and 9mg dose groups, which seems to be one of the reasons for patient's dropout. However, the mean exposure was higher in completers than in non-completers for the 6mg dose group.*

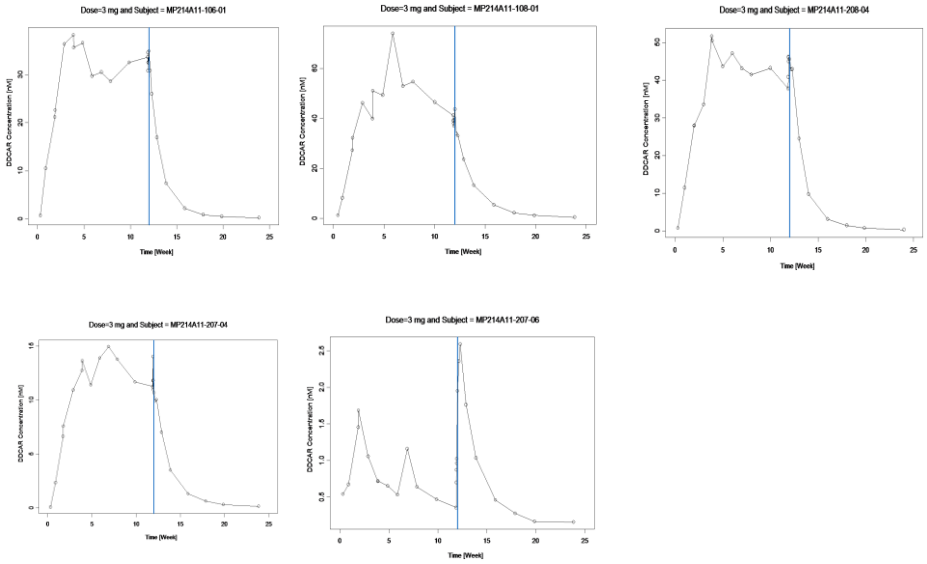
II. *For those who discontinued the study, patients in 9mg dose group did not drop out earlier than those in 3mg or 6mg dose groups. The last sample available for patients who dropped out was 692hr, 692hr, and 1176hr post first dose, for the 3mg, 6mg, and 9mg dose groups, respectively.*

6) Individual DDCAR concentration time profile for patients who completed the study (analysis performed by Dr. Hao Zhu).
   a) 3mg dose group

Subgroup 1:

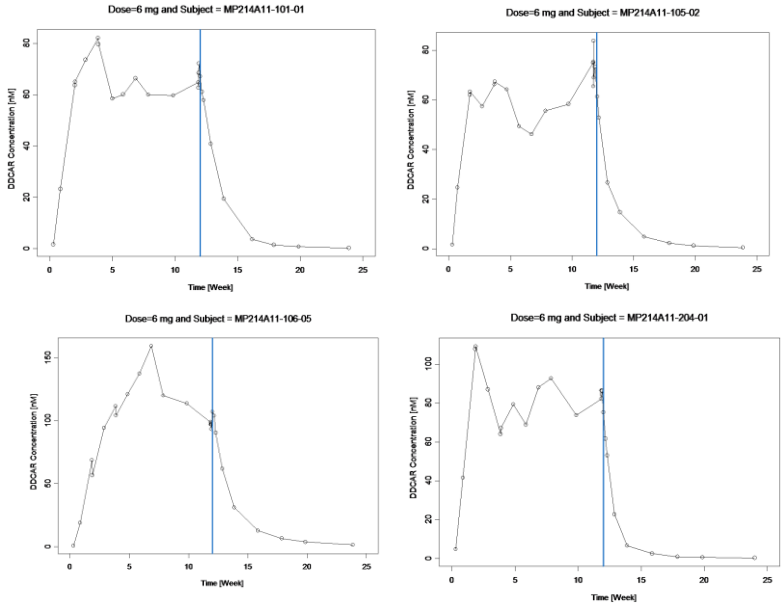


Subgroup 2:

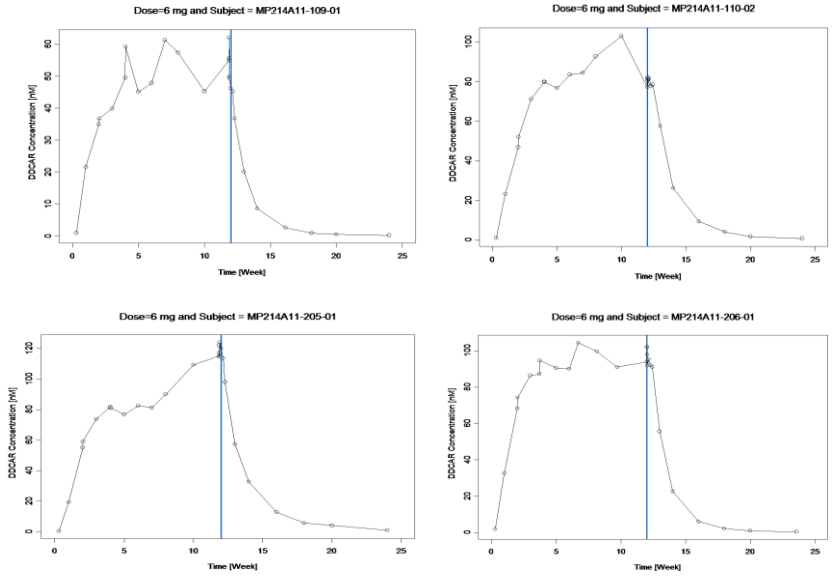


b) 6mg dose group

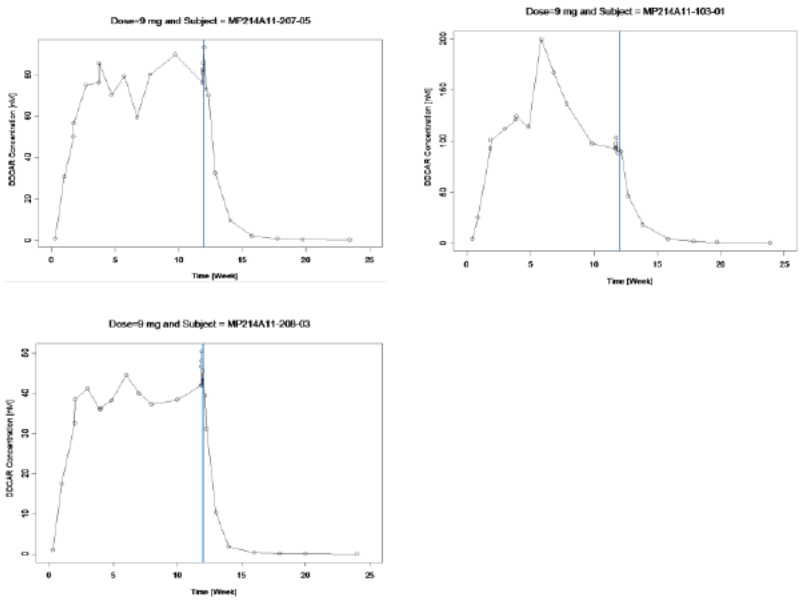
Subgroup 1:



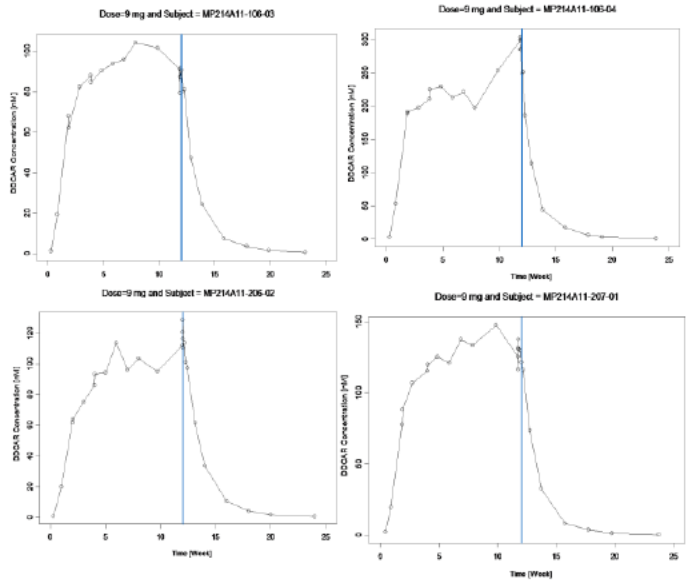
Subgroup 2:



c) 9mg dose group
Subgroup 1:



Subgroup 2:



<u>Summary of the subgroup analysis:</u> in some of the patients who completed the trial, DDCAR concentration reached maximum at Week3/4 then dropped down to a somewhat steady lower level; For other patients, DDCAR concentration kept rising even till Week12, though at a smaller rate of rising after Week3/4.

3.2 Pharmacometrics Review

3.2.1 Phase 2/3 Data Analysis

Plasma concentration time course of DDCAR in clinical trials showed patterns that suggest some patients were not taking cariprazine as scheduled. To understand accumulation and time to reach steady state for DDCAR in various clinical studies, a sensitivity analysis was conducted. Percentage change in DDCAR concentrations relative to those measured at previous week was calculated in each patient. These calculations were done on data collected at Weeks 4, 5 and 6 in Study RGH-MD-04 and RGH-MD-16 (Table 1).

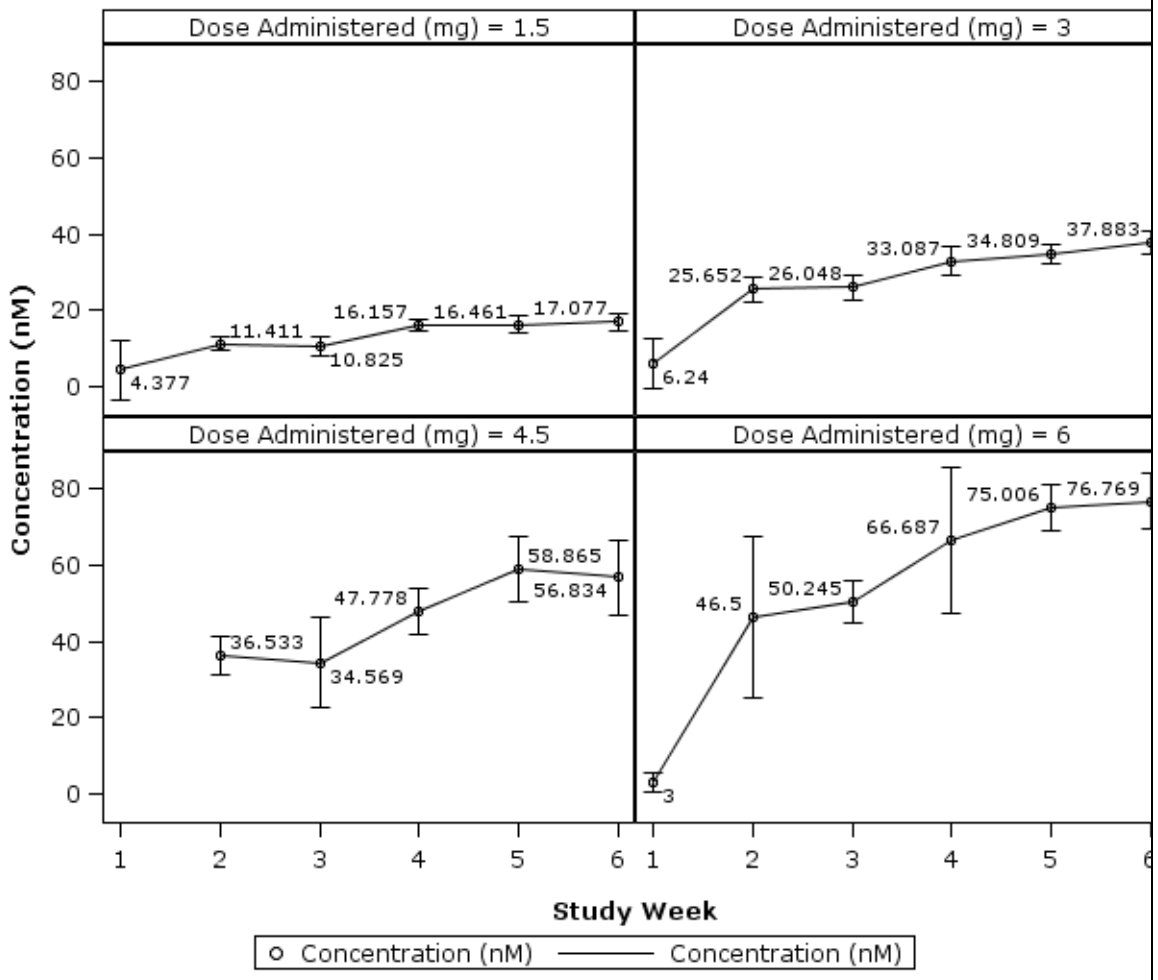
Table 1. Studies Included in the Population Pharmacokinetic Analysis of Cariprazine

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)	Othe
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	Hospitali
RGH-MD-02	1b	Schizophrenia	50	1.5, 12, 18	35	Hospitali
RGH-MD-03	2	Schizophrenia	250 (125 per group)	4.5, 12	42	Hospitali minimum 21 days of tr
RGH-MD-04	3	Schizophrenia	300 (150 per group)	3, 6	42	Hospitali minimum 28 days of tr
RGH-MD-05	3	Schizophrenia	300 (150 per group)	4.5, 6, 7.5, 9	42	Hospitali minimum 28 days of tr
RGH-MD-11	3	Schizophrenia (open-label)	600	3, 6, 9	336	Hospitalize week of tre new patien patients Study RGH- and Study RGH-
RGH-MD-16	2b	Schizophrenia	405 (135 per group)	1.5, 3.0, 4.5	42	Hospitali minimum 28 days of tr

Source: Table 1 on Page 70 in rgh-ms-01.pdf

Patients in whom concentrations at Week 5 and/or Week 6 were less than 20% of those observed at Week 4 were removed and the overall mean concentrations of DDCAR were calculated. Figure 1 shows the mean concentrations of DDCAR at various doses after removing patients who showed a drop in concentrations of 20% relative to previous visit.

Figure 1. Mean DDCAR Concentrations in Study RGH-MD-04 and RGH-MD16.



Values shown are mean and 95%CI.

3.2 2. Summary of Findings of Study A11

3.2. 2.1 Key Review Questions

The purpose of this review is to address the following key questions.

3.2.2.1.1 Did sponsor's re-analysis of pharmacokinetic data, by including data from additional clinical study (A002-A11), change previous findings (original submission review cycle)?

No.

The objectives for the analysis update to the population PK analysis were to

- Further develop the 3 base structural population PK models, previously defined in the RGH-MS-01 report, describing the disposition of cariprazine and its 2 major active metabolites, desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR), including the data from Study A002-A11, which provided more full concentration-time profile data for 12 weeks of dosing, and including, whenever possible, data previously excluded from population pharmacokinetic (PK) analysis;
- Re-assess the statistical significance of covariates that were statistically significant in the previous population PK analysis (RGH-MS-01) and assess the influence of creatinine clearance (CrCL) on the apparent clearance (CL) of each moiety;
- Evaluate model performance in describing the data using a prediction-corrected visual predictive check (PCVPC) technique and using a nonparametric bootstrap resampling technique;
- Re-assess the influence of cytochrome P450 (CYP)2D6 metabolizer status on key PK parameters or exposure measures for each moiety;
- Re-assess the impact of the statistically significant covariates on key PK parameters or exposure measures for each moiety; and
- Calculate model-predicted time to achieve steady state, terminal half-life ($t_{1/2}$), and functional $t_{1/2}$ for each moiety.

Table 1 shows the comparison of findings from the updated analysis (rgh-ms-08.pdf, November 21, 2014) to the findings from analysis in the original review cycle (rgh-ms-01.pdf, September 28, 2012). Data from a new clinical study (A002-A11) was added to the analysis database. For details of A002-A11, please refer to the review by Dr Huixia Zhang (Reviewer, Division of Clinical Pharmacology-1, OCP). Changes to the structural models for cariprazine, DCAR and DDCAR were made in an attempt to provide better description of terminal half-life. The updated analyses did not change the conclusions regarding the effects of various intrinsic/extrinsic factors on the pharmacokinetics of cariprazine, DCAR and DDCAR. Since no new labeling statements have been proposed based on the updated population pharmacokinetic analysis, the reviewer did not conduct independent analysis of the data.

Table 2. Comparision of Findings From Population PK Analyses Conducted in Original Review Cycle and Re-Submission Cycle

Findings From Population PK Analysis (Original Submission Review Cycle)	Findings From Population PK Analysis (Re-Submission Review Cycle)
Data Description: Data for this analysis were obtained from **12** studies (three Phase 1 [RGH-MD-01, RGH-MD-02, and RGH-MD-18], three Phase 2 [RGH-MD-03, RGH-MD-16, and RGH-MD-17], and six Phase 3 [RGH-MD-04, RGH-MD-05, RGH-MD-11, RGH-MD-32, RGH-MD-33, and RGH-MD-36]). **Population Pharmacokinetic Conclusions:** • The pharmacokinetics of cariprazine, DCAR, and DDCAR were described with sequential linear models: o The pharmacokinetics of cariprazine over a dosing interval were described by a linear 2-compartment model with zero-order input of the dose followed by first-order absorption and first-order elimination. o The pharmacokinetics of DCAR over a dosing interval were described by a linear 1-compartment model with first-order elimination and the elimination rate of cariprazine serving as the formation rate of DCAR. o The pharmacokinetics of DDCAR over a dosing interval were also described by a linear 1-compartment model with first-order elimination and the elimination rate of DCAR serving as the formation rate of DDCAR. • The concomitant administration of CYP2D6 inhibitors (5.2% of patients), CYP3A4 inhibitors (1.0% of patients), and P450 inducers (2.5% of patients) did not show a statistically significant effect on the apparent CL of cariprazine, DCAR, or DDCAR. However, because of study exclusion criteria, relatively few patients co-administered the medications were included. • There was not a statistically significant difference in the AUC_{0-24} of cariprazine and DCAR for patients classified as CYP2D6 poor metabolizers as compared to patients classified as CYP2D6 extensive metabolizers. There was a statistically significant difference in the AUC_{0-24} of DDCAR and total drug for patients classified as CYP2D6 poor metabolizers as compared to patients classified as CYP2D6 extensive metabolizers. However, the average differences in DDCAR and total drug exposure were less than 16%. • Ideal body weight, black and Asian races, female sex, and age were statistically significant predictors of pharmacokinetic parameters. However, the differences in total exposures were within 30% of the relevant comparator groups. • The covariate analysis showed that CrCL is not a statistically significant predictor of cariprazine, DCAR, or DDCAR clearance. Additionally, for the analysis population, a power analysis indicated that there was at least 95%, 63%, and 93% power to detect a CrCL effect on the clearance (ranging in size from 10% to 50%) of cariprazine, DCAR, and DDCAR, respectively. • The median time to 90% of steady state was 4, 4, 31, and 27 days for cariprazine, DCAR, DDCAR, and total drug, respectively. • The median functional half-life was 1.1, 1.1, 8.9, and 7.7 days for cariprazine, DCAR, DDCAR, and total drug, respectively.	Data Description: Data for this analysis were obtained from **13** studies (three Phase 1 [RGH-MD-01, RGH-MD-02, and RGH-MD-18], three Phase 2 [RGH-MD-03, RGH-MD-16, and RGH-MD-17], and seven Phase 3 [RGH-MD-04, RGH-MD-05, RGH-MD-11, RGH-MD-32, RGH-MD-33, RGH-MD-36, and **A002-A11**]). **Population Pharmacokinetic Conclusions:** • The pharmacokinetics of cariprazine, DCAR, and DDCAR were described with sequential linear elimination models: o The pharmacokinetics of cariprazine were described by a 3-compartment model with zero-order input of the dose followed by first-order absorption and first-order elimination. This model incorporated shifts in the apparent central volume of distribution and the intercompartmental clearance and volume of distribution for the first peripheral compartment for the first day of dosing. o The pharmacokinetics of DCAR were described by a 2-compartment model with first-order elimination and the elimination rate of cariprazine serving as the formation rate of DCAR. This model incorporated shifts in the apparent central volume of distribution and peripheral volume of distribution for the first day of dosing. o The pharmacokinetics of DDCAR following multiple doses were also described by a 2-compartment model with first-order elimination and the elimination rate of DCAR serving as delayed formation of DDCAR via a transit compartment. o While many other models incorporating nonlinear elimination, nonlinear distribution, and non-stationary processes were evaluated, none were able to adequately describe concentrations following both the first dose and multiple doses. • There was not a statistically significant difference in the AUC_{0-24} 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. • Weight, race, sex, and age were statistically significant predictors of PK parameters. However, the differences in Total CAR exposures were within 36% of the relevant comparator groups. • The covariate analysis showed that CrCL is not a statistically significant predictor of 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 $t_{1/2}$ was 1.5, 1.5, 6.3, and 5.4 days for cariprazine, DCAR, DDCAR, and Total CAR, respectively.

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/s/

HUIXIA ZHANG
05/29/2015

VENKATESH A BHATTARAM
05/30/2015

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05/31/2015

HAO ZHU
05/31/2015

Clinical Pharmacology Review

NDA #	204, 370
NDA Type	Standard
Proposed Brand Name	Vraylar
Generic Name	Cariprazine HCl
Dosage Form	Immediate-Release Hard Gelatin Capsule
Dosage Strength (mg)	1.5, 3, 4.5, 6, (b) (4)
Indication	Schizophrenia and Bipolar Mania
Sponsor	Forest Lab
Submission Type	505(b)(1) NME
Submission Date	Nov. 19, 2012; Dec. 18, 2012
OCP Review Team	Huixia Zhang, Joo-Yeon Lee, Atul Bhattaram, Hao Zhu

OCP Required Office-Level Briefing was held on July 16, 2013.

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1. EXECUTIVE SUMMARY

Forest Lab is seeking approval of cariprazine immediate release capsule for the treatment of (1) schizophrenia, and (2) manic and mixed episodes associated with bipolar I disorder in adult patients, via 505(b)(1) approach. Cariprazine is an orally active and potent dopamine D_2/D_3 receptor partial agonist with preferential binding to D_3 receptor and partial agonist at serotonin $(5\text{-HT})_{1A}$ receptor.

The proposed maintenance doses are (b) (4) mg once daily for schizophrenic patients and (b) (4) mg once daily for bipolar mania patients. Cariprazine should be administered starting with 1.5 mg on Day 1 and increasing to 3 mg on Day 2. Depending upon clinical response and patient tolerability, dose adjustments can be made upward or downward in 1.5 mg or 3 mg increments.

The efficacy and safety of cariprazine in treating schizophrenia was established in three 6-week controlled studies in adult patients at doses of 1.5 to 9 mg administered orally once daily. The efficacy and safety of cariprazine in treating bipolar mania was established in three 3-week controlled studies in adult patients at doses of 3 to 12 mg administered orally once daily.

Pharmacokinetics (PK) of cariprazine and its two active metabolites (desmethylcariprazine [DCAR] and didesmethylcariprazine[DDCAR]) was characterized in healthy volunteers and patients. The effects of intrinsic factors (i.e., hepatic impairment, renal impairment, gender, and race) and extrinsic factors (i.e., ketoconazole, and food) on PK of cariprazine and its two active metabolites were evaluated.

The findings from the Office of Clinical Pharmacology are summarized as follows:

- Based on the risk and benefit profiles, the maximal recommended maintenance doses for the treatment of schizophrenia and bipolar mania are 6 mg/day and 4.5 mg/day, respectively.
- Following a short term treatment (i.e., <1 week), cariprazine is the major moiety contributing to the clinical effectiveness and safety. As shown in a study in subjects receiving 1 mg/day dose, concentration levels of DCAR and DDCAR (the two major active metabolites equipotent to cariprazine) are close to the quantification limits in the first 2-3 days.
- Following a long term treatment (i.e., $\geq$ 2 weeks), the total exposure of the active moieties increases substantially over time (~25-fold increase between Day 1 and Day 14 following 0.5mg cariprazine once daily dosing). The main contributor to the clinical effectiveness and safety is DDCAR, which has an estimated mean half life of approximate 2-3 weeks after 0.5-1mg once daily dosing. As shown in a study in patients receiving 12.5 mg/day for 27 days, DDCAR exposure was about 3 fold higher than that for cariprazine, accounting for approximately 70% of total activity.
- Cariprazine can be taken with or without food.
- No dose adjustment is necessary in patients with different race, gender, renal dysfunction (mild to moderate renal impairment), hepatic dysfunction (mild to moderate hepatic impairment), CYP2D6 genotype status, or in patients coadministered with a CYP2D6 inhibitor. Effect of severe hepatic impairment or renal impairment on

the PK after cariprazine administration remains unknown, hence cariprazine is not recommended in these patient populations.

- Cariprazine dose should be reduced by half in patients coadministered with strong CYP3A4 inhibitors.
- No significant QTc prolongation effect of cariprazine at the doses of 9 mg (on day 20) and 18 mg (on day 34) was detected in the thorough QT study.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP I) has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of cariprazine. The acceptability of specific drug information is provided below.

Decision	**Acceptable to OCP?**	**Comment**
Overall	☒ Yes ☐ No ☐ NA	Pending labeling
Evidence of effectiveness	☒ Yes ☐ No ☐ NA	Three positive registration trials in adult patients for each indication.
Proposed doses for adult patients	☐ Yes ☒ No ☐ NA	The proposed starting dosing regimen is 1.5 mg on Day 1 and 3mg on Day 2. OCP recommended maximal maintenance doses are 6 mg/day and 4.5 mg/day for schizophrenia patients and bipolar patients, respectively.
Proposed dose for subgroups of patients or patients receiving comedications.	☐ Yes ☒ No ☐ NA	--Findings: 1. No dose adjustment is necessary in patients with different race, gender, renal dysfunction (up to moderate renal impairment), hepatic dysfunction (mild to moderate hepatic impairment), CYP2D6 genotype status, or in patients coadministered with a CYP2D6 inhibitor. 2. Cariprazine dose should be reduced by half in patients coadministered with a strong CYP3A4 inhibitor. --Pending issues: 1. In vitro evaluation of cariprazine and its two major metabolites on inhibition potential toward CYP2C8 (PMC). 2. In vitro evaluation of cariprazine and its two major metabolites on induction potential toward CYP2B6 (PMC). 3. In vitro evaluation of cariprazine on induction potential toward CYP3A4 and CYP1A2 (PMC). 4. In vitro evaluation of desmethylcariprazine and didesmethylcariprazine on inhibition potential toward CYP2B6 and CYP2C19

		(PMC). 5. In vivo drug-drug interaction study when cariprazine is coadministered with a proton pump inhibitor (PMC).
Labeling	☐ Yes ☒ No ☐ NA	Pending satisfactory agreement with sponsor

1.2 Post-Marketing Studies

Office of Clinical Pharmacology proposes the following post-marketing studies.

PMC or PMR	Key Drug Development Question	Rationale	Design Summary (TBD)
☒ PMC ☐ PMR	Should cariprazine dose be adjusted in patients when coadministered with proton pump inhibitors (PPIs)? If so, by how much?	Cariprazine has pH-dependent solubility. Coadministration with PPIs could affect its absorption.	Study population: healthy subjects Study design: parallel Sample size: 20% SE for Mean AUC Dose(s):esomeprazole 40mg QD x 6 days and then coadministered with 1.5 mg single dose of cariprazine Study length: 4 half lives of cariprazine Endpoints: AUC, Cmax Submit protocol by: Jul-14 Start study by: Oct-14
☒ PMC ☐ PMR	Are cariprazine, desmethylcariprazine and didesmethylcariprazine inhibitors of CYP2C8? Are desmethylcariprazine and didesmethylcariprazine inhibitors of CYP2B6 and CYP2C19?	Inhibition potentials toward major CYPs need to be evaluated.	Method: liver microsome incubation. Submit protocol by: Oct-14 Start study by: Dec-14
☒ PMC ☐ PMR	Is caripazine a CYP3A4 or a CYP1A2 inducer? Are cariprazine and its two active metabolites inducers of CYP2B6?	Induction potentials toward CYP3A4, CYP1A2, and CYP2B6 need to be evaluated.	Method: incubation with hepatocytes prepared from at least three individual donor livers. Submit protocol by: Oct-14 Start study by: Dec-14

Recommendation to DPP:

Given the information of significant accumulation of cariprazine and DDCAR due to their long half lives, OCP recommends to further characterize maintenance dosing regimens of cariprazine as part of the post-marketing studies. Following the long term treatment, a reduced maintenance dose and/or less frequent dosing should be evaluated.

1.3 Summary of Clinical Pharmacology Findings

In the current submission, the sponsor has submitted 14 clinical pharmacology studies (10 in healthy subjects and 4 in patients), and 35 in vitro studies. The submitted studies include 6 PK studies (2 single ascending dose PK studies in healthy volunteers, 2 multiple dose PK studies in healthy volunteers, and 2 multiple dose PK studies in patients), 3 intrinsic factor studies (hepatic impairment, race and gender studies), 2 extrinsic factor studies (food and ketoconazole studies), 2 receptor binding studies, and 1 thorough QT study. Population PK and ER analyses were also performed. Below summarizes the key findings from these studies:

- Absolute bioavailability of cariprazine is unknown.
- Tmax for cariprazine was generally attained within 3-6 hr after dosing.
- Cariprazine was mainly metabolized by CYP3A and, to a lesser extent, by CYP2D6; only about 1% of the dose was excreted as unchanged parent drug in urine.
- After single dose administration of cariprazine (≤1mg), circulation levels of desmethylcariprazine (DCAR) and didesmethylcariprazine (DDCAR) were low (close to quantification limit).
- Half lives of cariprazine and its major active metabolites were long. Mean values for cariprazine, DCAR and DDCAR were about 3-9 days, 2-4 days, and 2-3 weeks, respectively. After multiple dosing, significant accumulation was observed for cariprazine and its two active metabolites (~25-fold increase in total effective exposure between Day 1 and Day 14 following 0.5 mg once daily dosing).
- DCAR and DDCAR were the two major circulating active metabolites (equipotent to the parent compound). After multiple dosing of 12.5mg cariprazine for 27 days, DDCAR circulated at a level about 3-fold higher than the parent; DCAR circulated at a level about 42% of the parent.
- After multiple dose administration, cariprazine demonstrated approximate dose proportionality in the dose range of 1.5 mg to 21 mg. Slightly more than dose proportional increase in AUC and Cmax was observed for DCAR, and more than dose proportional change in AUC and Cmax was observed for DDCAR. Within the dose range of 3 to 5 mg/day, the nonlinearity of DDCAR does not appear to be apparent. Hence, cariprazine, DCAR and DDCAR can be considered following approximately linear pharmacokinetics in this dose range.
- Food did not significantly affect the C_{max} or AUC of cariprazine. Cariprazine can be administered without regard to food.
- Total effective exposure (sum of cariprazine, DCAR and DDCAR) was not significantly changed by mild or moderate hepatic impairment. No dose adjustment is necessary.

- Race did not significantly change the total effective exposure. No dose adjustment is necessary.

- Females yielded about 13% higher total effective exposure compared with males given the same dose under fed conditions. This difference was not considered clinically significant. No dose adjustment is necessary.

- Coadministration of ketoconazole increased the total effective exposure about 100%. Dose should be reduced by half in patients receiving strong CYP3A4 inhibitors.

- There was concentration-dependent relationship shown for both efficacy and safety in schizophrenia patients. However, there was no clear concentration-dependent benefit shown in exposure-efficacy relationship in bipolar mania patients whereas it was clear that the risk of adverse events increased as concentration increased.

2. QUESTION BASED REVIEW

2.1 Specific Questions

2.1.1 Does ER analysis support the proposed dosing regimen? What would be the maximum dose given the benefit and risk profiles of cariprazine?

(b) (4)

Our recommended maximal maintenance doses for schizophrenic and bipolar mania patients are 6 mg and 4.5 mg once daily, respectively, given the benefit and risk profiles of cariprazine. Our recommendations are based on nonclinical, clinical pharmacology, and clinical findings of cariparzine and its major metabolites.

A high incidence of events relevant to safety was found in animal studies (refer to Dr. Elzbieta Chalecka-Franaszek Pharmacology/Toxicology review). Quantitative whole body phosphor imaging studies have demonstrated binding of cariprazine to many tissues of pigmented rats with slow elimination. The choroid layer of the eye and the adrenal gland were among the organs with highest cariprazine- and/or metabolite-related tissue radioactivity concentrations (radioactivity in the eyes were about 100-fold higher than that in plasma C_{max}). Ocular and adrenocortical toxicity was consistently identified in multiple animal studies and species. Administration of cariprazine in general toxicity and carcinogenicity studies also resulted in dose-dependent adverse effects on the adrenal cortex of rats, dogs, and/or mice (hypertrophy/hyperplasia, vacuolation/vesiculation, and/or phospholipidosis). Moreover, cariprazine-related phospholipidosis was observed in the lungs of these species. Preclinical findings suggest that high cariprazine dose may yield high risks of adverse events which can be anticipated especially following long-term treatment, therefore higher than necessary doses should be avoided.

Clinical pharmacology studies have shown significant accumulation of DDCAR, which is equipotent to cariprazine, over time. DDCAR showed an average half life of 2-3 weeks at the

dose of 0.5 mg/day, and it demonstrated more than dose-proportional increase in exposure over the dose range from 1.5 mg to 21 mg when cariprazine is administered once daily. DDCAR becomes the major contributor to effectiveness and safety following long term treatment. As shown in a study in patients receiving 12.5 mg/day for 27 days, DDCAR exposure is about 3 fold higher than that for cariprazine, accounting for approximately 70% of total activity. As a result from accumulations of DDCAR, DCAR, and cariprazine, the total exposures of active moieties substantially increased over time. For example, following 0.5 mg once daily dosing, about 25-fold increase in total effective exposure was observed between Day 1 and Day 14. Hence, it is reasonable to control dose in order to prevent excessive accumulation of DDCAR and other active moieties.

In clinical trials, several adverse events, such as akathisia, extrapyramidal syndrome, parkinsonism, and nausea/vomiting, are all exposure-dependent. The incidences are typically increased drastically at exposures beyond 4.5 mg/day for both schizophrenia and bipolar patients. Beyond those commonly seen adverse events, several cases of severe ocular toxicity in patients were reported in the open label studies, even though it is unclear whether the severity is dose-dependant (refer to Dr. Francis Becker clinical review). These safety findings indicate that it is reasonable to avoid overexposing the patients.

Efficacy wise, it has been shown that in bipolar patients, there is no concentration-dependent improvement in the YMRS total score. The exposure level at 4.5 mg already provided efficacy similar to higher doses. In patients with schizophrenia, even though exposure-dependent improvement was identified, most patients were maintained at doses of 6 mg and below in the long term safety studies.

In summary, the recommended maximal maintenance cariprazine doses should be 4.5 mg/day for bipolar patients and 6 mg/day for schizophrenia patients based on the preclinical, clinical pharmacology, and clinical findings.

2.1.2 Should dose of cariprazine be adjusted with concomitant use of CYP3A4 inhibitors?

The dose of cariprazine should be reduced to half of the original dose when cariprazine is coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole). The impact of moderate or mild CYP3A4 inhibitors has not been evaluated.

In vivo data showed that a strong CYP3A4 inhibitor (i.e., ketoconazole) increased the total effective exposure after cariprazine administration by about 100% (study RGH-PK-07). Due to dose-dependent AEs for cariprazine, the dose should be adjusted (details see Section 2.2.4.4.1).

2.1.3 Should cariprazine dose be adjusted in patients with mild to moderate renal impairment?

No. Cariprazine is mainly eliminated by hepatic metabolism with less than 10% of the parent and two major metabolites excreted unchanged. Population PK analysis did not reveal significant PK difference between mild/moderate renal impairment patients and patients with normal kidney function. Therefore no dose adjustment is necessary in patients with mild to moderate renal impairment.

No adequate information of potential exposure change in patients with severe renal impairment can be obtained. Given the safety profile of this product and potential function change of phase 2 enzymes, cariprazine is not recommended in patients with severe renal impairment.

2.1.4 Is a drug-drug interaction study of cariprazine with proton-pump inhibitors needed?

Cariprazine HCl shows pH-dependent solubility change at 37°C (Table 1). Its solubility increased about 3-fold when pH was increased from 1 to 3. A significant decrease in solubility was observed when pH was further increased. At pH values between 6 to 7, cariprazine solubility decreased 20-fold (from 0.02 to 0.001mg/mL). Cariprazine is considered as a BCS 2 compound, for which dissolution and solubility can be the rate limiting step for absorption. According to OCP's internal decision tree (per communication with Dr. Lei Zhang), if (1) the value of the maximal recommended dose divided by 250mL is greater than the aqueous solubility at pH6-7; and (2) the drug has a clear pH dependent solubility property, an in vivo DDI study with a PPI is recommended. For cariprazine, the abovementioned two criterions are met. Under the maximal recommended dose, the calculated value (i.e., 6mg/250mL = 0.024mg/mL) is higher than the aqueous solubility of cariprazine at pH6 (0.02mg/mL, Table 1). In addition, clear pH-dependent solubility was observed (Table 1). Therefore, it is clinically meaningful to conduct a drug-drug interaction study to further assess this effect.

Table 1: Solubility of Cariprazine HCl in Aqueous Buffer

pH	Solubility (mg/mL)
1	3.25
2	8.93
3	11.03
4	3.23
5	0.35
6	0.02
7	0.001

-source: study report PRD-RPT-EXP-00022

2.2 Standard Questions

2.2.1 PK Characteristics

2.2.1.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy volunteers?

Single Dose

Due to poor tolerability of cariprazine in healthy subjects, pharmacokinetic data after single dose administration in healthy subjects are only available at low doses of cariprazine (0.2 to 2.5 mg, Study RGH-188-001). At the lowest evaluated dose of 0.2 mg, concentrations of cariprazine and its two major active metabolites (DCAR and DDCAR) were generally below the lower limit of quantification (LLOQ). PK parameters for cariprazine obtained from other dose levels were shown in Table 2. No PK parameters for DCAR and DDCAR were estimated in Study RGH-188-001.

Table 2: PK Parameters (Mean and %CV) for Cariprazine after Single Dose Administration of Cariprazine in Healthy Volunteers

Parameters	**0.5mg**	**1.0mg**	**1.5mg**	**2mg**	**2.5 mg**
C_{max} (ng/mL)	0.14(48.7)	0.76(35)	1.19(41.4)	2.53(30.5)	2.50(32.4)
T_{max} (hr)#	6(3-96)	3(2-4)	3(2.43-3)	3(3-3)	4(3-8)
$AUC_{0\text{-}last}$(hr.ng/mL)	14.1(41.8)	54.5(31.2)	56.9(39.2)	124.6(48.1)	122.5(20.1)
$AUC_{0\text{-}\infty}$(hr.ng/mL)	39.1(32.9)	71.1(30.2)	67.2(19.2)	138.3(46.5)	136.7(17.3)
%AUC extrapolation	57.3(13.1)	23.8(29.9)	27.7(23.2)	10.5(23.0)	10.6(57.5)
$T_{1/2}$ (hr)	217(27)	185(22)	130(24)	130(38)	139(62)
# median(range); n=6, each dose group					

PK parameters for DCAR and DDCAR after 1mg cariprazine single dose administration were evaluated in Study RGH-PK-04 (Table 3) in healthy volunteers. Because of the low circulation levels and quantification limit, $T_{1/2}$ and $AUC_{0\text{-}\infty}$ for DCAR and DDCAR could not be reliably estimated.

Table 3: Mean (SD) Pharmacokinetic Parameters for Cariprazine, Desmethylcariprazine (DCAR), and Didesmethylcariprazine (DDCAR) after Single-Dose Oral Administration of 1.0 mg Cariprazine in Healthy Volunteers (RGH-PK-04).

Parameters	**Cariprazine**	**DCAR**	**DDCAR**
C_{max} (ng/mL)	0.62(0.24)	0.12(0.03)	0.10(0.03)
T_{max} (hr)	6.38(2.72)	24.0(6.41)	315(108)
$AUC0_{\text{-}last}$(hr.ng/mL)	39.2(10.7)	10.7(2.93)	52.2(15.0)
$AUC_{0\text{-}\infty}$(hr.ng/mL)	46.5(11.1)	-	-
$T_{1/2}$ (hr)	175(27.7)	-	-

Multiple Dose

PK of cariprazine and its two active metabolites were evaluated at two dose levels after multiple dosing in healthy subjects: 0.5 mg/day (14 days, Study RGH-PK-04) and 1 mg/day (21 days, Study RGH-188-002). PK parameters obtained from those studies were shown in Table 4 (Study RGH-PK-04) and Table 5 (Study RGH-188-002).

Table 4: Mean (SD) Pharmacokinetic Parameters for Cariprazine, Desmethylcariprazine (DCAR), and Didesmethylcariprazine (DDCAR) after Administration of 0.5 mg Cariprazine for 14 Days (n=8).

Parameters	**Cariprazine**	**DCAR**	**DDCAR**
Cmax (ng/mL)	1.19(0.45)	0.47(0.22)	2.03(0.74)
T_{max} (hr)	3.63(1.77)	6.5(3.8)	18.1(8.8)

AUC_{0-24}(hr.ng/mL)	21.4(8.7)	9.5(5.0)	44.5(15.4)
Cl/F(L/hr)	30.8(24.1)	-	-
$T_{1/2}$ (hr)	290(141)	103(62)	399(90)

Table 5: Mean (±SD) Pharmacokinetic Parameters for Pariprazine, Desmethylcariprazine (DCAR), and Didesmethylcariprazine (DDCAR) after Administration of 1mg Cariprazine for 21 Days (n=5).

Parameters	**Cariprazine**	**DCAR**	**DDCAR**
C_{max} (ng/mL)	3.9±0.7	0.7±0.2	3.2±1.3
T_{max} (hr)	2(2-3)	3(2-6)	6 (3-12)
AUC_{0-24}(hr.ng/mL)	56.8±10.3	13.8±3.7	65.1±29.4
$T_{1/2}$ (hr)	115±39.1	36.3±7.2	331±43

2.2.1.2 Based on PK parameters, what is the degree of the linearity or non-linearity in the dose-concentration relationship?

After multiple dose administration, cariprazine demonstrated approximate dose proportionality in the dose range of 1.5 mg to 12.5 mg (Study RGH-MD-01). Slightly more than dose proportional increase in AUC and Cmax was observed for DCAR and more than dose proportional change in AUC and Cmax was observed for DDCAR. However, within the dose range of 3 to 5 mg/day, the nonlinearity of DDCAR does not appear to be apparent (Table 6).

Table 6: Cmax and AUC_{0-24} Ratios for Cariprazine, DCAR, and DDCAR in Patients With Schizophrenia After the Last Dose Administration on Day 22 and for Cohort G on Day 30 in Study RGH-MD-01

Cohort	***N***	***Dose, mg***	Dose Ratio	Cariprazine		DCAR		DDCAR	
				C_{max} ratio	AUC_{0-24} ratio	C_{max} ratio	AUC_{0-24} ratio	C_{max} ratio	AUC_{0-24} ratio
A	5	1.5	1	1	1	1	1	1	1
B	5	2.0	1.3	1.3	1.3	1.3	1.3	1.7	1.9
C	3	3.0	2.0	2.0	1.8	1.9	1.9	2.7	2.9
D	4	4.0	2.7	2.9	2.9	3.9	3.9	4.8	4.9
H	3	5.0	3.3	3.4	3.2	4.3	4.3	5.8	6.3
G*	4	12.5	8.3	9.0	7.7	17.4	17.2	25.2	27.8

*Cohort G patients were on 12.5 mg for 27 days, for other cohorts, patients were on the final dose for 14 days.

In Study RGH-188-02, another multiple dose study in healthy volunteers, 1 mg cariprazine once daily was administered to the subjects for 21 days, and the mean predose levels of cariprazine, DCAR, and DDCAR over time were shown in the Figure 1. It is clear that during the study treatment period (21 days), the concentrations of DDCAR kept rising. Steady state seemed to be reached for cariprazine by Day 14.

Results from study RGH-188-02 indicated that from dosing Day 1 to Day 16, the parent compound, cariprazine, was the predominant moiety in the circulation; while after that, DDCAR levels succeeded that of the parent and became the most abundant moiety. By Day 21, the mean predose level of DDCAR was about 13% higher than cariprazine steady state predose level. While in Cohort G of Study RGH-MD-01, after 12.5 mg cariprazine once daily dosing for 27 days, significant accumulation for DDCAR was observed. As shown in Figure 2, AUC_{0-24} for DDCAR was about 3-fold of cariprazine on the 27th day of dosing. Comparing the two study results (RGH-188-002 vs RGH-MD-01), it is unlikely that six more days of dosing (12.5mg of cariprazine for 27 days vs 1 mg of cariprazine for 21 days) may cause significant accumulation of DDCAR, raising its concentration ratio to cariparzine from 1.13-fold on Day 21 to 3-fold on Day 27) following linear PK assumption. This piece of information also indicated that PK non-linearity of DDCAR from 1 mg to 12.5 mg.

Figure 1: Mean plasma predose levels of cariprazine (RGH-188) and its metabolites after 1mg daily dosing of cariprazine for 21 days (Cohort 4 in Study RGH-188-002)

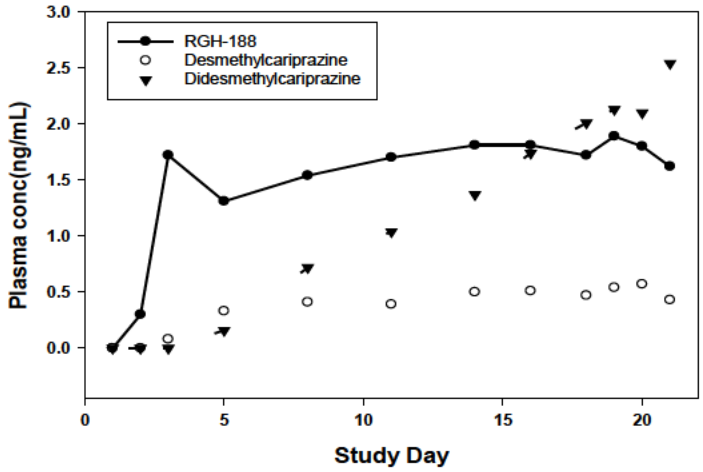
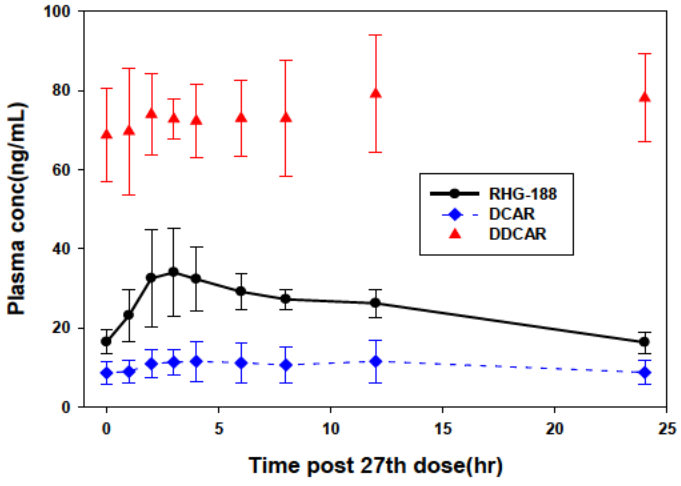


Figure 2: Plasma concentration (mean±SD) of for cariprazine (RGH-188), desmethylcariprazine (DCAR) and didesmethylcariprazine (DDCAR) in schizophrenic patients (cohort G) after dosing 12.5 mg cariprazine for 27 days (n=4).



PK parameters were also evaluated in the thorough QT study (RGH-MD-02). Comparing Day 20 (9mg cariprazine) and Day 35 (18mg cariprazine), mean concentrations (Table 5 in IRT review) for cariprazine showed approximately dose-proportional increase, while for DCAR and DDCAR, more than dose proportional increased was observed (19ng/mL on Day 20 [9mg dose] vs 55ng/mL on Day 35 [18mg dose]).

PK parameters of cariprazine and its two active metabolites after high doses (i.e., 18mg and 21 mg) of cariprazine administration (14 days treatment) were evaluated in schizophrenic patients in study RGH-MD-18. A cross study comparison between RGH-MD-01 and RGH-MD-18, indicated more than dose-proportional increase for DCAR and DDCAR (Table 7).

Table 7: Cross study comparison of AUC_{0-24} Ratios for Cariprazine, DCAR, and DDCAR in Patients With Schizophrenia After Cariprazine Administration in Study RGH-MD-01 (1.5-12.5mg) and Study RGH-MD-18 (18 and 21mg)

Dose (mg)	1.5	2.0	3.0	4.0	5.0	12.5*	18	21
Dose Ratio	**1**	**1.3**	**2.0**	**2.7**	**3.3**	**8.3**	**12**	**14**
Cariprazine AUC Ratio	1	1.3	1.8	2.9	3.2	7.7	13	18
DCAR AUC Ratio	1	1.3	1.9	3.8	4.2	17	25	33
DDCAR AUC Ratio	1	1.9	2.9	4.9	6.3	28	29	41

*:12.5mg once daily was given for 27 days; all other dose levels were given for 14 days.

Combining all the data from Phase 1 studies (RGH-188-002, RGH-MD-18, RGH-MD-01, and RGH-MD-02), it seemed to suggest that cariprazine demonstrated approximate linear kinetics, while DCAR and DDCAR demonstrated non-linear kinetics with more than dose-proportional increase in exposure observed in the dose range of 1.5 to 21mg. However, in a narrower dose range of 3 to 5mg, all three moieties seem to demonstrate approximate linear kinetics.

2.2.1.3 How do the PK parameters change with time following chronic dosing?

There was no evidence of time-dependent pharmacokinetics for cariprazine, DCAR or DDCAR, as indicated by the similar values between AUC after single-dose administration and $AUC_{0-\tau}$ after multiple dosing of cariprazine for 21 days (Table 8). Only data from low doses (1 mg) are presented for comparison, since single doses were only administered at low dose levels due to tolerability issues. AUC_{0-t} values were used for DCAR and DDCAR as no reliable $AUC_{0-\infty}$ values were available. Even using AUC_{0-t}, the values are close to $AUC_{0-\tau}$ after multiple dosing of cariprazine.

Table 8: Comparison of Single-Dose AUC to Multiple-Dose AUC

Study	Dose[a]	AUC (ng•h/mL)[b]

Cariprazine		
RGH-PK-04	1 mg SD	46.5 ± 11.14
RGH-188-002	1 mg QD	56.8 ± 10.27
Desmethyl Cariprazine (DCAR)		
RGH-PK-04	1 mg SD	10.7± 2.93
RGH-188-002	1 mg QD	13.8± 3.67
Didesmethyl Cariprazine (DDCAR)		
RGH-PK-04	1 mg SD	52.2 ± 15.0
RGH-188-002	1 mg QD	65.1 ± 29.43

a. SD is single dose, QD is once daily dosing for 21 days.

b. AUC represents $AUC_{0\text{-}t}$ for DCAR and DDCAR, $AUC_{0\text{-}\infty}$ for carirpazine after single-dose administration and $AUC_{0\text{-}\tau}$ for multiple-dose administration.

2.2.1.4 What are the general ADME (Absorption, Distribution, Metabolism and Elimination) characteristics of Cariprazine and its two major active metabolites?

• What are the characteristics of drug absorption and production of the metabolites?

The absolute bioavailability of cariprazine is unknown. Absorption of cariprazine is a relatively slow process. After single dose administration, T_{max} of cariprazine was between 3-6 hours. DCAR is formed following demethylation of cariprazine and Tmax was reached around 6-10 hours postdose. For DDCAR, T_{max} occurred around 336 hours postdose. Following single dose administration, cariprazine was the most prominent moiety in plasma.

After multiple-dose administration, T_{max} was around 3-4 hours for cariprazine, and 4-8 hours for DCAR and DDCAR. Following long-term treatment (> 14 days), DDCAR is the prominent moiety, with exposure (AUC) about 3-fold higher than cariprazine at the dose of 12.5 mg/day for 27 days. Steady-state exposure of DCAR is about 42% of cariprazine.

• What are the characteristics of drug distribution?

Protein binding for cariprazine, DCAR, and DDCAR were approximately 96%, 94%, and 92%, respectively. Red blood cell binding of cariprazine in human blood was approximately 30%. Based on the population PK model, cariprazine is extensively distributed into tissues with an estimated volume of distribution of central compartment of 454 L and a peripheral volume of distribution of 412 L.

• Does the mass balance study suggest renal or hepatic as the major route of elimination?

Following once daily administration of 12.5 mg cariprazine for 27 days to patients, average total daily excretion of cariprazine and its metabolites in excreta (urine and feces) was approximately 70% of the daily dose. The overall average daily excretion of cariprazine and its metabolites in urine and feces was approximately 24% and 46% of daily dose, suggesting that both renal and hepatic routes are important for elimination. Only 4.9% of the daily dose was excreted as unchanged cariprazine in urine and feces while the majority of the dose was excreted as its metabolites.

• What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

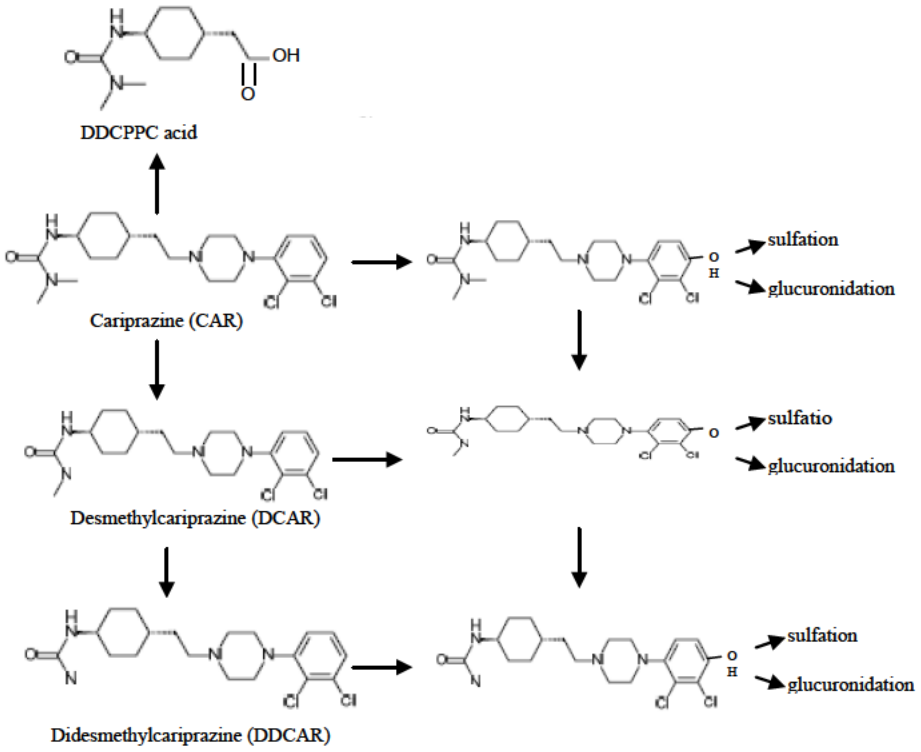
No radioactive-labeled drug was administered in the mass balance study. Mass balance and metabolite profiling was conducted in schizophrenia patients following multiple-dose administration of 12.5 mg/day non-radioactive cariprazine.

Following 12.5mg cariprazine treatment for 27 days, cariprazine, DCAR, and DDCAR represented the major circulating moieties in plasma with DDCAR, at the plasma concentration level about 3-fold higher than cariprazine, being the most abundant moiety. The DCAR exposure was around 42% of cariprazine exposure. Plasma exposures of hydroxy cariprazine glucuronide and hydroxy DDCAR glucuronide were similar to that of DCAR; while plasma exposures of hydroxy cariprazine sulfate and hydroxy DCAR glucuronide were around 30% of cariprazine exposure.

• **What are the characteristics of drug metabolism?**

Cariprazine is extensively metabolized in humans and is eliminated by both hydroxylation and demethylation pathways, with hydroxylation being predominant. In vitro study indicated that CYP3A4 and, to a lesser extent, CYP2D6 appeared to be the two major enzymes involved in the metabolism of cariprazine and its metabolites. Excretion of unchanged cariprazine in urine is low (about 1% of the dose). The metabolic pathway in humans is presented in Figure 3 below.

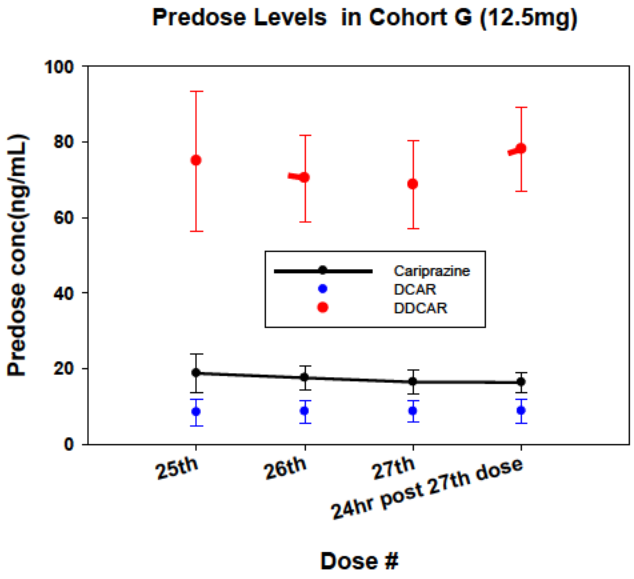
Figure 3: Metabolic Scheme of Cariprazine



2.2.1.5 Are steady state PK well characterized for cariprazine and its two active metabolites (DCAR and DDCAR)?

Terminal elimination half lives of cariprazine and its two major active metabolites were found to be long and variable. Mean $T_{½}$ values of cariprazine, DCAR and DDCAR ranged between 3-9 days, 2-4 days, and 2-3 weeks, respectively. Because of the long half lives, steady state seemed to be reached for cariprazine and DCAR in studies where cariprazine doses were given 14 days or longer (Figure 4), while for DDCAR, steady state was not expected to be reached (though close to) by Day 27, which was the longest treatment duration in clinical pharmacology trials.

Figure 4: Predose Plasma Concentration of Cariprazine, DCAR and DDCAR in Patients after Multiple Dosing of 12.5 mg Carirprazine (Study RGH-MD-01, Cohort G)



The PK parameters for cariprazine, DCAR and DDCAR on their last dosing day were shown in Table 9-11 below.

Table 9: Steady State PK Parameters (Mean(sd)) of Cariprazine in Patients (Study RGH-MD-01)

Cohort	Dose (mg)	AUC_{0-24} (hr. ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (hr)*	$T_{1/2}$ (hr)
A (n=5)	1.5	76.7(15.8)	4.46(0.89)	2.57(0.5)	3.0(2-4)	58.5(15)
B (n=5)	2.0	97.4 (7.7)	5.73(0.64)	3.23(0.56)	4(3-8)	44.3(7.2)
C (n=3)	3.0	137.4 (17.1)	8.79(0.67)	4.44(0.51)	3(2-4)	44.3(22.8)
D (n=4)	4.0	220.9(36.3)	13(2.10)	7.80(2.07)	5(3-8)	40(8)
H (n=3)	5.0	248.3(58.3)	15.3(3.95)	7.36(1.48)	4(4-6)	46.8(12.8)
G (n=4)	12.5	593.3(55.6)	40.3(8.40)	16.3(2.71)	3.5(2-12)	-#

*median(minimum-maximum); #not estimable due to limited number of samples

Table 10: Steady State PK Parameters (mean(sd)) of DCAR in Patients after Multiple Dose Cariprazine Administration (Study RGH-MD-01)

Cohort	Dose (mg)	AUC_{0-24} (hr. ng/mL)	C_{max} (ng/mL)	T_{max} (hr)*	$T_{1/2}$ (hr)
A (n=5)	1.5	14.6(4.3)	0.73(0.89)	3(1-6)	45.7(10.6)
B (n=5)	2.0	18.5 (5.6)	0.92(0.28)	4(4-8)	41(6.1)
C (n=3)	3.0	27.2 (9.9)	1.41(0.42)	4(2-4)	61.1(10.3)
D (n=4)	4.0	54.8(16.0)	2.77(0.78)	6(4-8)	34.7(5.6)
H (n=3)	5.0	61.7(28.5)	3.13(1.43)	4(4-6)	37.5(4.2)
G (n=4)	12.5	250.6(102.3)	12.7(4.6)	7.5(2-12)	-#

*median(minimum-maximum); #not estimable due to limited number of samples

Table 11: PK Parameters (Mean(sd)) of DDCAR on Last Cariprazine Dosing Day (Cohort G, 27th Day; Other Cohorts 14th Day, Study RGH-MD-01)

Cohort	Dose (mg)	AUC_{0-24} (hr. ng/mL)	C_{max} (ng/mL)	T_{max} (hr)*	$T_{1/2}$ (hr)
A (n=5)	1.5	65.6(29.0)	3.3(1.4)	3(1-72)	NC
B (n=5)	2.0	123.9 (35.4)	5.7(1.4)	4(2-24)	244(77)
C (n=3)	3.0	192.1 (46.2)	9.0(2.0)	2(1-48)	206(34)
D (n=4)	4.0	318.9(102.8)	15.7(5.1)	2.5(2-12)	-#
H (n=3)	5.0	414(235)	19.2(10.7)	2(1-8)	211(29)
G (n=4)	12.5	1826(284)	83.0(13.4)	12(8-48)	-#

*median(minimum-maximum); #not estimable due to limited number of samples

2.2.2 Exposure-Response

2.2.2.1 What are the design features of the clinical studies used to support dosing or claims?

The efficacy and safety of cariprazine in schizophrenia was established in three 6-week controlled studies of adult patients at doses of 1.5 to 9 mg administered orally once daily. The efficacy and safety of cariprazine in bipolar mania was established in three 3-week controlled studies in adult patients at doses of 3 to 12 mg administered orally once daily. Design features for these trials were shown in Table 12.

Table 12: Design Features of Pivotal Clinical Trials.

Pivotal Trials	Design Features	Drugs/Dose/Duration
Schizophrenia		
RGH-MD-04	Phase 3, randomized, double-blind, placebo- and active-controlled, parallel-group, fixed-dose, efficacy and safety study	Cariprazine 3 mg/day Cariprazine 6 mg/day Aripiprazole 10 mg/day 6 weeks duration
RGH-MD-05	Phase 3, randomized, double-blind, placebo- controlled, parallel-group, fixed/flexible-dose, efficacy and safety study	Cariprazine 3-6 mg/day Cariprazine 6-9 mg/day 6 weeks duration

RGH-MD-16	Phase 3, randomized, double-blind, placebo- and active-controlled, parallel-group, fixed-dose, efficacy and safety study	Cariprazine 1.5mg/day Cariprazine 3 mg/day Cariprazine 4.5mg/day 6 weeks duration
Bipolar Disorder		
RGH-MD-31	Phase 2, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose, efficacy and safety study in acute mania	Cariprazine 3-12 mg/day 3 weeks duration
RGH-MD-32	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose, efficacy and safety study in acute mania	Cariprazine 3-12 mg/day 3 weeks duration
RGH-MD-33	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, fixed/flexible-dose, efficacy and safety study in acute mania	Cariprazine 3-6 mg/day Cariprazine 6-12 mg/day 3 weeks duration

2.2.2.2 What are the design features of the clinical pharmacology and biopharmaceutics studies?

Most of the clinical pharmacology studies were conducted under multiple dosing. This is because cariprazine has two active metabolites (equipotency to the parent) with long terminal half lives, especially for DDCAR (mean $T_{1/2}$: ~2-3 weeks). After long term treatment, DDCAR is the predominant circulating moiety and main contributor to pharmacological effect (about 70%).

2.2.2.3 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The endpoints for Clinical Pharmacology studies were PK measures (plasma and/or urine concentrations of cariprazine and its metabolites) or PD measures (QT, receptor binding). No biomarkers for the intended indication were evaluated in clinical pharmacology studies.

Standard endpoints for schizophrenia and bipolar disorder were employed in the efficacy and safety studies. The endpoints used in pivotal studies are described below.

Schizophrenia

The primary efficacy assessment in the 3 pivotal studies and the supportive studies was the PANSS total score, and the secondary efficacy assessment was the CGI-S score. Additional efficacy assessments varied by study and included the NSA-16, CGI-I, PANSS positive score, PANSS negative score, SQLS-R4, Cognitive Drug Research (CDR) System Attention Tests, and Color Trails Test (CTT).

Bipolar Mania

In all 3 pivotal studies, the primary efficacy assessment was the YMRS total score, and the secondary efficacy assessment was the CGI-S. Additional efficacy assessments in all 3 studies included the CGI-I, the MADRS, and PANSS.

2.2.2.4 What are the characteristics of the exposure-response relationship for efficacy? What is the time to the onset and offset of the desirable pharmacological response or clinical endpoint?

Schizophrenia

For the exposure-response analyses, the data from three pivotal studies (RGH-MD-04/ RGH-MD-05/ RGH-MD-16) with one supportive study (RGH-MD-03) was pooled. The primary measures of exposure were total average concentration (Cave), which was computed as follows:

$$Total\ Exposure(nM) = 1000\left(\frac{mL}{L}\right)\times \left[\frac{Cariprazine\ Exposure\left(\frac{ng}{mL}\right)}{427.41\left(\frac{ng}{nmole}\right)} + \frac{DCAR\ Exposure\left(\frac{ng}{mL}\right)}{413.38\left(\frac{ng}{nmole}\right)} + \frac{DDCAR\ Exposure\left(\frac{ng}{mL}\right)}{399.36\left(\frac{ng}{nmole}\right)}\right]$$

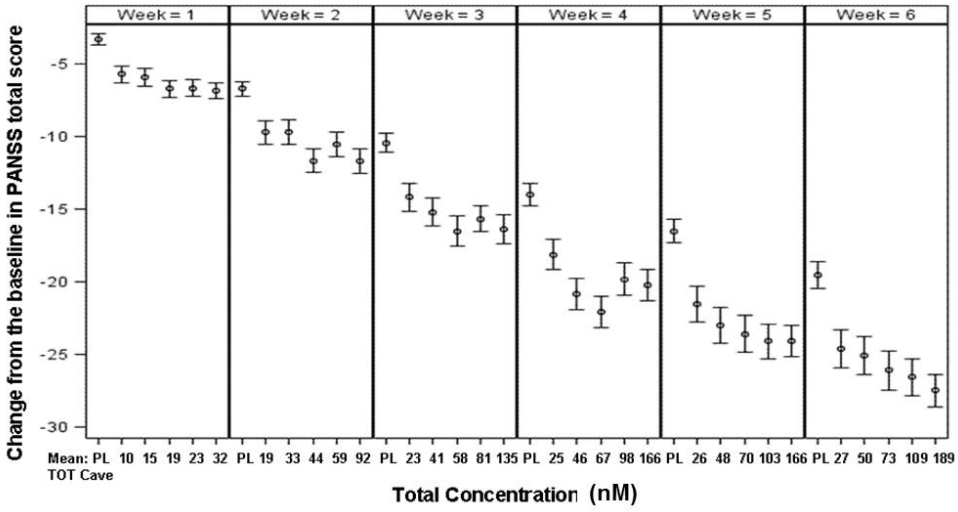
Where:
Exposure is the average plasma concentration (Cave) which was calculated between consecutive PANSS assessment visits.

Figure 5 shows the observed exposure– response relationship at each week. As shown in the figure, there is time-dependent improvement in PANSS total score for both placebo and cariprazine groups, which does not reach a plateau by week 6. In addition to the time effect, it shows that the PANSS total score is reduced as concentration increases within each week. Table 13 presents the mean of total Cave (nM) at each dose at week 6. Notice that the mean total Cave at 1st and 5th bins in Figure 5 corresponds to that at the doses of 1.5 mg and 9-12 mg. As shown in Figure 6, the magnitude of improvement in PANSS total score relative placebo is -4.6 to -7.5 given the exposure range.

Table 13: Mean of Total Cave (nM) at each dose level at week 6 in schizophrenia patients.

	1.5 mg	3 mg	4.5 mg	6 mg	9 mg	12 mg
Mean total Cave (nM)	27	52	80	108	160	212

Figure 5: Exposure-response relationship in schizophrenia patients. Each bar represents mean ± SE. X-axis indicates the mean total Cave at the percentile (5 bins) of total Cave. Y-axis is the change from the baseline in PANSS total score.



There has been a concern that the study duration in three pivotal studies is not long enough to reflect the long half-life of DDCAR (2-3 weeks). Therefore the reviewer analyzed the data from two long-term (48 weeks) open-label studies, RGH-MD-11 and RGH-MD-17. Both studies were continuation of three pivotal studies: A total of 92 patients from RGH-MD-16 continued to the study of RGH-MD-17, and out of 92 patients 52 patients were on cariprazine, 25 patients on risperidone group and 15 patients on placebo: In the study of RGH-MD-11, there were a total of 352 patients who continued from RGH-MD-04 /05, and out of 352 patients 211 patients were on cariprazine, 61 patients on aripiprazole and 80 patients on placebo. For the analyses the patients who were on cariprazine in the controlled trials were included. Regarding dosing scheme, the flexible dose of 3 mg-9 mg/day was applied in the RGH-MD-11 whereas lower dose level, 1.5 mg – 4.5 mg/day (flexible dose) was administered in study RGH-MD-17.

As shown in Figure 7 and Figure 8, more than 60 % of patients took 4.5 mg in study RGH-MD-17, and majority of patients took 6 mg in study RGH-MD-11. The estimated time to reach a steady state of DDCAR was approximately 12-18 weeks. The time profile of PANSS total score from study RGH-MD-17 also reached a plateau around week 18 whereas it took longer to reach a plateau in study RGH-MD-11. The time-profile of PANSS total score in RGH-MD-17 shows that the dose of 4.5 mg seems to maintain the efficacy throughout the study. However, this should be interpreted with caution as RGH-MD-17 is open-label study with no control arm.

Figure 6: The time-profile of PANSS total score (left) and the mean daily dose (right) from 211 patients who continued to the study RGH-MD-11 from the study of RGH-MD-04/05. Each bar represents the mean ± SE at each time point.

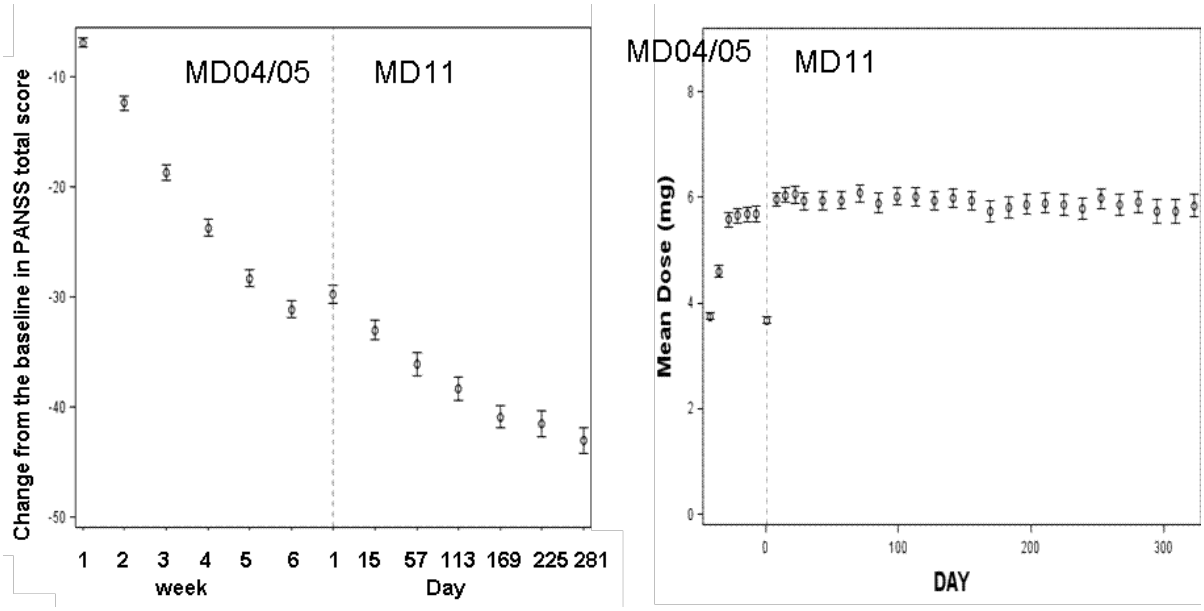


Figure 7: Time-profile of PANSS total score (left) and the mean daily dose (right) from 52 patients who continued to the study RGH-MD-17 from the study of RGH-MD-16. Each bar represents the mean ± SE at each time point.

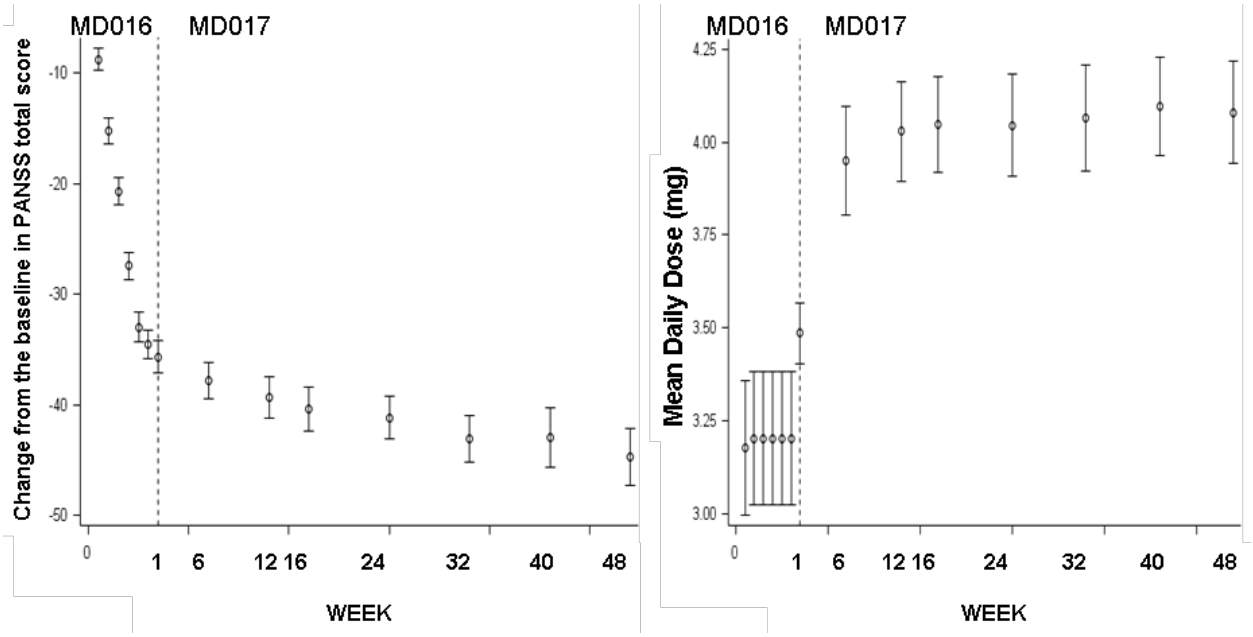
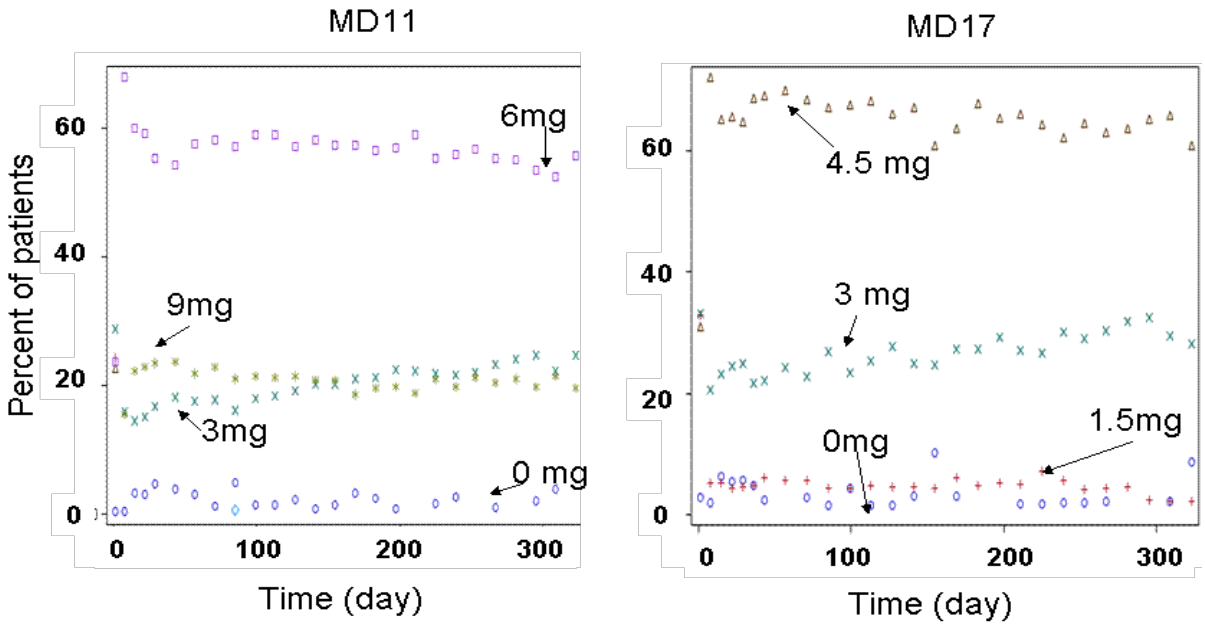


Figure 8: Percent of patients taking each dose at time points.



Bipolar mania

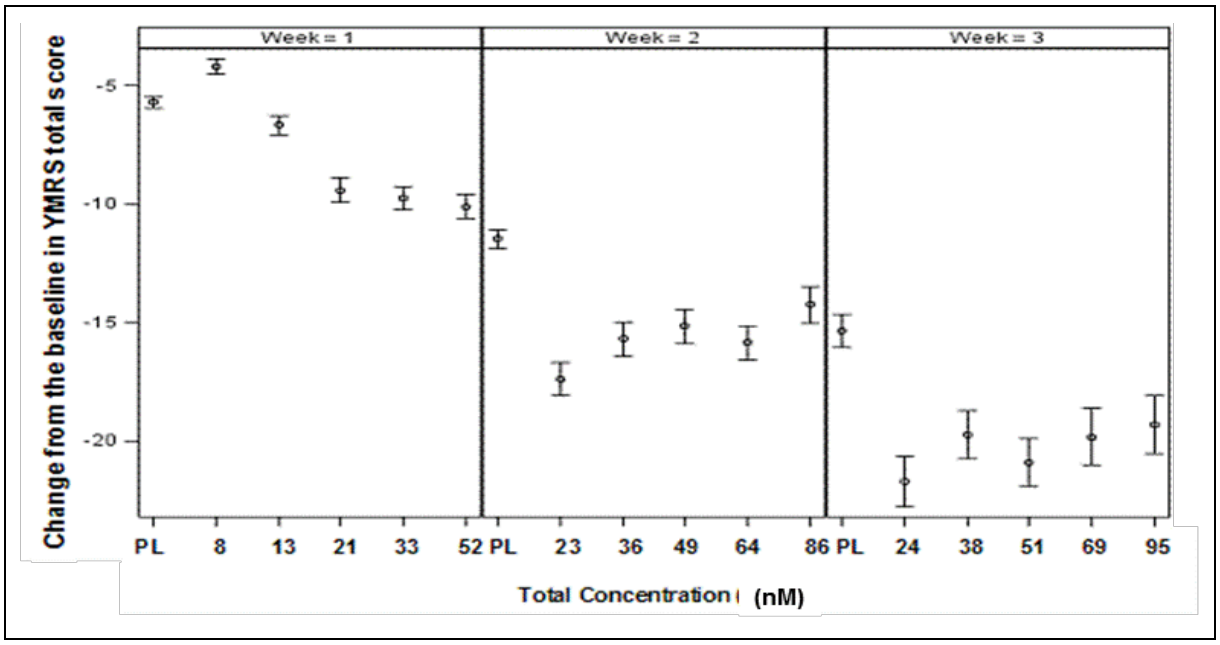
For the exposure-response analyses the data from two pivotal studies RGH-MD-32 and RGH-MD-33 were pooled to be consistent with the sponsor's exposure-response analyses. The total average concentration, which was calculated as same way as in schizophrenia patients (section 1.1.1) was used as an exposure and the primary endpoint, the change from the baseline in YMRS total score was analyzed as a response variable.

As shown in Figure 9, there is small improvement at week 1 with increasing concentration and reaches a plateau at the exposure level of ~ 21 nM. However, at weeks 2 and 3, higher concentration does not provide an additional benefit. In addition, the observed exposure-response relationship shows that the concentration of 23-24 nM, which is the approximate mean total Cave at the dose of 4.5 mg (Table 14) already provides similar efficacy to higher doses.

Table 14: Mean of Total Cave (nM) at each dose level at week 3 in bipolar mania patients.

	1.5 mg	3 mg	4.5 mg	6 mg	9 mg	12 mg
Mean Total Cave (nM)	10	19	28	38	55	72

Figure 9: Exposure-response relationship in bipolar mania patients. Each bar represents mean ± SE. X-axis indicates the mean total Cave at the percentile (5 bins) of total Cave. Y-axis is the change from the baseline in YMRS total score.



2.2.2.5 What are the characteristics of the exposure-response relationships for safety? What is the time to the onset and offset (or duration) of the undesirable pharmacological response or clinical endpoint?

Schizophrenia

For safety, four most commonly occurred adverse events were analyzed – akathisia, extrapyramidal symptoms without akathisia or restlessness (hereafter EPS), nausea and vomiting and parkinsonism cluster. The exposure measure used in the exposure-safety analyses was a time-weighted total C_{ave}. To calculate this exposure, the population PK model was used to estimate predicted cariprazine exposure measures on the day of the first incidence of each AE for those patients who experienced an AE. If a patient did not experience an AE, the highest predicted exposure measure over the course of the treatment period was used. These exposures were then 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 safety profile of cariprazine is displayed in Figure 10. Across all four adverse events it is apparent that the risk of having adverse event goes up with increasing concentration. Also the incidence rates of adverse events goes up sharply at doses higher than 4.5 mg - 6 mg, which is also supported by model-predicted probabilities (Table 15). Also the adverse events of akathisia, EPS and parkinsonism seem to increase gradually within two weeks but nausea and vomiting occurred rapidly but incidence rate remained low ~ 2% (Figure 11).

Figure 10: Safety profile of four adverse events: x-axis is the time-weighted total Cave and y-axis is the probability of having each AE during the study. The solid line (dotted lines) is the model-predicted relationship (95% prediction interval) and each dot indicates the observed proportion of patients having each AE, which is displayed at the median values of 5 bins of time-weighted total Cave and placebo (x-axis=0). Also 6 dotted vertical lines indicate the mean total Cave at each dose (1.5/3/4.5/6/9/12 mg).

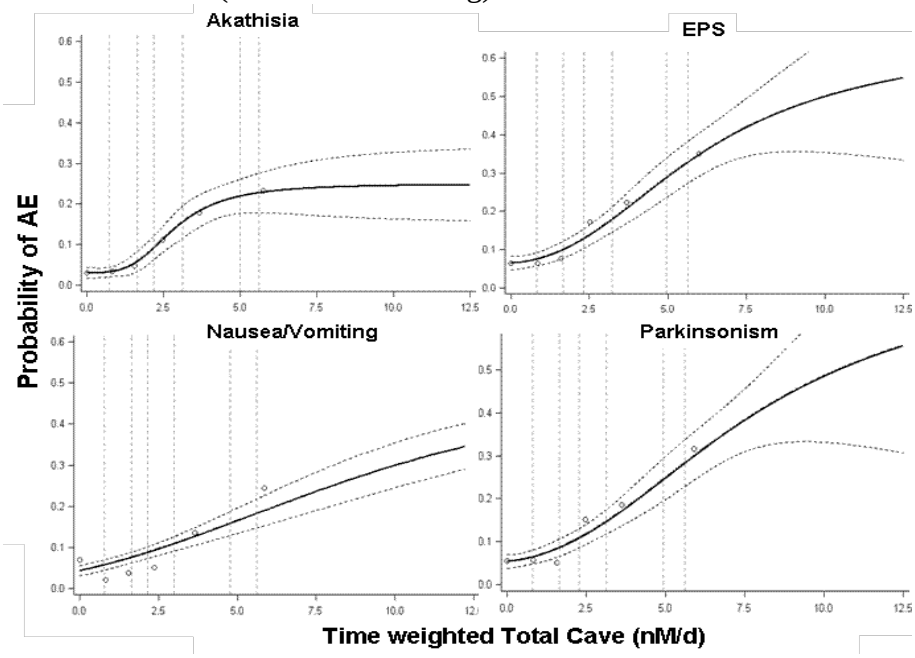
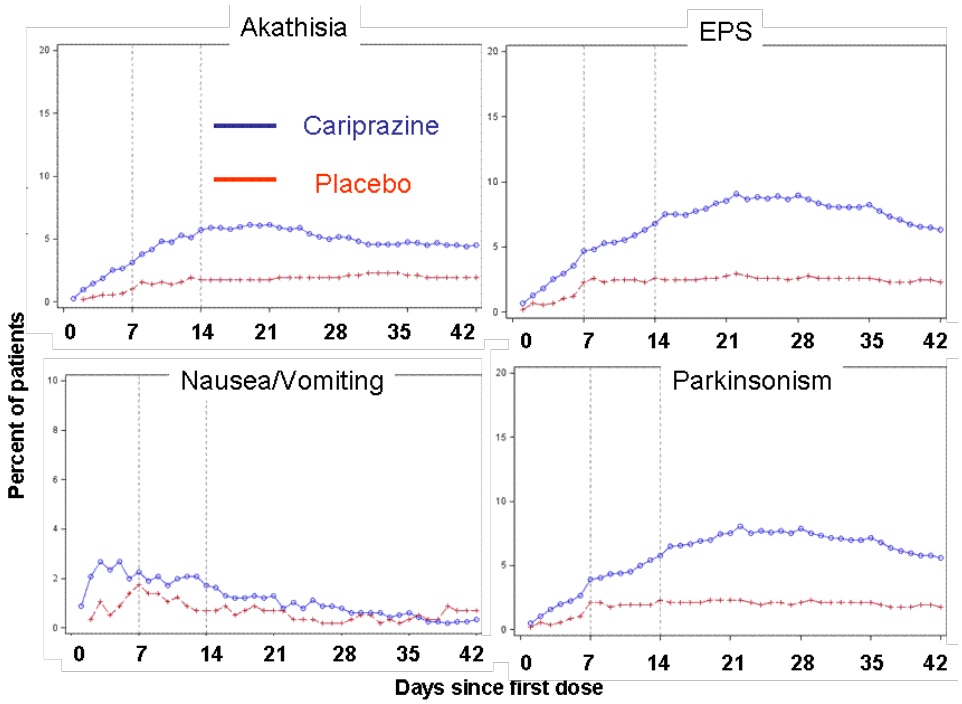


Table 15: Model-predicted probability of selected AEs at each dose.

	Placebo	1.5 mg	3 mg	4.5 mg	6 mg	9 mg	12 mg
Akathisia	3%	3%	6%	9%	16%	22%	23%
EPS	7%	8%	10%	13%	18%	29%	33%
Nausea/Vomiting	5%	6%	7%	8%	10%	15%	18%
Parkinsonism Cluster	5%	6%	9%	11%	14%	24%	28%

Figure 11: The time-profile of four adverse events in schizophrenia patients.



Bipolar Mania

For the safety, the same adverse events- akathisia, EPS, nausea and vomiting and parkinsonism as in schizophrenia patients were analyzed. The incidence of all the adverse events clearly increases in concentration-dependent manner (Table 16, Figure 12). Also the adverse events for akathisia, EPS and parkinsonism occurred gradually over time (Figure 13).

Figure 12: Safety profile of four adverse events: x-axis is the time-weighted total Cave and y-axis is the probability of having each AE during the study. The solid line (dotted lines) is the model-predicted relationship (95% prediction interval) and each dot indicates the observed proportion of patients having each AE, which was displayed at the median values of 5 bins of time-weighted total Cave and placebo (x-axis=0). Also 6 dotted vertical lines indicate the mean total Cave at each dose (1.5/3/4.5/6/9/12 mg).

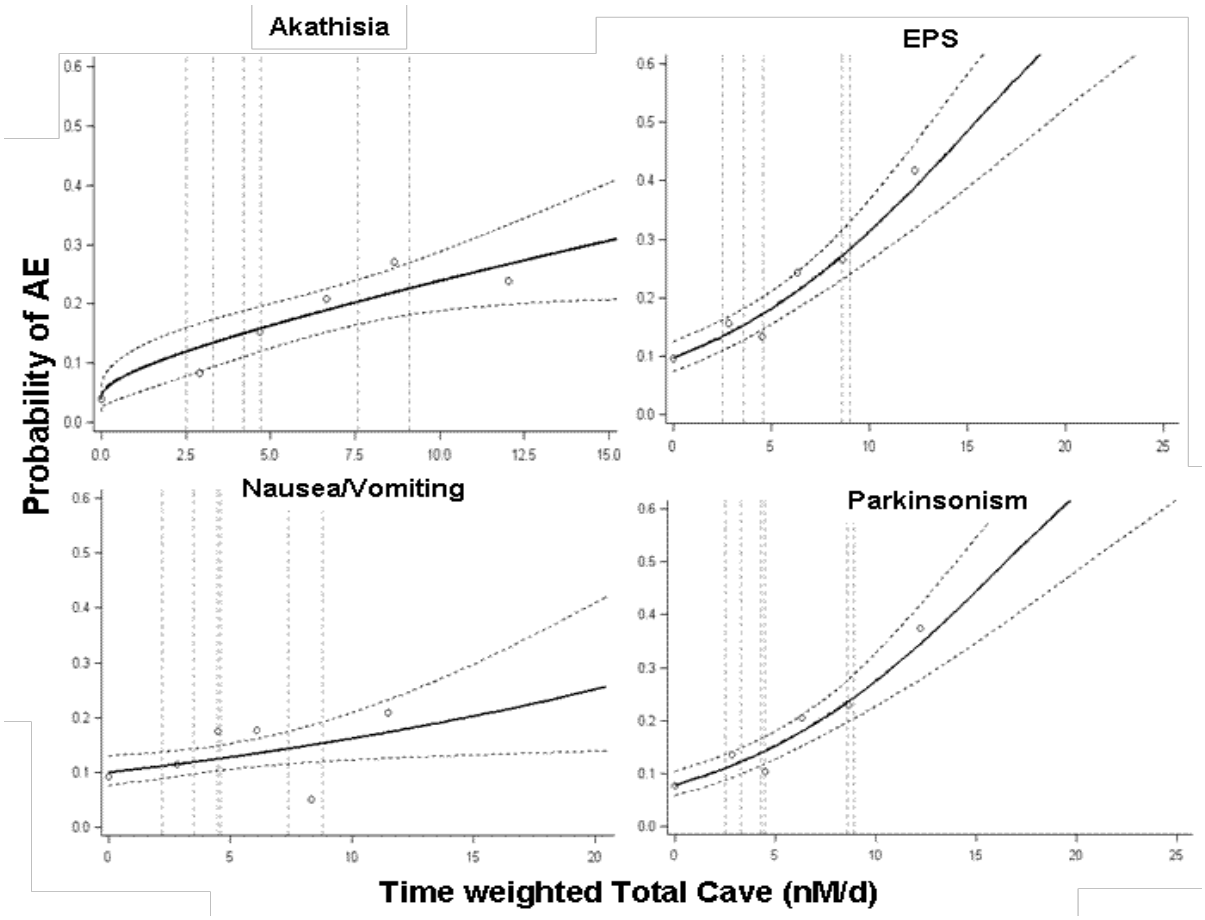
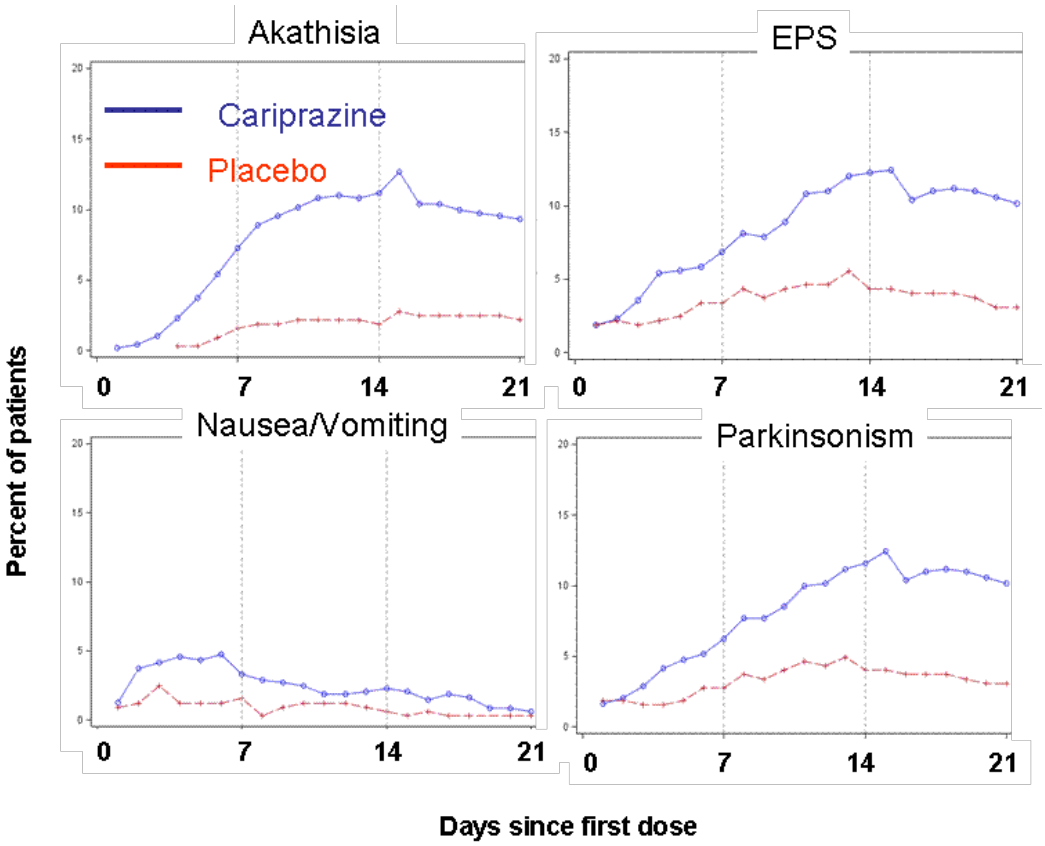


Table 16: Model-predicted probability of selected AEs at each dose.

	Placebo	1.5 mg	3 mg	4.5 mg	6 mg	9 mg	12 mg
Akathisia	4%	12%	13%	15%	16%	20%	23%
EPS	10%	13%	15%	17%	17%	27%	28%
Nausea/Vomiting	10%	11%	12%	12%	12%	15%	15%
Parkinsonism Cluster	8%	11%	14%	12%	14%	20%	24%

Figure 13: The time-profile of four adverse events in schizophrenia patients.



2.2.2.6 Does this drug prolong QT/QTc Interval?

No significant QTc prolongation effect of cariprazine (9 mg on day 20 and a supratherapeutic dosage of 18 mg on day 34) was detected in the TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between cariprazine and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

2.2.3 Intrinsic Factors

2.2.3.1 What intrinsic factors influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

CYP2D6 Polymorphism

Based on a population PK analysis, steady-state AUC_{0-24} of DDCAR in poor metabolizers of CYP2D6 was about 16% higher than in extensive metabolizers. This difference is not considered clinical relevant. No relevant changes associated with CYP2D6 status were observed for cariprazine or DCAR. For further details, refer to pharmacometrics review. The impact of CYP2D6 polymorphism on the PK of cariprazine and its major active metabolites was not clinically relevant.

Gender

Female subjects had about 35% and 13% (C_{max} and AUC, respectively) higher total effective exposure (sum of cariprazine, DCAR and DDCAR) than males (Table 17). This is

likely due to differences in body weight.

Table 17: PK parameters (Mean ±SD) for cariprazine and its metabolites after single dose administration of 2 mg cariprazine tablet to healthy subjects under *fed* conditions.

Parameters	Male (n=9)	Female (n=6)	Ratio (Female/male)
Cariprazine			
Cmax (ng/mL)	1.5±0.3	2.0±0.5	1.29
T_{max} (hr)#	8(6-12)	8(8-24)	-
$AUC_{0\text{-}last}$(hr.ng/mL)	83.6±19.7	102±25.5	1.21
$AUC_{0\text{-}\infty}$(hr.ng/mL)	91.6±22.2	106.8±26.5	1.17
Cl/F/BW(L/hr)	0.3±0.1	0.3±0.1	0.95
$T_{1/2}$ (hr)	212±81	140±34	0.69
Desmethylcariprazine			
Cmax (ng/mL)	0.3±0.1	0.4±0.1	1.64
$AUC_{0\text{-}last}$(hr.ng/mL)	20.1±4.3	32.7±3.3	1.65
$AUC_{0\text{-}\infty}$(hr.ng/mL)	24.6±3.8	35.8±4.0	1.47
Didesmethylcariprazine			
Cmax (ng/mL)	0.2±0.05	0.3±0.1	1.38
$AUC_{0\text{-}last}$(hr.ng/mL)	103±15	140±47	1.31
$AUC_{0\text{-}\infty}$(hr.ng/mL)	262±124	284±166	1.05
# values are presented as median (min-max)			

In a population PK analysis in 2341 patients including 780 female patients, there were no clinically relevant differences observed in AUC and C_{max} of the sum of cariprazine and major active metabolites compared to male patients (approximately 23% increase in both parameters).

The impact of gender on the PK of cariprazine and its major active metabolites was not considered clinically relevant. For further details, refer to pharmacometrics review.

Race

C_{max} for cariprazine and DCAR were about 50% lower in Caucasian than in Japanese. AUC for cariprazine was similar (Table 18).

Table 18: Comparison of C_{max} and $AUC_{0\text{-}last}$ between Caucasian and Japanese

Parameter	Caucasian	Japanese	Estimated ratio of geometric means (90% CI)
Cariprazine			
C_{max}	0.571	1.014	0.56 [0.46, 0.60]
$AUC_{0\text{-}last}$	25.71	24.62	1.04 [0.87, 1.25]
Desmethylcariprazine			
C_{max}	0.055	0.117	0.47 [0.36, 0.61]
$AUC_{0\text{-}last}$	4.50	7.88	0.57 [0.45, 0.72]
Didesmthylcariprazine			

C_{max}	0.036	0.044	0.80 [0.65,0.99]
$AUC_{0\text{-}last}$	42.04	44.35	0.95 [0.69, 1.31]

Population PK analyses demonstrated about 25% increase in systemic exposure (C_{max} and $AUC_{0\text{-}24}$) of total cariprazine (sum of cariprazine, DCAR, and DDCAR) in Asian compared to Caucasian and around 30% decrease in total systemic exposure in Blacks compared to Caucasian.

The impact of race on the PK of cariprazine and its major active metabolites was not clinically relevant. For further details, refer to pharmacometrics review.

Age
The impact of age on the pharmacokinetics of total cariprazine (sum of cariprazine, DCAR, and DDCAR) was evaluated in a population PK analysis in 2341 patients (age 18 to 65), which included 461 patients between the age of 50 and 65. There were no clinically relevant differences observed in AUC and Cmax compared to younger patients.
The impact of age (up to the age of 65 years) on the PK of cariprazine and its major active metabolites was not clinically relevant. For further details, refer to pharmacometrics review.

Body Weight
Based on population PK analyses, patients with ideal body weight [IBW] of 36-57 kg had, on average, 25% greater steady-state $AUC_{0\text{-}24}$ than those with IBW of 63-67 kg, whereas patients with IBW of 72-89 kg had, on average, 20% lower steady-state $AUC_{0\text{-}24}$ than those with IBW of 63-67 kg. Influence of the IBW on the steady-state Cmin and Cmax was comparable. Although IBW was identified as a statistically significant covariate in population PK analyses, its impact on total $AUC_{0\text{-}24}$, total Cmax and total Cmin was not of clinical significance. For further details, refer to pharmacometrics review.

Organ Impairment
Section 2.2.3.2 (hepatic impairment), section 2.2.3.3 (renal impairment)

2.2.3.2 Effect of Hepatic Impairment
The effect of mild and moderate hepatic impairment on the PK of cariprazine and its two active metabolites (DCAR and DDCAR) was evaluated after administration of 0.5 mg cariprazine for 14 days. The effect of severe hepatic impairment on PK of cariprazine has not been evaluated. The effective exposure was 57.3, 61.1, and 75.4 in patients with mild hepatic impairment, moderate hepatic impairment, and normal liver function, respectively (Table 19). No dose adjustments are needed for these patients.

Table 19: Mean PK Parameters in Hepatic Impairment and Healthy Volunteers on Day 14

	Mild Hepatic Impairment	Moderate Hepatic Impairment	Healthy Subjects	Geometric Mean Ratio(90%CI)	
				Mildly /Healthy	Moderately/ Healthy

Cariprazine					
Cmax (ng.mL)	1.16	1.36	1.19	103.9 (71-151.8)	122.6 (82.5-182.2)
$AUC_{0-\tau}$ (hr.ng/mL	20.2	24.6	21.4	102.7 (69-153)	125.5 (81.8-192.7)
DCAR					
Cmax (ng.mL)	0.36	0.33	0.47	80.9 (50.3-130)	73.3 (44.1-121.8)
$AUC_{0-\tau}$ (hr.ng/mL	7.3	7.0	9.5	84.9 (50.6-142)	79.4 (44.5-141.7)
DDCAR					
Cmax (ng.mL)	1.34	1.41	2.03	65.7 (42.8-101)	71.5 (47.5-107.8)
$AUC_{0-\tau}$ (hr.ng/mL	29.8	29.5	44.5	66.3 (43-102.5)	67.8 (44.5-103.4)

2.2.3.3 Effect of Renal Impairment

The effect of renal impairment on PK of cariprazine and its two active metabolites has not been evaluated in designated studies. Population PK analysis indicated no meaningful difference between patients with normal renal function and patients with mild or moderate impaired renal function. For further details, refer to pharmacometrics review.

The effect of severe renal impairment on the PK of cariprazine and its two active metabolites was not evaluated.

2.2.4 Extrinsic Factors

2.2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or –response and what is the impact of any differences in exposure on response?

Food

Refer to Section 2.2.4.1.1

Ketoconazole

Refer to Section 2.2.4.4.1

CYP2D6 inhibitors

Refer to Section 2.2.4.4.2

2.2.4.1.1 What is the effect of food on bioavailability of Cariprazine?

The effect of food on cariprzine exposure was evaluated in the capsule formulation (clinical use and to-be-marketed formulation). High-fat food delayed absorption of cariprazine (delayed median Tmax about 5 hrs) and decreased Cmax about 4%. AUC of cariprazine was increased about 12% by food (Table 20). These changes are not considered clinically meaningful. Therefore, cariprazine can be administered without regard to food.

Table 20: PK Parameters (Mean ± SD) for Cariprazine, Desmethyl Cariprazine, and Didesmethyl Cariprazine after Administration of 1.5 mg Cariprazine under Fasting and Fed Conditions.

Parameters	Treatment A (fasting, n=18)	Treatment B (fed, n=23)	Ratio of Geometric Means (B/A, 90% CI)
Cariprazine			
Cmax (ng/mL)	1.64±0.65	1.56±0.55	0.96 (0.80-1.16)
T_{max} (hr)#	4.0(3.0-9.0)	9.0(2.0-12.0)	-
$AUC_{0-\infty}$(hr.ng/mL)	116.3±29.9	128.9±27.9	1.12 (0.97-1.29)
Desmethylcariprazine			
Cmax (ng/mL)	0.15±0.06	0.14±0.04	0.92 (0.76-1.12)
$AUC_{0-\infty}$(hr.ng/mL)	17.8±5.4	15.3±3.6	0.87 (0.74-1.03)
Didesmethylcariprazine			
Cmax (ng/mL)	0.08±0.05	0.08±0.03	0.97 (0.82-1.15)
$AUC_{0-\infty}$(hr.ng/mL)	NA	NA	-
# median(min-max)			

2.2.4.2 Is there an in vitro basis to suspect in vivo drug-drug interactions?
In vitro metabolism studies indicated that CYP3A4 and, to a lesser extent, CYP2D6 appear to be the two major enzymes involved in the metabolism of cariprazine and its metabolites. So there are potential interactions between cariprazine and CYP3A4 and CYP2D6 inducers and/or inhibitors.

2.2.4.3 Influence of cariprazine on other drugs
In vitro studies indicated that cariprazine and its two active metabolites are not potent inhibitors and/or inducers of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/3A5. Coadministration of cariprazine with drugs that are substrates of those enzymes is not likely to affect the PK of those drugs.

The potential for transporter-mediated drug interactions with cariprazine and its two active metabolites is also low as they are not or weak substrates or inhibitors of P-gp, BCRP, OATP1B1, OATP1B3, OAT3 or OCT2. Coadministration of cariprazine with drugs that are substrates of those transporters is not likely to affect the PK of those drugs.

2.2.4.4 Influence of other drugs on Cariprazine
2.2.4.4.1 DDI with Ketoconazole
Coadministration of ketoconazole with cariprazine (CAR) resulted in an increase in plasma exposure (C_{max} and $AUC_{0-\tau}$) by 3.42- to 3.88-fold for cariprazine and 1.43-fold for DDCAR; a decrease by 32% to 35% was observed for DCAR. The total effective exposure (sum of cariprazine, DCAR and DDCAR) was increased about 100% by ketoconazole (Table 21).

Dose adjustment is recommended for cariprazine in the presence of strong CYP3A4 inhibitors. For patients on a stabled cariprazine dose at the time when a strong CYP3A4 inhibitor (eg, ketoconazole) is initiated, to achieve plasma levels similar in terms of total cariprazine to plasma levels in the absence of ketoconazole, cariprazine dose is recommended to be reduced by half.

Table 21: Plasma PK Parameters (Mean ±SD) for CAR, DCAR and DDCAR after 0.5mg CAR Administration for 14 days

PK Parameters	Treatment A (Keto+CAR) N=16	Treatment B (CAR alone) N=18	Ratios of Means (A/B, 90% CI)
CAR			
Cmax (ng/mL)	5.13±1.08	1.57±0.64	342.4 (287.7-407.3)
AUC_{0-24} (hr.ng/mL)	92.6±17.2	24.5±7.6	387.9 (334.3-450.1)
DCAR			
Cmax (ng/mL)	0.34±0.08	0.55±0.30	64.9 (53.0-79.4)
AUC_{0-24} (hr.ng/mL)	6.76±1.74	10.5±5.54	68.3 (55.8-83.7)
DDCAR			
Cmax (ng/mL)	2.57±1.05	1.93±1.36	143.0 (105.4-194)
AUC_{0-24} (hr.ng/mL)	48.0±18.9	36.1±24.5	142.7 (106.5-191.1)

2.2.4.4.2 CYP2D6 inhibitors

Population PK analysis was used to evaluate the effect of concomitant medications that were CYP2D6 inhibitors on plasma clearance of cariprazine, DCAR, and DDCAR. A total of 5.2% of the patients in the population PK analysis were exposed to concomitant administration of CYP2D6 inhibitors. No statistically significant difference in plasma clearance for cariprazine, DCAR or DDCAR was found due to concomitant administration of CYP2D6 inhibitors. However, as stated by the sponsor, the analysis does not take into account the potency of various inducers and inhibitors.

Further analyses found that CYP2D6 poor metabolizers showed no difference in exposures of major moieties compared to patients with different CYP2D6 status and suggested no dose adjustment is needed in CYP2D6 poor metabolizers. This finding implied that CYP2D6 inhibitors are not expected to yield meaningful exposure changes of major metabolites and hence no dose adjustment is necessary.

2.2.5 General Biopharmaceutics

2.2.5.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation?

Cariprazine HCl appears to be a Biopharmaceutics Classification System (BCS) Class 2 (high permeability, low solubility) compound based on the evaluation of its solubility, permeability, and dissolution.

2.2.5.2 How is the proposed to-be-marketed formulation of cariprazine linked to the clinically used formulation?

There were two Immediate-release (IR) formulations developed for cariprazine: tablet and capsule. The tablet formulation was only used in early stage PK studies, and the capsule formulation was used in all Phase 3 trials, and it is the proposed commercialization formulation. The proposed to-be-marketed capsule formulation contains cariprazine HCl,

pregelatinized starch, and magnesium stearate. The proposed commercial strengths of cariprazine capsules are 1.5, 3, 4.5, 6, (b) (4) mg. Cariprazine capsules are qualitatively identical (b) (4) (Refer to ONDQA review). The same inactive ingredients (pregelatinized starch, magnesium stearate) are used for all strengths, and the (b) (4) .

(b) (4) to-be-marketed capsule formulation and clinical use capsule formulation, (b) (4) manufacture sites are different. The sponsor has requested and was agreed by the agency to wave bioequivalence studies based on in vitro dissolution test (Nov. 15, 2011 Type C meeting minutes).

2.2.6 General Attributes of the Drug

2.2.6.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the drug product?

The main properties of the drug substance are summarized in Figure 14 and Table 22.

Figure 14: Chemical structure of Cariprazine HCl (cariprazine base MW: 427.4 g/mol)

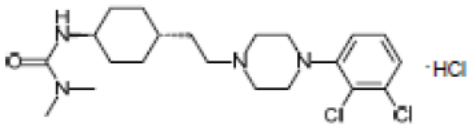


Table 22: Physiochemical Characteristics of the Drug Substance

Solubility in water:	Very slightly soluble
pH:	4.8 (b) (4)
"Apparent" pK_a:	8.182 ± 0.023
Log P:	4.428 ± 0.043
BCS Classification	BCS II (low solubility, high permeability)

Cariprazine HCl shows pH-dependent solubility at 37°C, with the maximal solubility observed at pH3 in aqueous buffer (Table 1). In the pH range of 1 to 5.5, cariprazine HCl exhibits high solubility (greater than 148 µg/mL). In the pH range of 6 to 7, cariprazine HCl exhibits low solubility (less than 19 µg/mL). In biorelavant buffer which contains the bile salt and lipids components in GI, the maximal solubility was obtained at pH5.0 (Table 23).

Table 23: Solubility of Cariprazine HCl in Biorelavent Buffer

Buffers	Solubility (mg/mL)
FeSSIF (pH5.0)	3.69
FaSSIF (pH6.8)	0.07

-source: study report PRD-RPT-EXP-00022

Cariprazine HCl exhibits high permeability in Caco-2 studies (Table 24).

Table 24: Caco-2 Permeability of Cariprazine HCl

Drug	PappB→A ($x10^{-5}$cm/s)	PappA→B ($x10^{-5}$cm/s)	Flux Ratio (PappB→A/PappA→B)
Cariprazine HCl	3.90±0.15	4.20±0.23	1.1
Labetalol	3.18±0.19	3.45±0.16	1.1

-source: study report PRD-RPT-EXP-00022

2.2.6.2 What are the proposed mechanism of action and therapeutic indications?

Cariprazine is a potent dopamine (DA) D_2/D_3 receptor partial agonist with preferential binding to D_3 receptor and a partial agonist to 5-HT_{1A} receptor. At antipsychotic-like effective doses, cariprazine occupies D_3 and D_2 receptors to a similar extent. Following chronic administration, cariprazine causes an upregulation (up to ~ 2-fold) of both D_2 and D_3 receptors. Cariprazine also upregulates 5-HT_{1A} receptor in cerebral cortex and hippocampal CA3 regions.

Carprazine intended for the treatment of schizophrenia and bipolar mania.

2.2.6.3 What are the proposed dosages and routes of administration?

Schizophrenia:

Cariprazine has been shown to be effective in a dose range of 1.5 to (b) (4) mg/day. The proposed starting dose of cariprazine is 1.5 mg once daily and cariprazine dose should be increased to 3 mg on Day 2. Depending on clinical response, cariprazine dose can be adjusted in increments of 1.5 mg or 3 mg (b) (4).

Bipolar Mania:

The proposed and target dose for cariprazine is (b) (4) mg once daily. The starting dose is 1.5 mg/day and the dose should be increased to 3 mg on day 2. Depending on individual patient response and patient tolerability, the dose can be increased in increments of 1.5 mg or 3 mg per day (b) (4).

The proposed commercial strengths of cariprazine capsules are 1.5, 3, 4.5, 6, (b) (4) mg.

2.2.7 List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

The current submission consisted of 14 clinical pharmacology studies and 35 in vitro studies (Ref: OCP NDA Filing and Review Form).

2.2.8 Analytical Section

2.2.8.1 Are the active moieties in plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. LC-MS/MS assay methods were developed to determine the concentrations of cariprazine and its two active metabolites (DCAR and DDCAR), in plasma/urine/feces in subjects.

2.2.8.2 What bioanalytical methods are used to assess concentrations and is the validation complete and acceptable?

During the development of cariprazine, 7 LC-MS/MS assay methods were developed for determination of cariprazine and its two active metabolites (DCAR and DDCAR) concentrations in human biomatrix samples.

The analytical methods developed for the analysis of cariprazine and its two active metabolites (DCAR and DDCAR) were adequately validated and acceptable. For detailed information, refer to individual study review under Appendix I.

SIGNATURES

Huixia Zhang, Ph.D.
Reviewer, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology

Joo-Yeon Lee, Ph.D.
Reviewer, Pharmacometrics
Office of Clinical Pharmacology

Atul Bhattaram, Ph.D.
Team Leader, Pharmacometrics
Office of Clinical Pharmacology

Hao Zhu, Ph.D.
Team Leader, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology

Mehul Mehta, Ph.D.
Division Director, DCP1
Office of Clinical Pharmacology

Cc: NDA 204370, DPP, DCP1 (Mehta, Uppoor, Zhu, Zhang)

3. NDA FILING FORM

Office of Clinical Pharmacology

1 *NEW DRUG APPLICATION FILING AND REVIEW FORM*

General Information About the Submission

	Information		Information
NDA/BLA Number	**204370**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Cariprazine**

Medical Division	**Psychiatry Drug Products**	**Drug Class**	**Antipsychotics**
OCP Reviewer	**Huixia Zhang**	**Indication(s)**	**Schizophrenia and Bipolar I**
OCP Team Leader	**Hao Zhu**	**Dosage Form**	**Immediate-Release Capsules**
Pharmacometrics Reviewer	**Joo-Yeon Lee**	**Dosing Regimen**	**Once Daily**
Genomics Team Leader	**Mike Pacanowski**	**Route of Administration**	**Oral**
Date of Submission	**11/19/2012**	**Sponsor**	**Forest**
Estimated Due Date of OCP Review	**6/1/2013**	**Priority Classification**	**Standard 12 Months**
Medical Division Due Date	**7/19/2013**		
PDUFA Due Date	**11/19/2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**	**14**		
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:	**x**	**1**		
Isozyme characterization:				
Blood/plasma ratio:	**x**	**1**		
Plasma protein binding:	**x**	**1**		
Pharmacokinetics (e.g., Phase I) -	**x**	**6**		
Healthy Volunteers-				
single dose:	**x**	**2**		
multiple dose:	**x**	**2**		
Patients-				
single dose:				
multiple dose:	**x**	**2**		
Dose proportionality -				
fasting / non-fasting single dose:	**x**	**2**		
fasting / non-fasting multiple dose:	**x**	**2**		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**x**	**1**		
In-vivo effects of primary drug:				
In-vitro:	**x**	**35**		
Subpopulation studies -				
ethnicity:	**x**	**1**		
gender:	**x**	**1**		
pediatrics:				
geriatrics:	**x**	**1**		
renal impairment:				
hepatic impairment:	**x**	**1**		
PD -				
Phase 2:	**x**	**1**		
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**3**		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**x**	**1**		
Data sparse:	**x**	**1**		
II. Biopharmaceutics				

Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**2**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**			**Requests for Waiver & Deferral submitted**
Literature References	**x**	**92**		
Total Number of Studies		**49**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	Biowaiver is requested; no BE needed
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	Have mass balance information
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets	x			

	submitted in the appropriate format?				
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			DDI interaction with ketoconazole, hepatic impairment study submitted
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			PK simulations were performed and assessed w.r.t. a therapeutic range.
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Requests for Waiver & Deferral submitted
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Requests for Waiver & Deferral submitted
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Please submit individual plasma concentration data for RGH-188, DCAR and DDCAR for each clinical pharmacology studies and those in efficacy and safety studies in SAS .xpt format. The dataset should include columns specifying the following variables: protocol number, subject ID, dose, analyte, day from first dose, scheduled PK time, actual PK time, and

concentration. Please provide “define.pdf” file to define your variables. Please submit data in two weeks.

2. We acknowledge receipt of your submission on Dec.18, 2012. To make a better understanding of the information, please resubmit the datasets, summary tables and plots by weeks since first dose and by dose groups. Please submit data in two weeks.

Huixia Zhang	1/16/2013
Reviewing Clinical Pharmacologist	Date
Hao Zhu	1/16/2013
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUIXIA ZHANG
07/19/2013

JOO YEON LEE
07/19/2013
I sign-off on behalf of Dr. Atul Bhattaram and myself.

HAO ZHU
07/19/2013

MEHUL U MEHTA
07/19/2013

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 204370	**Reviewer:** Sandra Suarez Sharp, PhD	
Division:	DPP		
Applicant:	Forest Laboratories, Inc.	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Trade Name:	---	**Biopharmaceutics Supervisory Lead (acting)**: Richard Lostritto, Ph.D.	
Generic Name:	Cariprazine Capsules	**Date Assigned:**	Nov 25, 2012
Indication	Treatment of Schizophrenia and manic or mixed episodes associated with bipolar I disorder	**Date of Review:**	July 15, 2013
Formulation/ Strength	Immediate Release (IR) Capsules/ 1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg, (b) (4)		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	Date of informal/Formal Consult	Primary Review due in DARRTS
Nov 19, 2012; Feb 26, 2013 April 08, 2013; May 05, 2013	Nov 21, 2012	July 22, 2013

Type of Submission:	Original 505 (b)(1) Application
Review Key Points:	▪ Dissolution method and acceptance criteria ▪ Manufacturing site/process/equipment changes ▪ Waiver Request (b) (4)

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

In NDA 204370, Forest Laboratories, Inc. seeks approval to market Cariprazine IR capsules for the once-daily treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. The proposed commercial strengths of cariprazine capsules (hard gelatin) are 1.5, 3, 4.5, 6, (b) (4) mg. Cariprazine capsules are qualitatively identical and can be considered (b) (4).

The development program supporting this submission consisted of six pharmacokinetic studies (dose linearity, proportionality, food effect, single-dose and steady-state pharmacokinetics) and several efficacy/safety trials. All the PK studies are being reviewed by OCP. The pivotal and supportive clinical studies were conducted using the 1.5, 3, and 6 mg capsule strengths. A biowaiver request is included in the submission for the 4.5, (b) (4) strengths.

This review evaluates and makes recommendations on the acceptability of the dissolution method and acceptance criteria, the adequacy of the data supporting the approval of the 4.5 mg, (b) (4) strengths, and the acceptability of the data provided to support a manufacturing

site/process change.

1) DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

The following dissolution method and acceptance criteria for Cariprazine IR Capsules, 1.5 mg, 3 mg, 4,5 mg, 6 mg, (b) (4) have been agreed upon with the Applicant (refer to submission dated April 08, 2013) and are deemed acceptable:

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
I/100 rpm	Sodium acetate buffer, pH 5.0	500 mL	▪ **For 1.5 mg, 3 mg, 4,5 mg and 6 mg**: Q= (b) (4)% at 15 min ▪ (b) (4)

The dissolution method was accepted during the IND stage[1]. Briefly, the dissolution method showed acceptable discriminating ability towards changes in (b) (4) API particle size distribution, and formulation composition. The dissolution acceptance criteria were based on the results of the performance of the pivotal clinical phase 3 and stability batches and on the reported (b) (4).

2) EVALUATON OF THE DATA PROVIDED TO SUPPORT THE MANUFACTURING CHANGES (SITE, EQUIPMENT AND PROCESS)

The pivotal and supportive clinical study formulations were manufactured at the Forest Plant in New York and the proposed commercial (to-be-marketed) formulations were manufactured in Forest Laboratories, Clonshaugh, Ireland. The manufacturing site change corresponds to a Level 3 change according to the SUPAC-IR guidance. (b) (4) Upon consultation with the CMC review team it was found acceptable to consider the proposed equipment/process changes as (b) (4). Therefore, the Applicant's justification for providing the dissolution documentation according to Case B requirement, in accordance with SUPAC-IR in support of adding the Ireland manufacturing site/process/equipment changes is adequate. The proposed manufacturing site/process/equipment changes are acceptable given that all the similarity factors were > 50, indicating similar dissolution profiles.

3) EVALUATION OF THE DATA PROVIDED TO SUPPORT THE WAIVER OF THE BE REQUIREMENTS FOR THE 4.5, (b) (4) mg STRENGHTS

The clinical Phase 3 primary efficacy trials were conducted with the 1.5 mg, 3.0 mg, and 6.0 mg capsule strengths. In the present submission the Applicant is requesting a biowaiver of the required BA/BE studies for the 4.5 mg, (b) (4). The following information/data were included in support of the biowaiver:

1. Clinical safety and/or efficacy data covering the proposed therapeutic range,
2. Demonstration of linear elimination kinetics information over the therapeutic dose range
3. Evidence of (b) (4) for which the same manufacturer has conducted an appropriate *in vivo* study;
4. Dissolution profile comparison data and f2 values in three media (pH (b) (4)) using the same dissolution testing procedures.

[1] ONDQA-Biopharmaceutics review entered in DARRTS by Drs. Marroum and Chickhale on March 2011.

According to the Applicant, cariprazine was generally well-tolerated in patients with bipolar mania [redacted] (refer to the clinical review for more information on the safety and efficacy of the product). [redacted] In addition, the clinical pharmacology team confirmed, during the mid-cycle meeting, that the PK of cariprazine is linear [redacted] (also refer to Dr. Huixia Zhang).

A bracketing approach was presented to demonstrate [redacted] and is deemed acceptable Base on these bracketing approach all the f2 values were higher than 50. Therefore, the waiver in granted.

As communicated to the review team during the mid-cycle meeting, [redacted] leading to a potentially different safety/efficacy profile. Therefore, the clinical pharmacology and clinical teams were informed to consider the evaluation of this potential risk based on what is known about the safety/efficacy dose-response relationship for this drug product and on the likelihood for swichtability between strengths.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 204-370 and its amendments submitted on Feb 26, 2016, April 08, 2013 and May 05, 2013. The following dissolution method and dissolution acceptance criteria for Cariprazine IR Capsules, 1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg, [redacted] have been agreed upon with the Applicant (refer to submission dated April 08, 2013) :

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
I/100 rpm	Sodium acetate buffer, pH 5.0	500 mL	▪ For 1.5 mg, 3 mg, 4.5 mg and 6 mg: Q= [redacted]% at 15 min [redacted]

From the Biopharmaceutics perspective, NDA 204-370 for Cariprazine IR Capsules 1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg, [redacted] is recommended for APPROVAL.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: R Lostritto;

BIOPHARMACEUTICS ASSESSMENT

1. BACKGROUND

Submission: Cariprazine (RGH-188) is an orally active and potent dopamine D2/D3 receptor partial agonist with preferential binding to D3 receptors. The Applicant is seeking approval to market Cariprazine IR capsules for the once-daily treatment of two indications: 1) schizophrenia and 2) manic or mixed episodes associated with bipolar I disorder.

The safety and efficacy of cariprazine has been established in schizophrenia clinical trials in doses from 1.5 to 9 mg/day and in bipolar mania clinical trials in doses from 3 to 12 mg/day. (b) (4). Cariprazine should be administered starting with 1.5 mg on Day 1 and increased to 3 mg on Day 2. Depending upon clinical response and tolerability, dose adjustments can be made upwards or downwards in 1.5 or 3 mg increments. (b) (4)

The development program supporting this submission consisted of thirteen phase 1 studies and 18 Phase 2/3 studies. The Phase I studies evaluated the safety, pharmacodynamics (PD), and pharmacokinetics (PK) of cariprazine in healthy subjects and in patients with schizophrenia. All the PK studies are being reviewed by OCP.

Review: The Biopharmaceutics review is focused on the acceptability of the dissolution method and acceptance criteria, the adequacy of the data supporting the approval of the 4.5 mg, (b) (4) strengths, and the acceptability of the data provided to support a manufacturing site and process change.

Drug Substance

According to the Applicant, cariprazine HCl is a BCS Class 2 compound. However, it presents a high solubility at pH values of 1 to 5 (upper gastrointestinal tract conditions) which represent the physiological pH range of the human stomach (pH of 1 to 3 and 4 to 5 in the fasted state and in the fed state, respectively). It exhibits maximum solubility at approximately pH 3.

Drug Product

The proposed commercial (to-be-marketed) drug product comprises of hard gelatin capsules containing cariprazine HCl, pregelatinized starch, and magnesium stearate. The proposed commercial strengths of cariprazine capsules are 1.5, 3, 4.5, 6, (b) (4) mg. Cariprazine capsules are qualitatively identical (b) (4). Table 1 summarizes the formulation of Cariprazine IR Capsules.

Table 1. Components and Quantitative Composition of Cariprazine Capsules

Component	*Pharmaceutical Function*	*Quality Standard*	Unit Dose Composition							
			1.5 mg		*3.0 mg*		*4.5 mg*		*6.0 mg*	
			% w/w	mg/cap	% w/w	mg/cap	% w/w	mg/cap	% w/w	mg/cap
Cariprazine HCl	Drug Substance	In-house[a]	(b) (4)							
Pregelatinized starch	(b) (4)	USP/NF								
Magnesium stearate (b) (4)		USP/NF								
Total (b) (4) Weight										
Empty hard gelatin capsule, size 4	Capsule shell	In-house								
Empty hard gelatin capsule, size 3	Capsule shell	In-house								

(b) (4)

(b) (4)

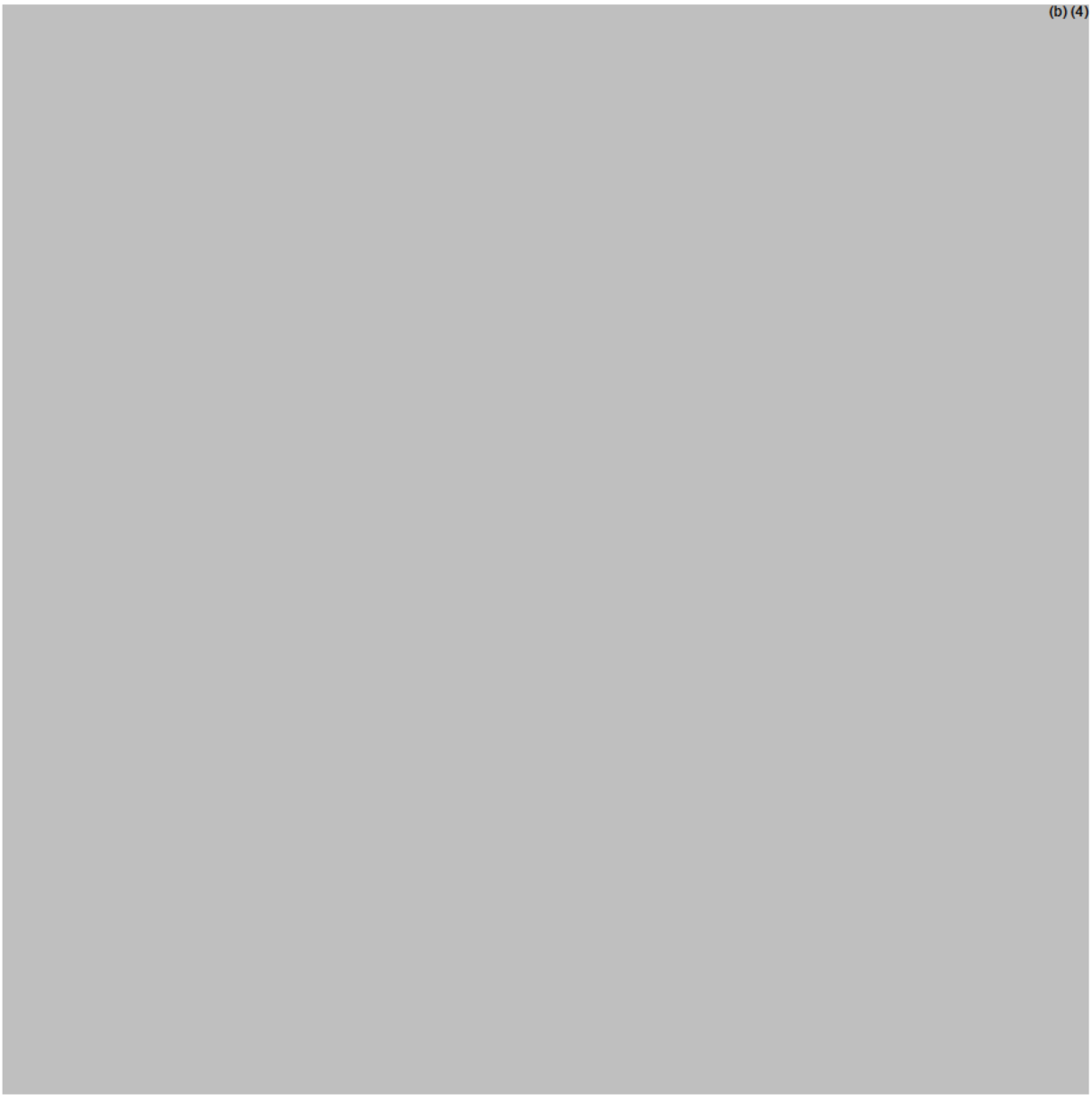
Reviewer's Comments

As noted above, the pivotal and supportive clinical studies were conducted using the 1.5, 3, and 6 mg capsule strengths and a request of biowaiver from conducting in vivo studies for cariprazine capsule strengths of 4.5, (b) (4) *mg is included in the submission. As shown in Table 1, the strengths used in the clinical trials* (b) (4)

(b) (4)

Development Program

(b) (4)



2. DISSOLUTION METHOD

Dissolution testing is performed at release and on stability. The dissolution method being proposed for all the strengths of Cariprazine IR capsules is summarized below:

USP Apparatus	Agitation Speed	Medium	Volume
I	100 rpm	Sodium acetate buffer, pH 5.0	500 mL

Reviewer's Comments

The dissolution method was reviewed during the IND stage by Drs. Chickhale and Marroum and was deemed acceptable[2]. [redacted]

In terms of discriminating ability, the method was challenge in terms of its ability to discriminate for changes in [redacted] *According to the Biopharmaceutics Reviewer, Dr. Chikhale, the results indicated that the proposed dissolution conditions can discriminate significant changes in* [redacted] *API particle size distribution, and formulation composition.*

3. DISSOLUTION ACCEPTANCE CRITERION

Applicant's Originally Proposed Dissolution Acceptance Criterion

The proposed dissolution acceptance criteria for all strengths of the proposed [redacted] product are as follows:

Proposed Acceptance Criterion
Q= [redacted]% at [redacted] minutes

Reviewer's Comments

The following comments were conveyed to the Applicant as part of the 74-day letter:

- ***Your proposed dissolution acceptance criterion of Q= [redacted]% at [redacted] min is not justified. Provide the following information to support the selection of the dissolution acceptance criterion:***
  - ***Dissolution profile data (mean and raw data in tabulated and graphical form) from the pivotal clinical batches and primary (registration) stability batches***

On February 26, 2013 the Applicant submitted the requested data which can be summarized in Figure 2 below.

According to the Applicant, the proposed acceptance criterion was revised to Q= [redacted]% at [redacted] min for all the strengths. The Applicant stated that this criterion was chosen based on

[2] Biopharmaceutics review for INDs 71958, 77726 and [redacted] amendment #s 241, 145 and 52 entered in DARRTS by Dr. Chikhale on March 2011.

(b) (4) (Table 2). The Applicant stated that the stability data and the data generated at time of manufacture indicate that the specification of Q = (b) (4)% @ (b) (4) minutes is appropriate for the dissolution of drug product.

Table 2. Dissolution Testing - (b) (4)

(b) (4)

(b) (4)

Figure 2. Comparative Dissolution Profiles (Mean Data): Cariprazine NDA Lots (modified from Figure 1.2.1-11 provided on submission dated Feb 26, 2013).

Based on the data presented above (Table 2, Figure 2), the following comments were conveyed to the Applicant as part of the mid-cycle IR letter:

- ***Your proposal for adopting a dissolution acceptance criterion of Q= (b) (4) % at (b) (4) min (b) (4).***
- ***The following acceptance criterion should be implemented (b) (4) : Q= (b) (4) % at 15 min***
- ***Note that the data needed to set dissolution acceptance criterion excludes data from accelerated stability studies. Therefore, the occurrences of (b) (4) listed in Table 1.2.1-1 are not appropriate since the estimations were made based on data from accelerated storage condition (b) (4).***

On a submission dated May 05, 2013, the Applicant agreed to set a dissolution acceptance criterion to Q= (b) (4) % at 15 min for the 1.5 mg, 3 mg, 4.5 mg and 6 mg strengths (b) (4) (b) (4) The following summarizes the agreed upon dissolution acceptance criteria for all the strengths:

Agreed upon Acceptance Criteria for Cariprazine IR Capsules
1.5, 3, 4.5, and 6 mg Strengths: **Q= (b) (4) % at 15 min** (b) (4)

4. EVALUATION OF THE DATA PROVIDED TO SUPPORT THE MANUFACTURING SITE/PROCESS/EQUIPMENT CHANGE

According to the Applicant, NDA registration batches and proposed commercial supplies utilize the same formulations and manufacturing processes as those used in the manufacture of the pivotal and supportive clinical study formulations with the exception of (b) (4) manufacturing site.

The pivotal and supportive clinical study formulations were manufactured at the Forest Plant in New York and the proposed commercial (to-be-marketed) formulations were manufactured in Ireland. The manufacturing site corresponds to a Level 3 according to the SUPAC-IR guidance.

Although the proposed alternate manufacturing site is considered a Level 3 manufacturing site change as per SUPAC-IR requiring dissolution documentation using Case B testing, during the initial review and evaluation of the data it was noted that the

proposed change also affected the equipment used and the process itself. These changes in process/equipment were classified as Level (b) (4) change according to the CMC Reviewer, Dr. Sherita McLamore (email exchange communication). (b) (4)

- (b) (4)

In the submission dated Apr 08, 2013, the Applicant provided justification to (b) (4)

(b) (4)

Table 3. Summary of Manufacturing Process Differences: Phase 3 Clinical and NDA Batches

Parameter	*Phase 3 Clinical Efficacy*	*NDA Batches (To-be-Commercial)*
Manufacturing Site	(b) (4)	
Batch Size		
Manufacturing Equipment		

Reference: Table 2.3-1 submission dated April 8, 2013.

Based on the information presented in the submission dated April 08, 2013, and upon consultation with the CMC reviewing team, it was found acceptable to consider the proposed equipment/process changes as (b) (4) the Applicant's justification for providing the dissolution documentation according to Case B requirement in accordance with SUPAC-IR in support of adding the Ireland manufacturing site/process/equipment changes is adequate.

For the strengths used in the clinical Phase 3 studies, the calculated similarity factors (f_2) between the dissolution profiles of capsules manufactured at both sites are presented in Table 4. All the similarity factors are ≥ 50, indicating similar dissolution profiles.

Table 4. pH 5.0 Similarity Factors (f2) using Proposed QC medium (acetate buffer pH 5) for Clinical Batches (reference) vs. NDA Batches (test)

Similarity Factor (f_2) Clinical (reference) vs. NDA		*Clinical Efficacy Batches (Strength/Lot#)*			
		1.5 mg BN0006814	**3.0 mg BN0007320**	**3.0 mg BN0006824**	**6.0 mg BN0006817**
NDA Batches	1.5 mg Lot# L0004141	61[a]			
	3.0 mg Lot# L0004286		67[a]	90[a]	
	6.0 mg Lot# L0004151				82[a]

[a] Dissolution was (b) (4) % in 15 minutes for both lots compared. All five time-points used to calculate f2. Reference Table 4.3–1

It should be noted that, despite the justification provided to follow Case B dissolution, the Applicant did provide dissolution profile comparison in different media as shown in the Table 5. Dissolution profile comparisons (e.g. 1.5 mg current site vs. 1.5 mg proposed site) were higher than 50 in all media except water (refer to section 3.5, PRD-RPT-ANL-00378, submission dated Apr 08, 2013).

Table 5. Dissolution Conditions for Multi-pH Comparative Dissolutions

Apparatus:	USP Apparatus 1 (Baskets)
Rotation Speed:	100 RPM
Medium:	(b) (4) □ pH 5.0 Acetate Buffer (b) (4)
Volume:	500 mL
Temperature:	37°C
Sampling Intervals:	15, (b) (4) minutes
Units:	N = 12 capsules

5. EVALUATION OF THE DATA PROVIDED TO SUPPORT THE WAIVER OF THE BE REQUIREMENTS FOR THE 4.5, (b) (4) STRENGHTS

As mentioned above, the to-be-marketed drug product for the cariprazine capsules was developed as an immediate-release dosage form in (b) (4) 1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg, (b) (4). The primary NDA registration batches of the to-be-marketed formulation were manufactured at Forest Laboratories, Clonshaugh, Ireland (commercial site). The clinical Phase 3 primary efficacy trials were conducted with the 1.5 mg, 3.0 mg, and 6.0 mg capsule strengths. In the present submission the Applicant is requesting a biowaiver of the required BA/BE studies for the 4.5 mg, (b) (4)

A waiver of the *in vivo* studies for different strengths of a drug product can be granted when the following requirements are met:

5. The drug product is in the same dosage form, but in different strength;
6. [redacted] for which the same manufacturer has conducted an appropriate *in vivo* study;
7. Clinical safety and/or efficacy data covering the proposed therapeutic range,
8. Demonstration of linear elimination kinetics information over the therapeutic dose range,
9. Dissolution profile comparison data and f2 values in three media (pH [redacted]) using the same dissolution testing procedures.

Supporting Data

Manufacturing process and Chemical Composition

The drug product manufacturing processes [redacted]. The drug product formulation compositions [redacted] for the pivotal and supportive clinical study formulations and the proposed commercial (to-be-marketed) formulations.

The quantitative compositions of Cariprazine Capsules are presented in Table 1 above. The total weight of all formulations remains within [redacted]% of the total weight of the strengths on which the biostudy was performed [redacted] the same inactive ingredients (pregelatinized starch, magnesium stearate) are used for all strengths, and [redacted] are within the limits defined by the SUPAC-IR guidance up to and including Level [redacted], requiring dissolution profile comparison in different media.

[redacted]

Dissolution Profile Comparisons

During the review cycle it was noted that no data were submitted in different media other than the QC medium. Therefore, the following comment was conveyed to the Applicant as part of the 74 day letter:

- ***(b) (4) are within the limits defined by the FDA's SUPAC - IR Guidance for Industry up to and including Level (b) (4). To support these changes, please submit multi-point dissolution profile comparisons performed in (b) (4) for all the proposed strengths. Include f2 statistical testing.***

In a submission dated April 8, 2013, the Applicant stated based on the solubility profile of cariprazine HCl drug substance which was observed to decrease with increasing pH (b) (4) that comparing in vitro dissolution data at pH (b) (4) or in water across all capsule strengths (i.e. from high to low strengths) is not appropriate due to the absence of sink conditions across all strengths. Additionally, water as dissolution medium is not appropriate since it is un-buffered and thereby dissolutions can be greatly affected by local, micro-environment pH effects. Nevertheless, comparative dissolution profiles were collected at multi-pH conditions in support of the bio-waiver for cariprazine capsules as summarized in Table 6. The results of the comparisons using these different media are summarized in Tables 7-11.

Table 6. Dissolution Conditions for Multi-pH Comparative Dissolutions

Apparatus:	USP Apparatus 1 (Baskets)
Rotation Speed:	100 RPM
Medium:	(b) (4) □ pH 5.0 Acetate Buffer (b) (4)
Volume:	500 mL
Temperature:	37°C
Sampling Intervals:	15, (b) (4) minutes
Units:	N = 12 capsules

Table 7. pH 1.2 Medium: Similarity Factors (f2) Across all Strengths of NDA Batches

Similarity Factor (f_2) *NDA Batches - All Strengths*		*NDA Batches (Strengths/Lot Numbers)*			
		1.5 mg L0004141	*3.0 mg L0004286*	*4.5 mg L0004147*	*6.0 mg L0004151*
	1.5 mg Lot# L0004141	(b) (4)	67[a]	83[a]	79[a]
	3.0 mg Lot# L0004286			76[a]	58[a]
	4.5 mg Lot# L0004147				69[a]
	6.0 mg Lot# L0004151				

(b) (4)

[a] Dissolution was (b) (4) % in 15 minutes for both lots compared, and according to FDA Guidance [3] the comparison of f2 values is not necessary to demonstrate similar profiles. However, the similarity factors (f2) were calculated for information purposes and all five time-points used to calculate f2

Table 8. pH 4.5 Medium: Similarity Factors (f2) Across all Strengths of NDA Batches

Similarity Factor (f_2) *NDA Batches - All Strengths*		*NDA Batches (Strengths/Lot Numbers)*			
		1.5 mg L0004141	*3.0 mg L0004286*	*4.5 mg L0004147*	*6.0 mg L0004151*
NDA Batches	1.5 mg Lot# L0004141	(b) (4)	64[a]	65[a]	95[a]
	3.0 mg Lot# L0004286			98[a]	61[a]
	4.5 mg Lot# L0004147				62[a]
	6.0 mg Lot# L0004151				

(b) (4)

[a] Dissolution was (b) (4) % in 15 minutes for both lots compared, and according to FDA Guidance [3] the comparison of f2 values is not necessary to demonstrate similar profiles. However, the similarity factors (f2) were calculated for information purposes and all five time-points used to calculate f2

Table 9. pH 5 Medium: Similarity Factors (f2) Across all Strengths of NDA Batches

Similarity Factor (f_2) *NDA Batches - All Strengths*		*NDA Batches (Strengths/Lot Numbers)*			
		1.5 mg L0004141	*3.0 mg L0004286*	*4.5 mg L0004147*	*6.0 mg L0004151*
NDA Batches	1.5 mg Lot# L0004141	(b) (4)	59[a]	63[a]	76[a]
	3.0 mg Lot# L0004286			83[a]	67[a]
	4.5 mg Lot# L0004147				69[a]
	6.0 mg Lot# L0004151				

(b) (4)

[a] Dissolution was (b) (4) % in 15 minutes for both lots compared, and according to FDA Guidance [3] the comparison of f2 values is not necessary to demonstrate similar profiles. However, the similarity factors (f2) were calculated for information purposes and all five time-points used to calculate f2

[b] f2 values calculated using all five time-points; provides a slightly lower f2 than if only two time-points were used.

Table 10. pH 6.8 Medium: Similarity Factors (f2) Across all Strengths of NDA Batches

Similarity Factor (f_2) NDA Batches - All Strengths		*NDA Batches (Strengths/Lot Numbers)*				
		1.5 mg L0004141	*3.0 mg L0004286*	*4.5 mg L0004147*	*6.0 mg L0004151*	(b) (4)
NDA Batches	1.5 mg Lot# L0004141		47	42	36	
	3.0 mg Lot# L0004286			72	54	
	4.5 mg Lot# L0004147				66	
	6.0 mg Lot# L0004151					
	(b) (4)					

According to the Applicant, sink conditions are not present at pH (b) (4) for any of the capsule strengths, therefore similarity factors less than 50 were expected when comparing across all strengths (e.g., highest to lowest). Capsule strengths (b) (4) that were not used in the Phase 3 studies were therefore bracketed for similarity factor comparison (b) (4) as presented in Table 11.

Table 11. pH 6.8 Medium: Similarity Factors (f2) by Bracketed Strengths of NDA Batches

Similarity Factor (f_2) NDA Batches - Strengths in Phase 3 Studies	*NDA Batches (Strengths/Lot Numbers) Strengths not in the Phase 3 Studies*	(b) (4)
	4.5 mg Lot# L0004147	
3.0 mg Lot# L0004286	72	
6.0 mg Lot# L0004151	66	

Reviewer's Comments

The bracketing approach presented in Table 11 is adequate for the reasons presented by the Applicant and given that (b) (4) *As communicated to the review team during the mid-cycle meeting,* (b) (4) *. Therefore, the clinical pharmacology and clinical teams were informed to consider the evaluation of this potential risk based on what is known about the safety dose-response relationship for this drug product and on the likelihood for swichtability between strengths.*

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/s/

SANDRA SUAREZ
07/15/2013

ANGELICA DORANTES
07/16/2013