NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental NDA
Application Number(s)	204370 S014, 015, 016, 017
Priority or Standard	Standard (S014) and Priority (S015, 016, 017)
Submit Date(s)	4/30/2025 (S014) and 06/18/25 (S015, 016, 017)
Received Date(s)	4/30/2025 and 06/18/25
PDUFA Goal Date	12/18/25
Division/Office	Division of Psychiatry / Office of Neuroscience
Review Completion Date	11/18/25
Established/Proper Name	Cariprazine
Trade Name	Vraylar
Pharmacologic Class	Atypical antipsychotic
Code name	
Applicant	AbbVie Inc.
Dosage form	Oral capsules
Applicant proposed Dosing Regimen	Cariprazine 0.5 mg orally once daily Cariprazine 1.5 mg orally once daily Cariprazine 3 mg orally once daily Cariprazine 4.5 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of schizophrenia in pediatric patients 13 to 17 years of age (S015); and for the acute treatment of manic or mixed episodes associated with bipolar I disorder in pediatric patients 10 to 17 years of age (S016)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	58214004 | Schizophrenia (disorder) 68569003 | Manic bipolar I disorder (disorder)
Recommendation on Regulatory Action	Approval for the proposed indications and populations (S015 and S016)
Recommended Indication(s)/Population(s) (if applicable)	Same as proposed by Applicant
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Same as proposed by Applicant
Recommended Dosing Regimen	Same as proposed by Applicant

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
PLT=Patient Labeling Team

Glossary

ABC-I	Aberrant Behavior Checklist-Irritability
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AEDC	adverse event leading to drug discontinuation
AIMS	Abnormal Involuntary Movement Scales
ALT	alanine aminotransferase
APA	American Psychiatric Association
AR	adverse reaction
ASD	autism spectrum disorder
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFB	Change from Baseline
CFR	Code of Federal Regulations
CGI-C	Clinical Rated Global Impression - Change
CGI-S	Clinical Rated Global Impression - Severity
CGSQ SF-7	Caregiver Strain Questionnaire Short Form 7-Item
CI	confidence interval
CK	creatine kinase
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	data monitoring committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
eCTD	electronic common technical document
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
GCP	good clinical practice
IND	Investigational New Drug
ITT	intent to treat
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
LS	least squares
LSMD	least squares mean difference
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effect model for repeated measures
mITT	modified intent to treat

NDA	new drug application
NMS	neuroleptic malignant syndrome
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OR	odds ratio
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetic
PMR	postmarketing requirement
PP	per protocol
PQ-LES-Q	Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire
PRAS-ASD	Parent-Rated Anxiety Scale for Youth with Autism Spectrum Disorder
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PWR	Pediatric Written Request
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Scale
SE	standard error of the least squares mean
SGA	second-generation antipsychotic
SI	suicidal ideation
SI/B	suicidal ideation/behavior
SOC	standard of care
sNDA	supplemental new drug application
TEAE	treatment emergent adverse event
USPI	United States Prescribing Information

1 Executive Summary

1.1. Product Introduction

Cariprazine is an atypical antipsychotic medication with partial agonist activity at central dopamine D2 and serotonin 5-HT1A receptors, and antagonist activity at serotonin 5-HT2A receptors. It is approved as Vraylar (NDA 204370) for adult patients for the treatment of schizophrenia, acute treatment of manic or mixed episodes associated with bipolar I disorder, treatment of depressive episodes associated with bipolar I disorder, and as adjunctive therapy to antidepressants for the treatment of major depressive disorder. Capsule dosage strengths of 1.5, 3, 4.5, and 6 mg are currently approved for oral ingestion once daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Based on (1) similarity of disease characteristics, (2) similarity of symptomatic changes observed in acute schizophrenia and bipolar I clinical trials in pediatric patients and adults receiving placebo, and (3) on an analysis of multiple antipsychotic drugs conducted by the FDA that demonstrated a similar exposure-response relationship in pediatric and adult patients with schizophrenia and bipolar I disorder, the Division has determined that it is acceptable to extrapolate effectiveness of drugs approved for the treatment of schizophrenia and bipolar I disorder in adults to pediatric patients 13 years of age and older and 10 years of age and older, respectively. Therefore, substantial evidence of effectiveness for the treatment of schizophrenia in pediatric patients 13 through 17 years of age and acute manic or mixed episodes associated with bipolar I disorder in pediatric patients 10 through 17 years of age is based upon extrapolation from cariprazine's known efficacy in the treatment of adult schizophrenia and bipolar I disorder. Extrapolation is supported by population pharmacokinetic (PK) report RD241815 and two PK studies: Study RGH-PK-18, a two-part, dose-escalation, multiple dose study in pediatric subjects ages 13 to 17 years with schizophrenia and ages 10 to 17 years with bipolar I disorder, and Study RGH-188-201, an open-label, multiple dose study in subjects ages 13 to 17 years and adults with schizophrenia, schizoaffective disorder, or schizophreniform disorder. To achieve similar exposures in pediatric patients as in adults, lower dosages are required. The Applicant has developed 0.5- and 0.75-mg strength capsules for this purpose and to simplify dose adjustments necessary in the context of drug-drug interactions.

In Study M21-465, a randomized, double-blind, placebo-controlled, 8-week study evaluating pediatric subjects 5 to 17 years of age with irritability associated with autism spectrum disorder (ASD), treatment with cariprazine was associated with improvement in symptoms. The treatment effect observed on the primary endpoint, the Aberrant Behavior Checklist-Irritability (ABC-I), was statistically significantly superior to placebo. However, in order to be granted an indication, substantial evidence of cariprazine's effectiveness for the treatment of irritability associated with ASD would require two positive adequate and well-controlled studies. Therefore, Study M21-465 does not, alone, support substantial evidence of effectiveness, and

the Applicant is not seeking an indication for the treatment of irritability associated with ASD.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In supplemental new drug applications (sNDAs) 015 and 016, the Applicant is proposing cariprazine for the treatment of schizophrenia in patients ages 13 to 17 years and acute manic or mixed episodes associated with bipolar disorder in patients ages 10 to 17 years. Cariprazine is an atypical antipsychotic medication that is approved for adult patients for the treatment, including maintenance, of schizophrenia; acute treatment of manic or mixed episodes associated with bipolar I disorder; treatment of depressive episodes associated with bipolar I disorder; and as adjunctive therapy to antidepressants for the treatment of major depressive disorder. Capsule dosage strengths of 1.5, 3, 4.5, and 6 mg are currently approved for oral ingestion once daily. New proposed dosage strengths of 0.5 and 0.75 mg (sNDA 014) are needed to achieve the pediatric dosing; these new strengths will also allow simplification of dosage and administration language related to drug-drug interactions.

Substantial evidence of effectiveness for the treatment of schizophrenia in pediatric patients 13 through 17 years of age and acute manic or mixed episodes associated with bipolar I disorder in pediatric patients 10 through 17 years of age is based upon extrapolation from cariprazine's known efficacy in the treatment of adult schizophrenia and bipolar I disorder. Extrapolation is supported by population PK report RD241815 and two PK studies: (1) Study RGH-PK-18, a two-part, dose-escalation, multiple dose study in pediatric subjects ages 13 to 17 years with schizophrenia and ages 10 to 17 years with bipolar I disorder, and (2) Study RGH-188-201, an open-label, multiple dose study in subjects ages 13 to 17 years and adults with schizophrenia, schizoaffective disorder, or schizophreniform disorder.

Additionally, in sNDA 017, to fulfill a Pediatric Written Request (PWR), the Applicant submitted the report for Study M21-465, a randomized, double-blind, placebo-controlled, 8-week study evaluating 161 pediatric subjects 5 to 17 years of age with irritability associated with ASD. Subjects received cariprazine oral capsule or solution 0.75 to 3.0 mg daily (Note: the oral solution is not an approved formulation). The treatment effect observed on the primary endpoint, the ABC-I, was statistically significantly superior to placebo. However, in order to be granted an indication, substantial evidence of cariprazine's effectiveness for the treatment of irritability associated with ASD would require two adequate and well-controlled studies. Therefore, Study M21-465 on its own cannot provide substantial evidence of effectiveness, and the Applicant is not currently seeking an indication for the treatment of irritability associated with ASD.

The safety profile of cariprazine in pediatric patients is generally similar to that in adult patients (with one exception regarding somnolence noted below), and there are no new safety issues that preclude the approval of these sNDAs. Study 3070-301-001 is an ongoing 52-week, multicenter, open-label, study of flexible doses of cariprazine oral capsule or solution 0.75 mg to 4.5 mg. To date, 306 pediatric subjects ages 13 to 17 years with schizophrenia, 10 to 17 years with bipolar I disorder, or 5 to 17 years with ASD have received at least one dose of study drug. The safety findings from Study 3070-301-001 are consistent with the known safety profile of cariprazine including risks for metabolic changes

and weight gain, extrapyramidal symptoms (EPS), suicidal ideation and behavior (SI/B), and cataracts– these are adequately described in current labeling. The safety findings from Study M21-465 are also generally consistent with the known safety profile of cariprazine as described in current labeling. However, the reported rate of somnolence was higher in pediatric subjects with ASD compared to adult subjects in the cariprazine pivotal studies. Safety data from this study will be included in Section 8.4.

Based upon review of the studies submitted, the Agency has concluded that the benefits of cariprazine outweigh its risks for the treatment of schizophrenia in patients ages 13 to 17 years and acute manic or mixed episodes associated with bipolar disorder in patients ages 10 to 17 years. Additionally, the submitted clinical studies, M21-465 and 3070-301-001, and PK studies, RGH-PK-18 and 2000-103-009, fulfill the pediatric written request; Study 3070-301-001 also fulfills Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) 2947-6.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Schizophrenia • Schizophrenia is a severe and persistent psychotic disorder characterized by disordered perception, thought, and behavior. Symptoms include positive symptoms (such as delusions or hallucinations); disorganized thought, speech, or behavior; negative symptoms (such as diminished emotional expression or avolition); and cognitive impairments (such as impairment in executive function, attention, or memory). Individuals with schizophrenia experience significant impairments in social and occupational functioning. • Onset of illness is typically between late adolescence and the third decade of life. • Diagnosis is clinical and based upon Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria. • Within the pediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents, and the symptoms in this age	• Schizophrenia and bipolar I disorder are serious and associated with significant disability. • Onset of illness may be in adolescence for both conditions. • Diagnostic criteria for both schizophrenia and bipolar I disorder are the same for the pediatric and adult populations. • ASD is a neuro-developmental disorder with symptoms present in early childhood. • ASD is heterogenous in presentation and outcome. Secondary behavioral features such as irritability can cause significant impairment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	group are generally similar to those in adults. The diagnostic criteria for schizophrenia are the same for the two populations. Bipolar I Disorder • Bipolar I disorder is a severe and persistent mental illness characterized by episode(s) of mania and, in the majority of cases, episodes of major depression. Functional impairment is significant. • The mean age at onset for the first mood episode is approximately 18 years, but the lower end of the age range for bipolar disorder is not clear. • Diagnosis is clinical and based upon DSM-5 criteria. • Bipolar disorder in the 10- to 17-year-old population is thought to be phenomenologically similar to bipolar disorder in adults, and diagnostic criteria for mania are the same for the pediatric and adult populations. Autism Spectrum Disorder • ASD is a neuro-developmental disorder characterized by social impairments and restricted, repetitive patterns of behavior, interests, or activities. There are many secondary behavioral features that are commonly associated with ASD, including irritability, which can be profoundly impairing and burdensome. Symptom presentation and outcome are heterogenous. • Symptoms are present from early childhood, often recognized in	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	children as young as 2 years old. • Diagnosis is clinical and based upon DSM-5 criteria.	
Current Treatment Options	• Practice guidelines for the treatment of schizophrenia recommend that antipsychotics should be initiated as soon as possible. Numerous atypical or second-generation antipsychotics (SGAs) are approved for the treatment of pediatric schizophrenia. • SGAs are part of various treatment guidelines for bipolar I disorder. Mood stabilizers and numerous SGAs are approved for the treatment of pediatric bipolar I disorder. • There are currently no medications approved for the treatment of the core features of ASD. The SGAs risperidone and aripiprazole are indicated for the treatment of irritability associated with ASD in patients 5 to 17 years of age. • Adverse reactions from antipsychotics vary between drugs but may include weight gain and metabolic effects, EPS, increased prolactin, sedation, and QT prolongation.	• Antipsychotics reduce the severity of symptoms of schizophrenia and manic and mixed episodes in bipolar I disorder. • Risperidone and aripiprazole improve irritability associated with ASD.
Benefit	• Extrapolation of the effectiveness of cariprazine for the treatment of schizophrenia in pediatric patients 13 through 17 years of age and acute manic or mixed episodes associated with bipolar I disorder in pediatric patients 10 through 17 years of age is supported by population PK report RD241815 and two PK studies: (1) Study RGH-PK-18, a two-part, dose-escalation, multiple dose study in pediatric subjects ages 13 to 17 years with schizophrenia and ages 10 to 17 years with bipolar I disorder, and (2) Study RGH-188-201, an open-	• Substantial evidence of effectiveness for the treatment of schizophrenia in pediatric patients 13 through 17 years of age and acute manic or mixed episodes associated with bipolar I disorder in pediatric patients 10 through 17 years of age is based upon extrapolation from cariprazine's known efficacy in the treatment of adult

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	label, multiple dose study in subjects ages 13 to 17 years and adults with schizophrenia, schizoaffective disorder, or schizophreniform disorder. • To fulfill a pediatric written request, the Applicant conducted Study M21-465, a randomized, double-blind, placebo-controlled, 8-week study evaluating 161 pediatric subjects 5 to 17 years of age with irritability associated with ASD. Subjects received cariprazine oral capsule or solution 0.75 to 3.0 mg daily. The study met its primary objective. Cariprazine demonstrated a statistically significant reduction from baseline in ABC-I subscale score at Week 8 compared to placebo. The least squares (LS) mean difference (SE) was -3.7 (1.56) (95% CI: -6.75, -0.57; p=0.0205).	schizophrenia and bipolar I disorder. • Study M21-465 is an adequate and well-controlled investigation in subjects ages 5 to 17 years with irritability associated with ASD. It demonstrated cariprazine separation from placebo on the ABC-I primary efficacy endpoint. However, Study M21-465 does not, alone, support an indication – substantial evidence of cariprazine's effectiveness for the treatment of irritability associated with ASD would require two adequate and well-controlled studies. The Applicant is not seeking this indication.
Risk and Risk Management	• The pediatric safety database included 520 subjects with schizophrenia, bipolar I disorder, or ASD who were exposed to cariprazine. • In Study 3070-301-001, 180 subjects were treated for >26 weeks. This meets the minimum requirement within the pediatric written request of a combined total of at least 100 patients with schizophrenia, ASD, or bipolar disorder exposed for at least 6 months to characterize the long-term safety of cariprazine. • In Study M21-45, the reported rate of somnolence was higher in pediatric subjects with ASD (18%) compared to adult subjects in the cariprazine pivotal studies (5 to 10%). • In both Studies M21-465 and 3070-301-001, increase in weight was	• The pediatric safety database for cariprazine in subjects with schizophrenia, bipolar I disorder, and ASD is adequate. • The reported rate of somnolence was higher in pediatric subjects with ASD compared to adult subjects in the cariprazine pivotal studies. This issue will be described in labeling Section 8.4. • Otherwise, the pediatric safety findings from Studies M21-465 and 3070-301-001 are generally consistent with the known safety profile of cariprazine, including the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	particularly marked in subjects with ASD. Metabolic changes, including increase in weight, are an already known antipsychotic drug class effect. Furthermore, the adolescent population has been identified as particularly at risk for SGA-induced weight gain and dyslipidemia. • Otherwise, in pediatric subjects, cariprazine adverse events and investigations (i.e., laboratory assessments, vital signs, and assessments for SI/B and EPS) were largely similar to those of adult subjects.	risks for metabolic changes and weight gain, as described in current labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8
		X	Observer reported outcome (ObsRO)	Section 8
		X	Clinician reported outcome (ClinRO)	Section 8
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Schizophrenia

Schizophrenia is a chronic and debilitating illness that has an estimated lifetime adult prevalence of 1%.[1] Onset of illness is typically between late adolescence and the third decade of life.[2] Symptoms include disorganized thought, speech, or behavior and cognitive impairment along with positive (e.g., hallucinations and delusions) and negative (e.g., social withdrawal and lack of emotion, energy, and motivation) symptoms. Diagnosis is made clinically, based on the DSM-5 criteria (see Table 1). According to the DSM-5, the diagnostic criteria for schizophrenia are the same for the pediatric and adult populations. Within the pediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents, and the symptoms in this age group are generally similar to those in adults. Schizophrenia has also been described in children, but it is thought to be rare.

[1] Association, A.P., Diagnostic and statistical manual of mental disorders (DSM-5). 2013: American Psych Pub.
[2] McClellan, J., Stock, S., and the American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (QI). Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia. J Am Acad Child Adolesc Psychiatry, 2013. 52(9):976-990.

Table 1: Diagnostic Criteria for Schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
    1. Delusions
    2. Hallucinations
    3. Disorganized speech (e.g., frequent derailment or incoherence)
    4. Grossly disorganized or catatonic behavior
    5. Negative symptoms (i.e., diminished emotional expression or avolition)
B. For a significant period of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Source: Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

Bipolar I Disorder

Bipolar I disorder is a severe and persistent mental illness affecting approximately 1% of the population.[3] The mean age at onset for the first mood episode is approximately 18 years; however, the lower end of the age range for bipolar disorder is not clear. This disease is characterized by episodic mania and, in the majority of cases, episodes of major depression. The diagnostic manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes. Diagnosis is based on the DSM-5 criteria (see Table 2). According to the DSM-5, the diagnostic criteria for mania are the same for the pediatric and adult populations. Bipolar disorder below the age of 10 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the 10- to 17-year-old population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults.

[3] Merikangas, K.R., et al., Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psych, 2007. 64(5):543-52.

Table 2: Diagnostic Criteria for Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
B. During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
    1. Inflated self-esteem or grandiosity
    2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
    3. More talkative than usual or pressure to keep talking
    4. Flight of ideas or subjective experience that thoughts are racing
    5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
    6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless, non-goal-directed activity)
    7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or to another medical condition.

Source: Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

Autism Spectrum Disorder

ASD is a neuro-developmental disorder characterized by (1) impairments in social communication and interaction and (2) restricted, repetitive patterns of behavior, interests, or activities. There are many secondary behavioral features that are commonly associated with ASD. These include irritability and tantrums, attention and/or hyperactivity disorders, self-injury, odd responses to sensory stimuli, lack of fear or excessive fearfulness, and many others. Many of these can profoundly impair functioning and cause substantial individual and family burden. The U.S. Centers for Disease Control and Prevention estimates that an average of 1 in 31 children in the United States has ASD.[4] The risk is three times higher in males than females. Diagnosis is made clinically (see Table 3). Symptoms are present from early childhood, often recognized in children as young as 2-years-old. Individuals with ASD vary substantially in terms of symptom presentation and outcome.

[4] CDC, 2025, Data and Statistics on Autism Spectrum Disorder, accessed October 10, 2025, https://www.cdc.gov/autism/data-research/index.html

Table 3: Diagnostic Criteria for ASD

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):
    1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
    2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
    3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):
    1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
    2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
    3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
    4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Source: Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

2.2. Analysis of Current Treatment Options

Schizophrenia

The American Psychiatric Association (APA) practice guideline for the treatment of schizophrenia recommends that antipsychotics should be initiated as soon as possible in an acute schizophrenia exacerbation and continued through the stable maintenance phase of the illness to reduce the risk of relapse.[5] Approved pharmacological treatments for pediatric

[5] Keepers, G.A., et al., The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Am Journal of Psychiatry, 2020. 177(9).

schizophrenia are the second-generation antipsychotics aripiprazole, olanzapine, quetiapine, risperidone, lurasidone, and paliperidone. The mechanism by which antipsychotics improve psychotic symptoms is not completely understood but may involve antagonism of dopamine D2 receptors and/or serotonin 5-HT2A receptors.

Some of the relevant class-based safety issues for antipsychotics include EPS, tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, weight gain, metabolic changes, seizures, blood dyscrasias, and an increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis.

Although there are a number of approved treatments for schizophrenia, an individual patient may require several trials with different antipsychotic drugs before an effective and reasonably tolerated treatment is identified. Additionally, most available medications predominantly affect positive symptoms but do not appear to meaningfully impact negative symptoms or cognitive impairment.

Bipolar I Disorder

In terms of pharmacological treatment for pediatric bipolar I disorder, the mood stabilizer mainstays of lithium and the antiepileptic valproate have been joined by multiple SGAs: aripiprazole, olanzapine, quetiapine, risperidone, and asenapine. As with schizophrenia, although there are a number of approved treatments for bipolar I disorder, individual patient response cannot be predicted. For an individual patient, several trials of different products may be required before an effective and tolerable treatment can be identified.

Table 4: Treatments for Pediatric Bipolar I Disorder

Lithium	Manic and maintenance treatment in patients 12 years and older
Valproate	Manic or mixed episodes in patients 10 years and older
Aripiprazole	Manic or mixed episodes in patients 10 years and older
Olanzapine	Manic or mixed episodes and maintenance treatment in patients 13 years and older
Quetiapine	Manic episodes in patients 10 years and older
Risperidone	Manic or mixed episodes in patients 10 years and older
Asenapine	Manic or mixed episodes in patients 10 years and older
Lurasidone	Bipolar depression in patients 10 years and older

Source: Clinical reviewer-generated

Autism Spectrum Disorder

There are currently no medications specifically approved in the United States for the treatment of the core features of ASD. The second-generation antipsychotics risperidone and aripiprazole are indicated for the treatment of irritability associated with autistic disorder in patients 5 to 17 years of age (6 to 17 years for aripiprazole, and 5 to 16 years for risperidone); this indication includes symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Cariprazine is marketed in the United States and in other countries. FDA approved cariprazine for the following indications in adults:

- September 17, 2015: Schizophrenia; mixed or manic episodes associated with bipolar I disorder
- May 24, 2019: Depressive episodes associated with bipolar I disorder (bipolar depression).

3.2. Summary of Presubmission/Submission Regulatory Activity

- Cariprazine was approved in adult patients for the treatment of schizophrenia (including maintenance treatment) in 2015 and 2017, acute manic or mixed episodes associated with bipolar I disorder in 2015, depressive episodes associated with bipolar I disorder in 2019, and as adjunctive therapy to antidepressants for major depressive disorder in 2022. The following PREA-related PMRs were issued at the times of approval of the respective adult patient indications:

    - 2947-3: PK, safety, and tolerability study in pediatric patients ages 10 to 17 years with a diagnosis of schizophrenia or bipolar disorder- fulfilled on March 19, 2021

    - 2947-4 and 2947-5: efficacy and safety studies in pediatric patients ages 13 to 17 years with schizophrenia and in pediatric patients ages 10 to 17 years with manic or mixed episodes associated with bipolar I disorder – released on September 11, 2020, based upon a General Advice letter dated January 13, 2020, which informed the Applicant that the Division had determined that it is acceptable to extrapolate the effectiveness of atypical antipsychotic drugs approved for the treatment of schizophrenia in adults to pediatric patients 13 years of age and older and the effectiveness of drugs approved for the treatment of bipolar I disorder in adults to pediatric patients 10 years of age and older

    - 2947-6: long-term, open-label safety study in pediatric patients ages 13 to 17 years with schizophrenia and 10 to 17 years with manic or mixed episodes associated with bipolar I disorder

    - 3619-1: efficacy and safety study in pediatric patients ages 10 to 17 years with acute bipolar depression

- The Division issued an initial PWR on February 3, 2017. Subsequently, four amendments to the PWR were issued on November 30, 2017, June 15, 2018, September 11, 2020, and December 6, 2024. The final PWR, Amendment 4, described the following studies:

    - Clinical Study 1: 12-week PK study in patients ages 5 to 12 years and 13 to 17 years with diagnoses of schizophrenia, bipolar I disorder, or ASD

    - Clinical Study 2: efficacy and safety study in patients ages 5 to 17 yrs with irritability associated w ASD

    - Clinical Study 3: pediatric long-term safety study in pediatric patients with schizophrenia, bipolar I disorder, or ASD

- In a Type C Meeting on January 16, 2020, the Division acknowledged that the PWR listed one efficacy and safety study to fulfill the requirement for irritability associated with ASD. This was an oversight. Although one study would satisfy the PWR for irritability in autism as currently written to obtain exclusivity, one study would not be sufficient for demonstrating substantial evidence of effectiveness. To be granted an indication, the Applicant would need to provide substantial evidence of cariprazine's effectiveness for the treatment of irritability associated with ASD; this would require two adequate and well-controlled studies. The data from the one study would be described in Section 8.4 of labeling (Pediatric Safety), but no claim of efficacy for treatment of irritability in ASD would be listed, nor would the study be cited in Section 14 of the label (Clinical Trials). Furthermore, the Division clarified that the indications of irritability in ASD and the core symptoms of ASD are independent from each other and should be studied separately because of differences in the existing regulatory paths. For consideration of approval of the novel indication of treatment of core symptoms of ASD, the Applicant would need two adequate and well-controlled studies, including the full age range of clinical concern (i.e., ages 3 to 17) and using an agreed-upon instrument as the primary endpoint in both studies.

- In a Type C Meeting- Written Responses Only on March 19, 2023, the Applicant described issues recruiting pediatric subjects with ASD for Study M21-465. The Division was concerned whether (b) (4) (b) (4) as proposed by the Applicant. Without agreement on this point , discussion of the applicability of the Applicant's proposed (b) (4) was premature.

- A Type D Meeting- Written Responses Only on November 3, 2023, was focused on nonclinical data regarding cataracts in dogs coupled with nonspecific blurred vision reported in 2 to 3% of patients that led to a description of cataracts in the cariprazine label and ocular monitoring requirements for ongoing trials. DP accepted the Applicant's proposals to lower the percentage of patients who received ocular monitoring in long-term

Study 3070-301- 001 (b) (4) to 75% and to (b) (4) in studies ≤8 weeks (i.e., (b) (4), M21-465).

- A Type B pre-sNDA Preliminary Comments on March 11, 2025, was focused on the planned sNDA submission to provide two new lower strengths and lower the indication age ranges for schizophrenia and bipolar I disorder to fulfil the remaining PREA PMR and PWR studies. The Division agreed with the following: (1) that the proposed scope of the safety information and general content appeared reasonable, (2) that the data submitted to fulfill PWR Clinical Study 3 would likely also suffice to fulfill PMR 2947-6 although this would be a matter of review, and (3) that on face, the proposed modeling and simulation strategy for the dose selection in pediatric patients with schizophrenia (13 to 17 years) and bipolar I disorder (10 to 17 years) appeared reasonable but would be a matter of review.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical

4.1. Office of Scientific Investigations (OSI)

Not applicable; as there were no major efficacy studies reviewed for this application, the primary team did not require OSI consultation.

4.2. Product Quality

Supplement 014 provides for additional capsule strengths of 0.5 mg and 0.75 mg, and addresses FDA concerns regarding (b) (4) . See Office of Pharmaceutical Quality review dated November 25, 2025, for details.

4.3. Clinical Microbiology

Not applicable; the drug does not require microbiological testing.

4.4. Devices and Companion Diagnostic Issues

Not applicable; no devices were involved in the reviewed indications.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted two sNDAs, S-015 and S-016, to expand their approved age range for the treatment of schizophrenia to pediatric patients 13 through 17 years of age and acute manic or mixed episodes associated with bipolar I disorder to pediatric patients 10 through 17 years of age. The Applicant submitted sNDA S-017 to satisfy a pediatric written request, to study the effectiveness of cariprazine for the treatment of irritability associated with ASD in pediatric patients 5 through 17 years of age. No nonclinical data were submitted in support of sNDA S-014.

To support the safety of cariprazine for treatment of pediatric patients, the Applicant conducted two nonclinical studies: A 9-week toxicity study in the juvenile rat and a 26-week toxicity study in the juvenile dog with final study reports (study nos. (b) (4) [ref. no. RGH-TX-53] and (b) (4) [ref. no. RGH-TX-51]) submitted to the NDA on April 3, 2018. Data from these juvenile animal toxicity studies, together with nonclinical data used to support approval of cariprazine in adult patients, are adequate to support approval of cariprazine for the treatment of the approved indications in pediatric patients in the expanded age range. For a detailed review of the studies conducted in juvenile animals see the nonclinical review by Dr. Darren Fegley signed into DARRTS on February 11, 2019 (NDA 204370). Refer to the nonclinical review by Dr. Elzbieta Chalecka-Franaszek under NDA 204370 for a detailed review of nonclinical studies conducted to support the original approval of cariprazine in adult patients. The following is a summary of the clinically relevant findings from nonclinical cariprazine studies, including the two studies conducted in juvenile animals. Most of the information is included in the currently approved label for cariprazine, except for the juvenile animal studies, which will be added to the label upon approval of the current supplements.

Although the exact mechanism of action of cariprazine in psychiatric disorders is not fully understood it is thought to be mediated through a combination of partial agonist activity at central nervous system dopamine D_3, D_2, and serotonin 5-HT_{1A} receptors and antagonist activity at serotonin 5-HT_{2B} and 5-HT_{2A} receptors. Cariprazine has little to no affinity for the following targets with known developmental toxicology liabilities: GABA or NMDA receptors, or calcium, potassium, or sodium channels.

Cariprazine is extensively metabolized in rats, dogs, and humans. Studies conducted in rats and dogs demonstrated qualitative, but not quantitative, similarity in the metabolic profile of cariprazine in animals and humans. Two metabolites of cariprazine, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), formed in humans and nonclinical species, and have pharmacological activity similar to cariprazine. DDCAR is the major human metabolite, representing ~63% to 70% of total circulating drug-related material at steady state. Adequate levels of DDCAR have been achieved in nonclinical studies in dogs but not in rats. Exposure to

cariprazine, DCAR, and DDCAR are quantitatively similar in juvenile and adult rats and dogs indicating limited potential for significant differences in PK profile in children and adolescents relative to adults.

Adult toxicology studies were conducted in Wistar rats (oral gavage), Beagle dogs (oral capsule), and Cynomolgus monkeys (oral capsule). Juvenile toxicology studies were conducted in Wistar rats (oral gavage) and Beagle dogs (oral capsule). In the 9-week juvenile rat toxicity study with an 8-week recovery period (study no. (b) (4), ref. no. RGH-TX-53), juvenile rats were administered cariprazine at doses of 0, 1, 3, and 10 mg/kg/day from postnatal day 28 to 90 by oral gavage. In the 26-week juvenile dog toxicology study with a 4-week recovery period (study no. (b) (4), ref. no. RGH-TX-51), juvenile dogs were administered cariprazine at doses of 1, 3, and 6 mg/kg/day from postnatal week 14 to 40 by oral gavage. Administration of cariprazine did not induce mortality in adult or juvenile animals at clinically relevant exposures; however, cariprazine significantly decreased body weight and body weight gain in both adult and juvenile animals at similar exposures. Although food consumption was generally reduced, there was not a consistent correlation between decreased body weight and food consumption for all studies indicating body weight effects were unlikely to be due solely to reduced food intake. Target organs of toxicity identified in both adult and juvenile animals include the central nervous system (CNS), eye, adrenal cortex, lungs, and reproductive organs. The sciatic nerve was a target organ of toxicity in adult but not juvenile rats. In addition, a significant decrease in plasma cholesterol and triglycerides levels was observed in adult rats, dogs, and mice. Decreased cholesterol levels was also observed in juvenile dogs, however, no similar effect on cholesterol was reported for juvenile rats.

Clinical signs characteristic of CNS depression and consistent with the known pharmacology of cariprazine were observed in adult and juvenile dogs and adult rats; however, in general, the signs became less severe as dosing progressed indicating the development of tolerance. Sensitivity to the adverse CNS effects were relatively similar in adult and juvenile animals, although juvenile dogs appeared to be slightly more sensitive.

The eye is a target organ of cariprazine toxicity in rats and dogs. Cariprazine caused adverse effects on eye structure in the 13-week and 1-year toxicology studies in adult dogs (cataracts, cystic degeneration, and detachment of the retina), the 26-week toxicology study in juvenile dogs (cataracts), the 28-day toxicology study in adult rats (eye opacity), and the 2-year carcinogenicity study in adult rats (retinal degeneration/atrophy). Similar eye findings were not observed in the rat juvenile toxicology study. Adverse effects on the structure of the eye are of major concern from a clinical perspective and are included in the drug label.

Phospholipidosis was observed in the lungs of juvenile and adult rats, adult dogs, and in the adrenal glands of juvenile and adult dogs. This finding had no impact on viability in adult or juvenile animals; however, it was accompanied by inflammation in the lungs of adult animals. Signs of chronic inflammation were not observed in the lungs of juvenile animals. Phospholipidosis and inflammation were observed in the lungs of adult rats and dogs with a low

margin of safety compared to human clinical exposures based on AUC. In addition, following administration of cariprazine to adult dogs for one year or juvenile dogs for 26-weeks, phospholipidosis and reversible hypertrophy/hyperplasia and vesiculation/vacuolation of the cortical zona fasciculata and zona glomerulosa of the adrenal gland were also observed with a low margin of safety compared to human clinical exposure based on AUC.

In general, the findings in the adult and juvenile animal toxicology studies were similar and juvenile animals do not appear to be significantly more sensitive to cariprazine-related toxicity. However, there are several endpoints that are not measured, or cannot be measured, in general toxicity studies with adult animals, which were evaluated in the juvenile animal studies. In the 9-week juvenile rat toxicology study administration of cariprazine was associated with adverse effects on growth and development. Sexual maturation was delayed in female rats, although this delay may in part be due to decreased body weight. In male rats, cariprazine administration resulted in altered bone geometry and a dose-dependent decrease in bone size with an associated decrease in bone mass. Although bone geometry and size were not affected in female rats, bone mass was similarly decreased. The changes in bone mass were still present following an 8-week recovery phase. Together, the effects on bone growth and development after cariprazine administration to juvenile rats suggest a lower rate of bone consolidation and/or formation and are considered adverse. Although an exact mechanism of action is unknown, it may, in part, be due to hyperprolactinemia resulting in reduced gonadotropin secretion and subsequent effects on growth and development including the decreased bone density. Although altered prolactin levels were not observed in the juvenile rat toxicology study, signs consistent with increased prolactin levels, for example focal decidualization in the uterus and mammary gland hyperplasia, were reported. It should be noted that prolactin levels were measured 15 days and 42 days following dose cessation and not during the dosing period and, therefore, may not have detected cariprazine-related increases if they occurred. Other atypical antipsychotics have been shown to decrease serum testosterone and progesterone levels and produce hypogonadism as well as decreased bone density when administered to juvenile dogs. The adverse effects on growth and development are of clinical relevance in particularly vulnerable populations such as patients with ASD.

In addition to effects on growth and development, cariprazine administration to juvenile rats also produced a significant and persistent increase in ambulatory and fine motor movements, persistent effects on startle habituation (increased maximum startle response and prolonged sensitization phase), and non-persistent adverse effects on performance in the Cincinnati Water Maze. The effects on neurobehavior, particularly learning and memory, although not persistent upon drug cessation, is of clinical relevance in pediatric populations already at risk for significant developmental delays.

Conclusion:
Based on the findings in the 9-week juvenile rat toxicology study, a dose of 10 mg/kg/day was considered adverse with the NOAEL set at 3 mg/kg/day.

Based on the findings in the 26-week juvenile dog toxicology study, a dose of 3 mg/kg/day was considered adverse with the NOAEL set at 1 mg/kg/day.

Table 5. Safety Margins at the Pediatric MRHD (4.5 mg)

Nonclinical				Clinical				
Species	NOAEL mg/kg/day	TAM Exposure		Patient Weight	TAM Exposure		Clinical Safety Margin	
		$C_{max,ss}$ (nM)	AUC_{ss} (nM·hr)		$C_{max,ss}$ (nM)	AUC_{ss} (nM·hr)	C_{max}	AUC
Rat	3	399	2552	< 40 kg	95.8	2083	4.2x	1.2x
				≥ 40 kg	84.5	1846	4.7x	1.4x
Dog	1	543	7116	< 40 kg	95.8	2083	5.7x	3.4x
				≥ 40 kg	84.5	1846	6.4x	3.9x

Source: Reviewer Generated
MRHD: Maximum Recommended Human Dose
TAM: Total Active Moiety (Cariprazine + DCAR+ DDCAR)

Although administration of cariprazine to juvenile animals resulted in adverse effects at clinically relevant exposures, the toxicities are generally in-line with those reported with cariprazine administration to adult animals and similar to findings of other atypical antipsychotics with approved pediatric indications. Therefore, based on the available nonclinical data, cariprazine does not pose a significantly greater risk to pediatric patients relative to adults and compared to other atypical antipsychotics with pediatric indications.

The findings from the 9-week juvenile rat and 26-week juvenile dog toxicology studies will be included in the Prescribing Information (label) under section 8.4.

6 Clinical Pharmacology

6.1. Executive Summary

Cariprazine is available as oral capsules in 1.5 mg, 3 mg, 4.5 mg, and 6 mg strengths. The Applicant recently developed two lower strengths cariprazine oral capsules (0.5 mg and 0.75 mg) to support the pediatric dosing and dose adjustment recommendations for drug-drug interactions (DDI) with strong or moderate CYP3A4 inhibitors.

The Applicant submitted the following efficacy supplements to support the labeling changes proposed in Sections 2 (dosage and administration), 8.4 (pediatric use), and 12.3 (clinical pharmacology) of the United States Prescribing Information (USPI) for VRAYLAR.

- Supplement 14 (S-14) includes the report of physiologically based pharmacokinetic (PBPK) modeling to support dose adjustment recommendations for DDIs with strong or moderate CYP3A4 inhibitors using two new strengths of cariprazine capsules

- S-15 and S-16 include the reports of multiple-dose PK and safety studies (RGH-PK-18 and RGH-188-201), and one long-term safety study (3070-301-001) in pediatric patients 13 to 17 years old with schizophrenia, pediatric patients 10 to 17 years with bipolar I disorder to support extrapolation of efficacy from adults to pediatric patients. (Study 3070-301-001 also enrolled pediatric patients ages 5 to 17 years with autism spectrum disorder.) S-15 is seeking approval for pediatric schizophrenia indication and S-16 is seeking approval for pediatric bipolar I disorder indication.

- S-17 includes the report of one multiple-dose PK and safety study (2000-103-009) and one efficacy study (m21-465) in pediatric patients with ASD 5 to 17 years old

The Applicant also submitted population PK modeling reports (R & D241815 and R&D250109) to characterize the PK of cariprazine in pediatric patients with schizophrenia, bipolar I disorder, and ASD.

Cariprazine is primarily metabolized by CYP3A4; strong or moderate CYP3A4 inhibitors are shown to significantly increase the exposures of total cariprazine (the sum of cariprazine and its two active metabolites, desmethylcariprazine and didesmethylcariprazine) and dose reduction is warranted. Currently, because 1.5 mg is the lowest available strength, the recommended initial dosage regimen of cariprazine when concomitantly administered with strong CYP3A4 inhibitors is 1.5 mg every 3 days and moderate CYP3A4 inhibitor is 1.5 mg every other day. However, less frequent (i.e., every 3 days or every other day) administration of cariprazine is expected to reduce patient adherence. Using previously established physiologically based pharmacokinetic (PBPK) model, the Applicant performed additional PK simulations to support daily dosing of cariprazine for patients taking concomitant strong or moderate CYP3A4 inhibitors. The daily dosing of cariprazine under drug-drug interaction (DDI) scenario is expected to improve patient adherence compared to less frequent dosing.

The Applicant is also seeking to extrapolate the efficacy of cariprazine for the treatment of schizophrenia in adults to pediatric patients 13 to 17 years of age with schizophrenia using the PK matching approach. Similarly, they are following an extrapolation approach to support an indication for the treatment of manic or mixed episodes associated with bipolar I disorder in adults to pediatric patients 10 to 17 years of age with bipolar I disorder. Steady-state exposures after 1.5 to 4.5 mg/day in pediatric patients 13 to 17 years with schizophrenia and steady-state exposures after 3 mg to 4.5 mg/day in pediatric patients 10 to 17 years with bipolar I disorder are within the efficacious exposure range for the corresponding adult patients, respectively.

The Applicant also evaluated PK, safety and tolerability of cariprazine using an unapproved oral solution formulation in pediatric patients aged 5 to 17 years diagnosed with ASD. Exposures of cariprazine in pediatric patients 10 to 12 years of age were similar to that of the adolescents (13 to 17 years of age); however, exposures in patients 5 to 9 years of age were 50% higher than those of the adolescents.

The Office of Clinical Pharmacology (OCP) reviewed the submitted studies and finds the proposed labeling changes to include the pediatric populations and the proposed dosing regimens in the pediatric populations appropriate. OCP recommends the approval of cariprazine for the treatment of schizophrenia in pediatric patients 13 to 17 years and acute treatment of manic or mixed episodes associated with bipolar I disorder in pediatric patients 10 to 17 years. The studies fulfill both the Pediatric Written Request (WR) and Postmarketing Requirement (PMR) 2947-6.

OCP also recommends the approval of dosage adjustment recommendations for cariprazine when concomitantly administered with strong or moderate CYP3A4 inhibitors. The review findings also support the approval of newer strengths of cariprazine, 0.5 and 0.75 mg for both pediatric dosing and dose adjustment recommendations for DDI with strong or moderate CYP3A4 inhibitors.

6.2. Summary of Clinical Pharmacology Assessment

Considering the newly available dose strengths of cariprazine (0.5 mg and 0.75 mg), the Applicant proposed dose adjustment recommendations for drug-drug interaction (DDI) with strong or moderate CYP3A4 inhibitors. The Applicant utilized a previously established PBPK model for cariprazine to perform additional PK simulations to support daily dosing of cariprazine for patients who use concomitant strong or moderate CYP3A4 inhibitors. PBPK simulations support the initial dosing regimen of cariprazine, 0.5 mg once daily, as a suitable alternative to 1.5 mg every 3 days when a strong CYP3A4 inhibitor is concomitantly administered. Similarly, the initial dosing regimen 0.75 mg once daily is a suitable alternative to 1.5 mg every other day when a moderate CYP3A4 inhibitor is concomitantly used.

The clinical pharmacology studies supported the extrapolation of efficacy from adult patients with schizophrenia or bipolar I disorder to pediatric patients 13 to 17 years old with schizophrenia or pediatric patients 10 to 17 years old with bipolar I disorder, respectively. Cariprazine (CAR) and its active metabolites desmethylcariprazine (DCAR), didesmethylcariprazine (DDCAR) are pharmacologically equipotent; therefore, total CAR was used for PK analysis. Major findings are listed below:

- Study RGH-188-201 compared multiple-dose exposures of cariprazine in adolescents with schizophrenia, schizoaffective and schizophreniform disorders to the adults. The findings from this study showed that:

    - at 1.5 or 3 mg/day, the geometric mean ratios (GMRs) of Cmax, AUCtau and Ctrough for total CAR were comparable between pediatric patients (13-to-14-year age group and 15-to-17-year age group) and adults.

- at 6 mg/day, the GMRs of Cmax, AUCtau and Ctrough for total CAR were 1.6-fold, 1.6-fold and 2.1-fold higher, respectively, in the pediatric patients 13 to <15 years, 1.3-fold, 1.3-fold, and 1.7-fold higher, respectively, in the pediatric patients 15 to 17 years, compared to those observed in adults.

- Study RGH-PK-18 evaluated PK, safety, and tolerability of cariprazine in pediatric patients with schizophrenia aged 13 to 17 years, or bipolar I disorder aged 10 to 17 years. Review of this study (archived on 1/8/2021) also showed that PK parameters observed for total CAR in pediatric patients 10 to 12 years of age and 13 to 17 years of age are comparable between doses of 1.5 to 4.5 mg/day. When compared to model-derived adult PK data, the average concentration for total CAR in pediatric patients were comparable to adult levels at the same dose levels.

- Study 2000-103-009 evaluated PK, safety, and tolerability of cariprazine in pediatric participants with ASD aged 5 to 17 years using an unapproved oral solution formulation of cariprazine. Review of this study showed that Cmax,ss and AUCtau,ss of total CAR were comparable in patients 10 to 12 years of age and adolescents 13 to 17 years of age. Cmax,ss and AUCtau,ss of total CAR in patients 5 to 9 years of age were approximately 1.5-fold higher, compared to those observed in adolescents.

- Population PK report RD241815 characterized the PK of cariprazine in pediatric subjects with schizophrenia or bipolar I disorder, and estimated the drug exposures in pediatric subjects for the proposed dosing regimen. The report concluded that doses of 1.5 to 4.5 mg/day simulated in adolescent patients 13 to 17 years of age yielded steady-state exposures that are within the efficacious exposure range simulated in adult patients with schizophrenia at 1.5 to 6 mg per day. Doses of 3 mg to 4.5 mg/day for pediatric patients 10 to 12 years of age and adolescent patients yielded simulated steady-state exposures within the efficacious exposure range in adult patients with bipolar mania at 3 mg to 6 mg per day.

6.2.1. General Dosing and Therapeutic Individualization

Recommended Dosage in Schizophrenia

Pediatric Patients (13 to 17 years of age)

The starting dosage of VRAYLAR is 0.5 mg orally once daily. The recommended dosage range is 1.5 mg to 4.5 mg orally once daily. Increase the dosage to 1.5 mg orally once daily on Day 3. Depending upon clinical response and tolerability, the dosage may be increased to 3 mg orally once daily starting on Day 5, and to 4.5 mg orally once daily starting on Day 8. The maximum recommended dosage is 4.5 mg orally once daily.

Recommended Dosage in Manic or Mixed Episodes Associated with Bipolar I Disorder

Pediatric Patients (10 to 17 years of age)

The starting dosage of VRAYLAR is 0.5 mg orally once daily. The recommended dosage is 3 mg or 4.5 mg orally once daily. Increase the dosage to 1.5 mg orally once daily on Day 3 and to 3 mg orally once daily on Day 5. Depending upon clinical response and tolerability, the dosage may be increased to 4.5 mg orally once daily starting on Day 8. The maximum recommended dosage is 4.5 mg orally once daily.

Dosage Modifications for CYP3A4 Inhibitors and Inducers

Initiating VRAYLAR While Taking a Strong or Moderate CYP3A4 Inhibitor

Dosage modifications for the starting dosage of VRAYLAR in adult patients taking a strong or moderate CYP3A4 inhibitor are presented in the table below:

Dosage Modifications for the Starting Dosage of VRAYLAR in Adult Patients Taking a Strong or Moderate CYP3A4 Inhibitor

Adult Patients	**VRAYLAR Starting Dosage**	
	When Taking a Strong CYP3A4 Inhibitor	**When Taking a Moderate CYP3A4 Inhibitor**
Schizophrenia Bipolar Mania	Start at 0.5 mg orally once daily; increase to 0.75 mg orally once daily, if needed*	Start at 0.75 mg orally once daily; increase to 1.5 mg orally daily, if needed*
Bipolar Depression Adjunctive therapy for treatment of MDD	0.5 mg orally once daily	0.75 mg orally once daily

*Depending upon clinical response and tolerability.

VRAYLAR is not recommended in pediatric patients who are starting a strong or moderate CYP3A4 Inhibitor.

Initiating a Strong or Moderate CYP3A4 Inhibitor While Taking a Stable Dosage of VRAYLAR

Dosage recommendations for adult and pediatric patients initiating a strong or moderate CYP3A4 inhibitor while on a stable dose of VRAYLAR (see Table below):

Dosage Modifications for VRAYLAR When Initiating a Strong or Moderate CYP3A4 Inhibitor and While Taking a Stable Dosage of VRAYLAR in Adult and Pediatric Patients

Currently on VRAYLAR Dosage	**VRAYLAR Dosage When Initiating a Strong CYP3A4 Inhibitor**	**VRAYLAR Dosage When Initiating a Moderate CYP3A4 Inhibitor**

1.5 mg or 3 mg once daily	0.5 mg orally once daily	0.75 mg orally once daily
4.5 mg or 6 mg once daily	0.75 mg orally once daily	1.5 mg orally once daily

When the strong or moderate CYP3A4 inhibitor is discontinued, the VRAYLAR dosage may need to be increased based on clinical response and tolerability [see Drug Interactions (7)].

Refer to the clinical pharmacology review for the original NDA204370 documented on 9/16/2015 for details.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Is there a PK Similarity between Pediatric Patients with Schizophrenia 13 to 17 years old or Pediatric Patients with Manic or Mixed Episodes with Bipolar I Disorder 10 to 17 years old?

Yes. The PK of total cariprazine (CAR) following administration of 1.5 mg to 4.5 mg per day in pediatric patients 13 to 17 years old with schizophrenia and pediatric patients 10 to 17 years with bipolar I disorder are similar to those observed with 1.5 mg to 6 mg/day in adults with schizophrenia and adults with bipolar I disorder, respectively.

Study RGH-188-201 compared PK of cariprazine in pediatric patients 13 to 17 years with adult patients at 1.5 mg, 3 mg, and 6 mg once daily for 4 weeks. At doses between 1.5 to 3 mg/day, geometric mean of total CAR for AUCtau, Cmax and Cmin were comparable between pediatric patients 13 to 17 years with schizophrenia and adults (Table 6). The geometric mean ratios (GMRs) were close to unity. However, at 6 mg/day, the GMRs of total CAR for AUCtau and Cmax were approximately 60% higher in the pediatric patients 13 to <15 years and 34% higher in the pediatric patients 15 to 17 years compared to that in adults. The Ctrough of total cariprazine was 2.1-fold in the pediatric patients 13 to <15 years and 1.7-fold in the pediatric patients 15 to 17 years, compared to that in adults (Table 7).

Table 6. Geometric Mean Observed PK Parameters for Total Cariprazine At 1.5 mg/day, 3 mg/day and 6 mg/day By Age Group in Study RGH-188-201 (PK Population)

Dose	PK parameter	Age Group	n	Geometric Mean	Geo CV%
1.5 mg/day	AUCtau (h*nmol/L)	13 to 14 yrs	6	588	36.7
		15 to 17 yrs	6	634	44.8
		18 to 40 yrs	6	618	29.6
	Cmax (nmol/L)	13 to 14 yrs	6	28.8	36.5
		15 to 17 yrs	6	30.8	42.9
		18 to 40 yrs	6	28.8	31.3
	Cmin (nmol/L)	13 to 14 yrs	6	18.7	50.3
		15 to 17 yrs	6	21.4	54.6
		18 to 40 yrs	6	19.5	36.5
3.0 mg/day	AUCtau (h*nmol/L)	13 to 14 yrs	9	998	77.7
		15 to 17 yrs	8	892	258
		18 to 40 yrs	8	930	84.8

Dose	PK parameter	Age Group	n	Geometric Mean	Geo CV%
	Cmax (nmol/L)	13 to 14 yrs	9	49.8	70.6
		15 to 17 yrs	8	42.3	250
		18 to 40 yrs	8	44.1	81.4
	Cmin (nmol/L)	13 to 14 yrs	9	28.1	179
		15 to 17 yrs	8	31.7	231
		18 to 40 yrs	8	24.8	297
6.0 mg/day	AUCtau (h*nmol/L)	13 to 14 yrs	6	2710	44.0
		15 to 17 yrs	6	2279	54.3
		18 to 40 yrs	6	1703	85.7
	Cmax (nmol/L)	13 to 14 yrs	6	133	46.3
		15 to 17 yrs	6	112	48.3
		18 to 40 yrs	6	82.5	82.5
	Cmin (nmol/L)	13 to 14 yrs	6	92.2	44.4
		15 to 17 yrs	6	75.9	65.3
		18 to 40 yrs	6	44.7	234

A: 13 to <15 years of age; B: 15 to <18 years of age, C: 18 to 40 years of age; AUCtau: area under the curve; Cmax: peak plasma concentration; Cmin: minimum plasma concentration; Geo CV%: geometric mean co-efficient of variation %
Source: Reviewer's analysis

Table 7. Geometric means ratios for PK Parameters of Total Cariprazine at 1.5 mg/day, 3 mg/day and 6 mg/day, by age group, in Study RGH-188-201 (PK population)

1.5 mg/day			
Analyte	**PK parameter**	**Comparison**	**Geometric Mean Ratio (90%CI)**
Total (CAR, DCAR AND DDCAR)	AUCtau	A/C (n=6/6)	95.07 (65.91, 137.1)
		B/C (n=6/6)	102.6 (71.13, 148.0)
	Cmax	A/C (n=6/6)	99.90 (69.44, 143.7)
		B/C (n=6/6)	106.7 (74.17, 153.5)
	Cmin	A/C (n=6/6)	95.80 (60.67, 151.3)
		B/C (n=6/6)	109.0 (69.05, 172.2)
3.0 mg/day			
Analyte	**PK parameter**	**Comparison**	**Geometric Mean Ratio (90%CI)**
Total (CAR, DCAR AND DDCAR)	AUCtau	A/C (n=9/8)	107.3 (46.72, 246.4)
		B/C (n=8/8)	95.88 (40.76, 225.6)
	Cmax	A/C (n=9/8)	112.9 (50.24, 253.5)
		B/C (n=8/8)	95.92 (41.72, 220.6)
	Cmin	A/C (n=9/8)	113.5 (36.58, 352.0)
		B/C (n=8/8)	127.9 (39.91, 410.1)
6.0 mg/day			
Analyte	**PK parameter**	**Comparison**	**Geometric Mean Ratio (90%CI)**
Total (CAR, DCAR AND DDCAR)	AUCtau	A/C (n=6/6)	159.1 (89.04, 284.2)
		B/C (n=6/6)	133.8 (74.90, 239.1)
	Cmax	A/C (n=6/6)	160.6 (91.60, 281.6)
		B/C (n=6/6)	135.8 (77.44, 238.1)
	Cmin	A/C (n=6/6)	206.0 (83.21, 509.9)
		B/C (n=6/6)	169.6 (68.52, 419.9)

A: 13 to <15 years of age; B: 15 to <18 years of age, C: 18 to 40 years of age; AUCtau: area under the curve; Cmax: peak plasma concentration; Cmin: minimum plasma concentration
Source: Reviewer's analysis

Study RGH-PK-18 evaluated daily dosing of cariprazine in pediatric patients 13 to 17 years with schizophrenia or pediatric patients 10 to 17 years with bipolar I disorder at dose levels range from 1.5 mg to 4.5 mg for a duration of 6 weeks. The study results indicate that these dose levels produce comparable exposures between patients aged 13 to 17 years and 10 to 12 years (Table 8). Average plasma concentrations for total CAR in the pediatric populations from study RGH-PK-18 are similar to those predicted in adults using population PK (PPK) model-based approach (Refer to Table 9).

Table 8. Mean Concentration Levels of CAR, DCAR, DDCAR and Total CAR on Day 42 Following Once Daily Cariprazine Administration in Study RGH-PK-18.

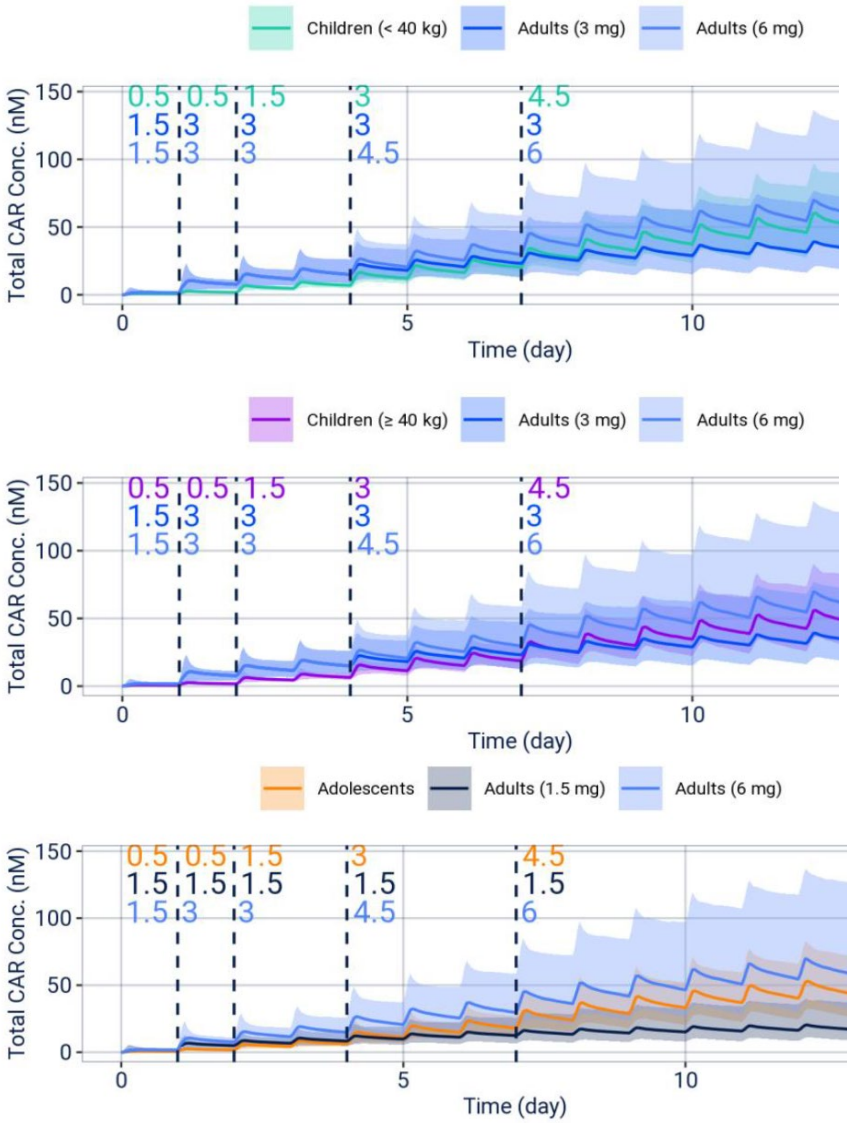
	Peds 10-12 yrs old			Peds 13-17 yrs old		
Cave (nM)	**1.5mg (n=6)**	**3mg (n=6)**	**4.5mg (n=6)**	**1.5mg (n=6)**	**3mg (n=6)**	**4.5mg (n=6)**
CAR	8.1	21.3	24.1	8.5	15.3	22
DCAR	1.3	3.7	4.4	1.7	2.7	5
DDCAR	12.2	29.5	35.3	13.4	21.9	35.2
Total CAR	22	55	64	24	40	62

Cave calculated as AUCtau/24hour
Source: Review archived on 01/08/2021 under NDA204370 (peds data: Tables 14.2.2 RGH-PK-18 clinical study report).

To explore the dosing in pediatric patients, PPK modeling and simulation was conducted (see the review of report R&D/24/1815 in Section 19.4 Pharmacometric Review for details). The Applicant's PPK analyses were conducted excluding one out of the n=103 subjects due to "extremely low concentrations of cariprazine and both metabolites." When re-running the analyses while including all n=103 subjects, all the PPK parameter estimates were comparable to the scenario of n=102 subjects (where the one subject with low concentrations is excluded). As such, the Applicant's PPK simulations from the PPK model described in report R&D/24/1815 are acceptable.

The PK simulations assessed titration as well as maintenance dosage regimens. During the initial titration phase, a dose titration scheme (with the starting dose of 0.5 mg daily on Day 1, increased to 1.5 mg daily on Day 3 and to 3 mg daily on Day 5) for all pediatric patients aged 10 to 17 years (children 10 to 12 years old weighing < 40 kg, and children 10 to 12 years old weighing ≥ 40 kg, adolescents 13 to 17 years old) was evaluated by simulations. The simulated PK during this initial titration phase (up to day 10) are shown in Figure 1.

Figure 1. Simulated Total CAR Concentrations in Adults, Adolescents, and Children (10-12 years old) of Dosing Regimens with Titration Over 10 Days



The solid lines represent the median of simulated concentrations, and shaded areas are 5th to 95th percentile of concentrations. The age groups were categorized as follows: children (10 to 12 years old), adolescents (13 to 17 years old), and adults (18 years and older).
Source: Cariprazine Population Pharmacokinetic Report R&D/24/1815, page 49.

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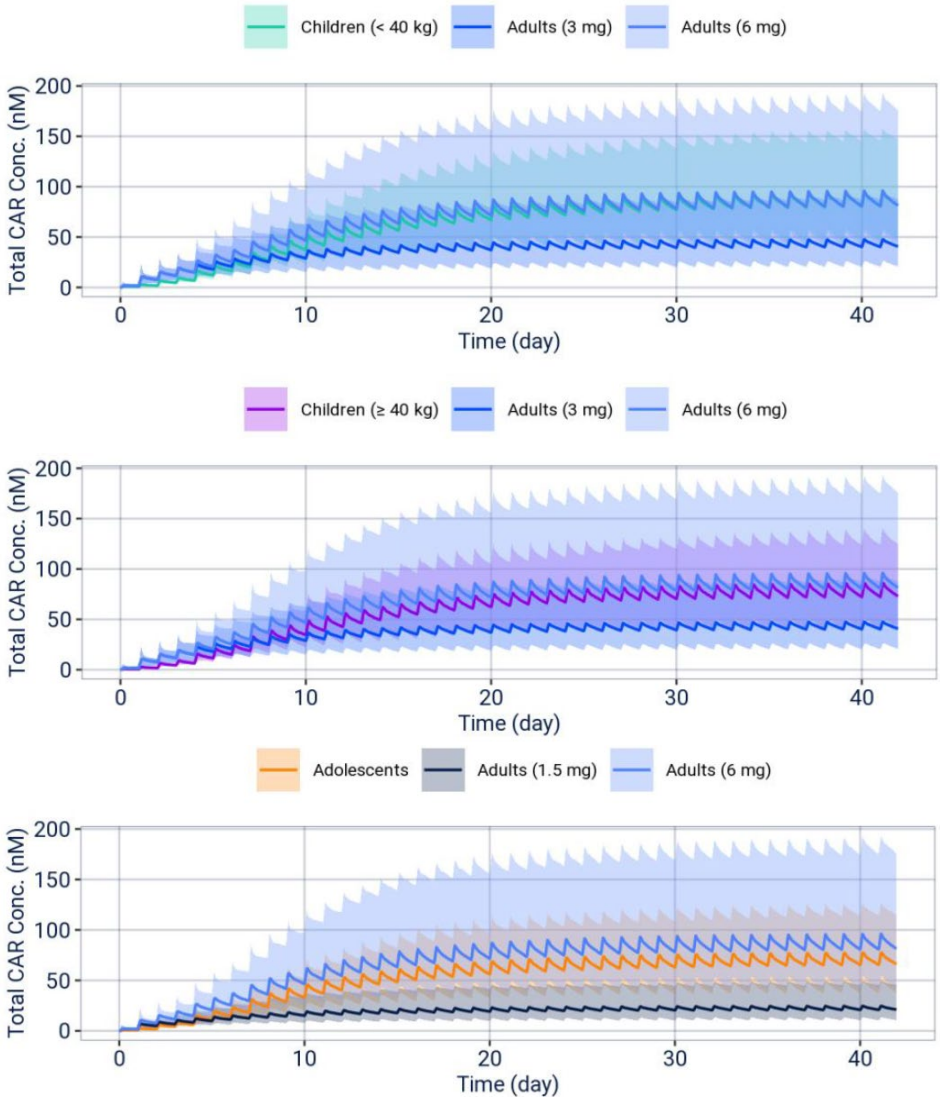
The simulated total cariprazine concentration profiles in pediatric patients were below that for adult patients under the recommended titration scheme (with the starting dose of 1.5 mg, increased to 3.0 mg daily on Day 2) (

Figure 1). The slower titration ensures a safer dose escalation for younger patients (while reaching target efficacious concentrations at steady state). The predicted steady-state exposures of total CAR for up to 42 days can be found in Figure 2, Table 9, and Figure 3.

Figure 2. Simulated Total CAR Concentrations in Adults (3 mg QD and 6 mg QD for Schizophrenia or 1.5 mg QD and 6 mg QD for Bipolar Mania), Adolescents (4.5 mg QD), and Children (4.5 mg QD) of Dosing Regimens with Titration over 42 Days

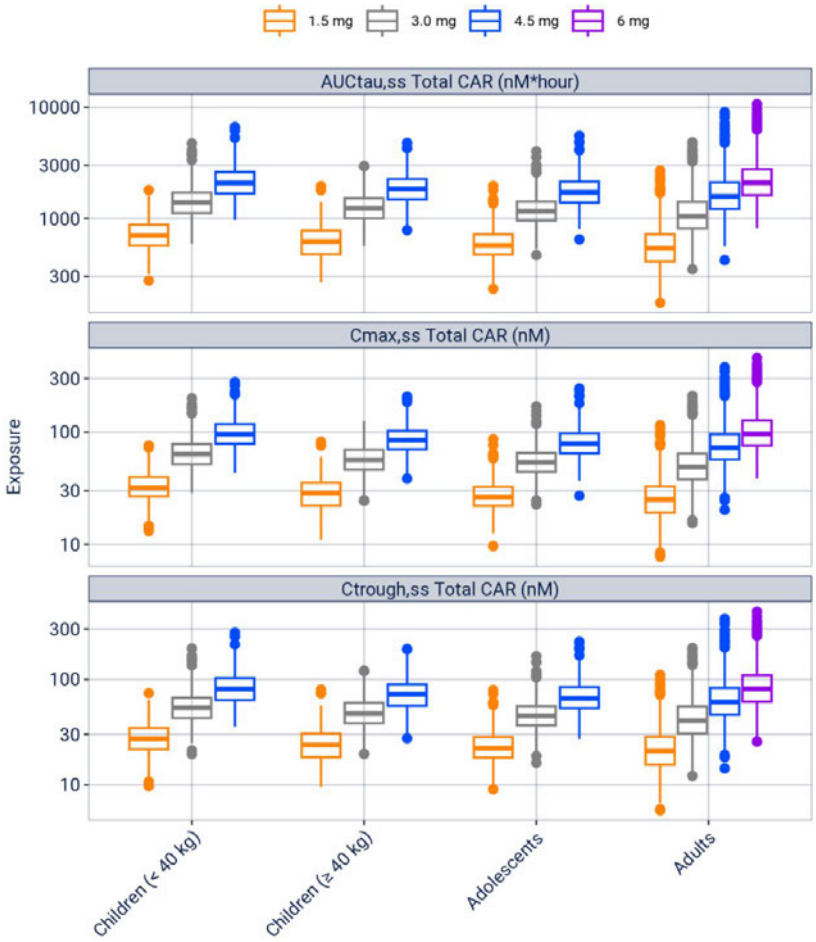


The solid lines represent the median of simulated concentrations, and shaded areas are 5th to 95th percentile of concentrations. The age groups were categorized as follows: children (10 - 12 years old), adolescents (13 - 17 years old), and adults (18 years and older). The top two panels represent the range of adult doses approved for Bipolar Mania (3 mg QD to 6 mg QD once daily). The bottom panel presents the range of adult doses approved for Schizophrenia (1.5 mg QD to 6 mg QD).
Source: Cariprazine Population Pharmacokinetic Report R&D/24/1815, page 50.

The above figure illustrates how the maximum proposed dose in pediatric patients compares to various adult dose levels over a period of 42 days.

A comparison of the predicted steady-state AUC, Cmax, and Ctrough for the total CAR are presented graphically in Figure 3 and presented in terms of summary statistics in Table 9.

Figure 3. Total CAR Steady-State AUCtau, Ctrough, and Cmax in Adults, Adolescents, and Children Following 42-Day Unaltered Dosing by Population



Boxes show the median, 25th to 75th percentiles (IQR) and whiskers represent the 1.5-fold IQR of exposures per population. The age groups were categorized as follows: children (10 to 12 years old), adolescents (13 to 17 years old), and adults (18 years and older).
Source: Cariprazine Population Pharmacokinetic Report R&D/24/1815, page 52.

Table 9. Summary Statistics (Median and 5th/95th Percentiles) of Model-Predicted Steady-State Exposures of Total CAR for Adults, Adolescents, and Children After 42 Daily Unaltered Dosing by Population

Population	Treatment Group	AUCtau,ss Total CAR (nM*hour)	Cmax,ss Total CAR (nM)	Ctrough,ss Total CAR (nM)
Children (< 40 kg)	1.5 mg	700 (425, 1161)	32.0 (21.1, 51.6)	27.2 (15.3, 45.9)
Children (< 40 kg)	3.0 mg	1394 (869, 2500)	63.5 (41.0, 108)	53.7 (31.9, 101)
Children (< 40 kg)	4.5 mg	2083 (1263, 3740)	95.8 (60.9, 165)	80.9 (46.6, 150)
Children (≥ 40 kg)	1.5 mg	619 (348, 1061)	28.6 (16.6, 47.5)	23.8 (13.2, 42.0)
Children (≥ 40 kg)	3.0 mg	1230 (738, 2059)	56.6 (34.2, 90.7)	47.3 (26.8, 82.0)
Children (≥ 40 kg)	4.5 mg	1846 (1111, 2976)	84.5 (52.5, 140)	72.1 (40.7, 120)
Adolescents	1.5 mg	570 (361, 985)	26.4 (17.1, 43.7)	22.1 (13.5, 39.3)
Adolescents	3.0 mg	1163 (728, 1995)	53.6 (33.8, 88.8)	45.0 (27.2, 79.6)
Adolescents	4.5 mg	1715 (1087, 3080)	78.8 (50.0, 139)	65.9 (39.9, 121)

Population	Treatment Group	AUCtau,ss Total CAR (nM*hour)	Cmax,ss Total CAR (nM)	Ctrough,ss Total CAR (nM)
Adults	1.5 mg	538 (289, 1136)	25.0 (13.5, 49.7)	20.9 (10.5, 45.7)
Adults	3.0 mg	1045 (582, 2233)	48.7 (27.4, 98.8)	40.5 (21.3, 89.7)
Adults	4.5 mg	1578 (860, 3319)	72.6 (40.2, 150)	60.9 (31.3, 134)
Adults	6 mg	2091 (1131, 4417)	96.5 (54.1, 194)	81.1 (41.9, 177)

Source: Cariprazine Population Pharmacokinetic Report R&D/24/1815, page 51.

The median predicted values of PK for pediatric patients and adults in Table 9 were compared. Table 10 shows the % difference of the median simulated steady-state total CAR PK metric for pediatric patients compared to adults at the same dose level.

Table 10. Percent Increase in Simulated Median PK Parameters in Pediatric Patients with Schizophrenia or Bipolar I Disorder Compared to Adults at the Same Dose Level

Population	Treatment Group	AUCtau,ss Total CAR (nM*hour)	Cmax,ss Total CAR (nM)	Ctrough,ss Total CAR (nM)
Children (< 40 kg)	1.5 mg	+30%	+28%	+30%
Children (< 40 kg)	3.0 mg	+33%	+30%	+33%
Children (< 40 kg)	4.5 mg	+32%	+32%	+33%
Children (≥ 40 kg)	1.5 mg	+15%	+14%	+14%
Children (≥ 40 kg)	3.0 mg	+18%	+16%	+17%
Children (≥ 40 kg)	4.5 mg	+17%	+16%	+18%
Adolescents	1.5 mg	+6%	+6%	+6%
Adolescents	3.0 mg	+11%	+10%	+11%
Adolescents	4.5 mg	+9%	+9%	+8%

The % change represents the difference in the median value for the pediatric group compared to the median value for adults receiving the same dose.
Source: Reviewer' analysis of data presented in Table 9, Cariprazine Population Pharmacokinetic Report R&D/24/1815, page 51.

Though the approved maximum dose for both schizophrenia and bipolar mania in adults is 6 mg, the Applicant is proposing to allow a maximum dose of 4.5 mg in pediatric as the total CAR exposure at 6 mg once daily in pediatric patients is expected to exceed that in adult patients at the same dose. The highest dose of cariprazine studied in the long-term safety Study 3070-301-001 was 4.5 mg per day. Therefore, the proposed maximum dose of 4.5 mg per day is reasonable for pediatric patients with schizophrenia or bipolar I disorder.

Table below shows a comparison of the predicted median steady-state total CAR PK for 4.5 mg once daily in pediatric patients versus 6 mg once daily in adults.

Table 11. Percent Decrease in Simulated Median PK Pediatric Patients Receiving 4.5 mg Once Daily Compared to Adults Receiving 6 mg Once Daily

Population	Treatment Group	AUCtau,ss Total CAR (nM*hour)	Cmax,ss Total CAR (nM)	Ctrough,ss Total CAR (nM)
children (< 40 kg)	4.5 mg	0%	-1%	0%
children (>= 40 kg)	4.5 mg	-12%	-12%	-11%
Adolescents	4.5 mg	-18%	-18%	-19%

The % change represents the difference in the median value for the pediatric group receiving 4.5 mg compared to the median value for adults receiving 6.0 mg.

Source: Reviewer' analysis of data presented in Table 9, Cariprazine Population Pharmacokinetic Report R&D/24/1815, page 51.

For schizophrenia, the Applicant has proposed 1.5 mg QD to 4.5 mg QD as maintenance dosage regimens in pediatric patients aged 13 to 17 years. Simulated steady-state exposures of total CAR at 1.5, 3, and 4.5 mg daily doses in adolescent patients were up to 33% higher (Table 10) than equivalent dose levels approved for adults with schizophrenia (1.5 mg to 4.5 mg daily) and no more than 19% lower (Table 11) than the highest approved adult dose for schizophrenia (4.5 mg QD in pediatric patients versus 6.0 mg QD in adults).

For bipolar mania, the Applicant has proposed 3 mg QD to 4.5 mg QD as maintenance dosage in pediatric patients aged 10 to 17 years. The simulated steady-state exposures of total CAR at 3 and 4.5 mg daily doses in adolescent patients were up to 14% higher (see Table 12) than the equivalent dose level approved for adults with bipolar I disorder (3 mg to 4.5 mg daily) and no more than 19% lower than the highest approved adult dose for bipolar mania (4.5 mg QD proposed in pediatric patients versus 6.0 mg QD approved in adults).

Table 12 shows the % difference of the median simulated steady-state total CAR PK metric for pediatric patients <40 kg compared to pediatric patients ≥ 40 kg at the same dose level, as well as the difference between pediatric patients ≥ 40 kg and adolescents receiving the same dose level.

Table 12. Percent Increase in Simulated Median PK Parameters in Pediatric Patients with Schizophrenia or Bipolar I Disorder < 40 kg vs ≥ 40 kg and ≥ 40 kg versus Adolescents at The Same Dose Level

Comparison	Treatment Group	AUCtau,ss total CAR (nM*h)	Cmax,ss total CAR (nM)	Ctrough,ss total CAR (nM)
Children < 40 kg vs Children ≥ 40 kg	1.5 mg	+13%	+12%	+14%
	3.0 mg	+13%	+12%	+14%
	4.5 mg	+13%	+13%	+12%
Children ≥ 40 kg vs Adolescents	1.5 mg	+9%	+8%	+8%
	3.0 mg	+6%	+6%	+5%
	4.5 mg	+8%	+7%	+9%

Top: The % change represents the difference in the median value for the pediatric patients < 40 kg compared to the median value for pediatric patients ≥ 40 kg receiving the same dose. Bottom: The % change represents the difference in the median value for the pediatric patients ≥ 40 kg compared to the median value for adolescents receiving the same dose.
Source: Reviewer' analysis of data presented in Table 9, Cariprazine Population Pharmacokinetic Report R&D/24/1815, page 51.

The pediatric patient population was stratified by body weight (i.e., <40 kg and ≥ 40 kg). The PK simulation results (Table 12) indicate that, for the same dose level, the exposures to total cariprazine in children < 40 kg were slightly higher (up to 14%) than those predicted for children ≥ 40 kg. Further, according to Table 12, children ≥ 40 kg have higher exposures (up to 9%) than adolescents. For 1.5 mg QD, the Cmax,ss of total CAR is 32, 28.6, 26.4, and 25 ng/mL in children < 40 kg, children ≥ 40 kg, adolescents, and adults, respectively (Table 9). When compared to adults, the percent increase in Cmax,ss of total CAR is 28%, 14%, and 6% higher in children < 40 kg, children ≥ 40 kg and adolescents, respectively (Table 10). A similar trend is apparent when

comparing pediatric patients to adults at the 3 mg and 4.5 mg QD dose levels. Though the systemic exposures of total CAR are numerically greater in younger patients than that in adults, the proposed non-weight-based and titration-based dosing (up to 4.5 mg QD) in pediatric patients can provide comparable efficacy to adults (up to 6 mg QD). Results from the long-term safety study 3070-301-001 in pediatric patients with schizophrenia, bipolar I disorder, or ASD also supports the safety of dosing regimens up to 4.5 mg QD.

Based on similarity of disease characteristics, similarity of symptomatic changes observed in acute schizophrenia and bipolar I disorder clinical trials in pediatric patients and adults receiving placebo, and an analysis of multiple antipsychotic drugs conducted by the FDA which demonstrated a similar exposure-response relationship in pediatric and adult patients with schizophrenia and mixed/manic bipolar I disorder, the FDA issued a General Advice Letter dated January 13, 2020, to support the extrapolation of the effectiveness of atypical antipsychotic drugs approved for the treatment of schizophrenia in adults to pediatric patients ≥13 years of age, and for the treatment of bipolar I disorder in adults to pediatric patients ≥10 years of age.

As the mechanism of action of cariprazine is similar to the approved atypical antipsychotic drugs and the PK similarity was established between pediatric patients with schizophrenia or bipolar I disorder and corresponding adult indications, the effectiveness of cariprazine for the treatment of pediatric patients 13 to 17 years old with schizophrenia can be extrapolated from adults with schizophrenia. Similarly, the effectiveness for pediatric patients with bipolar I disorder can be extrapolated from adults with bipolar I disorder.

Is the proposed dosing regimen for concomitant administration with strong or moderate CYP3A4 inhibitors appropriate?

Yes. The proposed daily dosing regimen is appropriate for adult patients initiating a CYP3A4 inhibitor while on a stable dose of cariprazine and for patients initiating cariprazine while on a stable dose of a CYP3A4 inhibitor.

As cariprazine is primarily metabolized by CYP3A4, strong or moderate CYP3A4 inhibitors have been shown to significantly increase the exposures of total cariprazine, and dose reduction is warranted. Based on the available dose strengths of 1.5 mg, 3 mg 4.5 mg and 6 mg, the currently approved dosage modification when initiating dosage of cariprazine in adult patients taking a strong or moderate CYP3A4 inhibitor is as follows:

<table>
<tr><th rowspan="2">Adult Patients</th><th colspan="2">VRAYLAR Starting Dosage</th></tr>
<tr><th>When Taking a Strong CYP3A4 Inhibitor</th><th>When Taking a Moderate CYP3A4 Inhibitor</th></tr>
<tr><td>Schizophrenia</td><td rowspan="2">Start at 1.5 mg orally every 3 days; increase to 1.5 mg orally every other day, if needed*</td><td rowspan="2">Start at 1.5 mg orally every other day; increase to 1.5 mg orally daily, if needed*</td></tr>
<tr><td>Bipolar Mania</td></tr>
<tr><td>Bipolar Depression</td><td rowspan="2">1.5 mg orally every 3 days</td><td rowspan="2">1.5 mg orally every other day</td></tr>
<tr><td>Adjunctive therapy for treatment of MDD</td></tr>
</table>

The currently approved dosage modification when initiating a strong or moderate CYP3A4 inhibitor in adult patients on a stable dosage of VRAYLAR is as follows:

Currently on VRAYLAR Dosage	**VRAYLAR Dosage When Initiating a Strong CYP3A4 Inhibitor**	**VRAYLAR Dosage When Initiating a Moderate CYP3A4 Inhibitor**
1.5 or 3 mg once daily	1.5 mg orally every 3 days	1.5 mg orally every other day
4.5 or 6 mg once daily	1.5 mg orally every other day	1.5 mg orally once daily

The Applicant developed two lower dose strengths (0.5 mg and 0.75 mg) and performed additional PBPK simulations using previously established PBPK model (refer to the clinical pharmacology review for S-12 (9/3/2024) for additional information) to support daily dosing. The daily dosing is expected to improve the patient compliance compared to the currently approved less frequent dosage regimen (every 3 days or every other day).

The simulated PK parameters of total cariprazine for the proposed daily dosage regimens are similar to the currently approved less frequent dosage regimens (Table 13). The results support the daily dosing regimens of cariprazine when concomitantly used with strong or moderate CYP3A4 inhibitors.

Table 13. Comparison of Predicted Total CAR PK Parameters Between the Newly Proposed Daily Dosage Regimens and Currently Approved Less Frequent Dosage Regimens of Cariprazine When Concomitantly Administered with Strong or Moderate CYP3A4 Inhibitor

DDI Scenario: A Strong CYP3A4 Inhibitor (Ketoconazole)			
Cariprazine	Predicted Total CAR PK At Steady State		
DDI Modified Dosing	Cmax (nM)	Cmin (nM)	Cavg (nM)
1.5 mg Q2D (Current)	58.22	49.01	53.56
0.75 mg QD (Proposed)	55.14	50.14	53.53
1.5 mg Q3D (Current)	41.16	32.47	34.68
0.5 mg QD (Proposed)	36.73	33.40	35.66
DDI Scenario: A Moderate CYP3A4 Inhibitor (Fluconazole)			
Cariprazine	Predicted Total CAR PK At Steady State		
DDI Modified Dosing	Cmax (nM)	Cmin (nM)	Cavg (nM)
1.5 mg Q2D (Current)	29.52	23.26	25.75
0.75 mg QD (Proposed)	27.22	24.17	25.78

PK data are geometric means of steady state Total cariprazine.
Cavg: average concentration of the drug in the central circulation during the dosing interval in steady state; Cmax: observed maximum concentration; Cmin: minimum blood plasma concentration reached by the drug during the dosing interval; QD: once daily; Q2D: every two days; Q3D: every three days.
Source: Tables 14 and 15 of the PBPK report R&D/22/0201 Version 3.

Dosage Modifications for the Starting Dosage of VRAYLAR in Patients Taking a Strong or Moderate CYP3A4 Inhibitor

	VRAYLAR Starting Dosage	
	When Taking a Strong CYP3A4 Inhibitor	**When Taking a Moderate CYP3A4 Inhibitor**
Schizophrenia	Start at 0.5 mg orally once daily; increase to 0.75 mg orally once daily, if needed*	Start at 0.75 mg orally once daily; increase to 1.5 mg orally daily, if needed*
Bipolar Mania		
Bipolar Depression	0.5 mg orally once daily	0.75 mg orally once daily
Adjunctive therapy for treatment of MDD		

*Depending upon clinical response and tolerability

Dosage Modifications for VRAYLAR When Initiating a Strong or Moderate CYP3A4 Inhibitor and While Taking a Stable Dose of VRAYLAR

Currently on VRAYLAR Dosage	VRAYLAR Dosage When Initiating a Strong CYP3A4 Inhibitor	VRAYLAR Dosage When Initiating a Moderate CYP3A4 Inhibitor
1.5 or 3 mg once daily	0.5 mg orally once daily	0.75 mg orally once daily
4.5 or 6 mg once daily	0.75 mg orally once daily	1.5 mg orally once daily

Details of the PBPK analysis are presented in Section 15.4 of the Appendix.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 14: Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
Controlled Studies to Support Efficacy and Safety						
M21-465	Randomized, double-blind, placebo-controlled, flexible-dose	Cariprazine 0.75 mg to 3.0 mg oral capsules or solution daily	ABC-I	8 weeks	155	Subjects ages 5 to 17 years with ASD
Studies to Support Safety						
3070-301-001	Open-label, flexible-dose	Cariprazine 0.75 mg to 4.5 mg oral capsules or solution daily	AEs	52 weeks	303	Subjects ages 13 to 17 years with schizophrenia, 10 to 17 years with bipolar I disorder, or 5 to 17 years with ASD
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
RGH-PK-18	Open-label, multiple-dose	Cariprazine 0.5 mg to 4.5 mg oral capsule daily	PK parameters	42 days	36	Subjects ages 13 to 17 years with schizophrenia or 10 to 17 years with bipolar I disorder
RGH-188-201	Open-label, multiple-dose	Cariprazine 0.5 mg to 6.0 mg oral capsule daily	PK parameters	28 days	43	Subjects ages 13 to 17 years or adults with schizophrenia
2000-103-009	Open-label, multiple-dose	Cariprazine 0.5 mg to 3.0 mg oral solution daily	PK parameters	42 days	25	Subjects ages 5 to 17 years with ASD

7.2. Review Strategy

The Applicant submitted two sNDAs, S015 and S016, to expand cariprazine's indicated populations for the treatment of schizophrenia to pediatric patients 13 through 17 years of age and acute manic or mixed episodes associated with bipolar I disorder to pediatric patients 10 through 17 years of age. Additionally, the Applicant submitted a third sNDA, S017, to satisfy part of the pediatric written request with Clinical Study 2 in pediatric patients 5 through 17 years of age with irritability associated with ASD. Finally, S014 provides for the additional dosage strengths necessary to achieve the recommended pediatric dosing, but contains no clinical data.

Substantial evidence of effectiveness for the treatment of schizophrenia in pediatric patients 13 through 17 years of age and acute manic or mixed episodes associated with bipolar I disorder in pediatric patients 10 through 17 years of age is based upon extrapolation from cariprazine's known efficacy in the treatment of adult schizophrenia and bipolar I disorder. The Office of Clinical Pharmacology's PK analyses to support pediatric extrapolation of the adult indications can be found in Section 6, Clinical Pharmacology. The efficacy review focuses on Study M21-465, the short-term study in pediatric subjects with irritability associated with ASD. Analyses were performed by the Applicant and by Office of Biometrics reviewer Dr. Semhar Ogbagaber. However, this study does not, alone, support substantial evidence of effectiveness, and the Applicant is not at this time planning another study or seeking an indication for the treatment of irritability associated with ASD.

The safety review focuses on Study M21-465 along with a brief review of Study 3070-301-001, an ongoing open-label, 52-week (originally 26-week) safety study in pediatric subjects 13 to 17 years of age with schizophrenia, 10 to 17 years of age with bipolar I disorder, and 5 to 17 years of age with irritability associated with ASD. This team also reviewed the 120-Day Safety Update.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study M21-465 (Treatment of Irritability in Autism Spectrum Disorder)

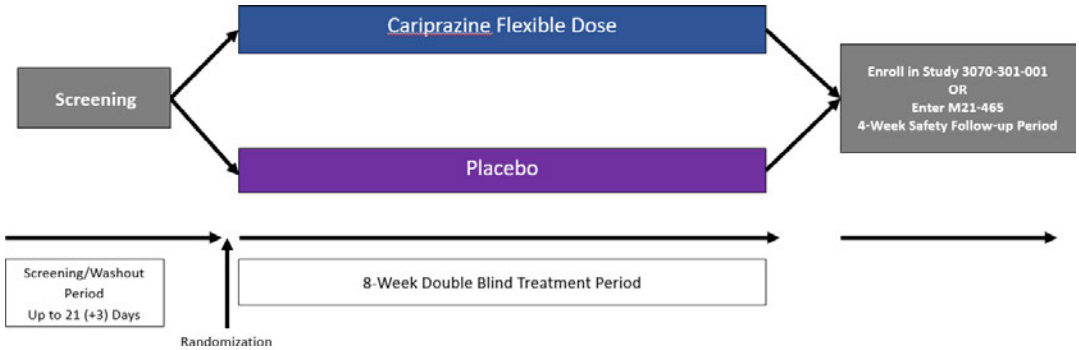
Trial Design

Study M21-465 was an 8-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase 3 study of the efficacy and safety of age- and weight-dependent flexible doses of cariprazine (0.75 mg to 3 mg) compared to placebo in the treatment of pediatric subjects aged 5 to 17 years (inclusive) with ASD.

The study consisted of a 3-week screening period, an 8-week treatment period, and a 4-week safety follow-up period, with an in-person safety follow-up visit 4 weeks after last dose of study drug (Study Week 12). The study had a planned enrollment of approximately 152 subjects (76 subjects per treatment group), randomized on Day 1 (Visit 2) in a 1:1 ratio to placebo or flexible-dose cariprazine 0.75 mg to 3 mg, with randomization stratified by age and weight group. For subjects ages 5 to 9 years old, all body weights, and 10 to 12 years old with body weight < 40 kg, dosages were titrated from cariprazine 0.5 mg daily up to 1.5 mg daily on Day 8. For subjects 10 to 12 years old with body weight ≥ 40 kg, 13 to 17 years old with body weight < 40 kg, or 13 to 17 years old with body weight ≥ 40 kg, dosages were titrated from cariprazine 0.5 mg daily up to 3 mg daily on Day 15. Notably, an oral solution formulation of cariprazine, rather than the approved capsule formulation, was used for the younger age cohort, subjects ages 5 to 9 years.

Study sites, subjects, and Applicant were blinded to treatment assignment for the duration of the study. Below is the study schema.

Figure 4. Study M21-465 Study Schema



Source: Applicant page 25, CSR (Figure 1)

The study enrolled male and female subjects, aged 5 to 17 years of age, with a DSM-5 primary diagnosis of ASD, confirmed by Kiddie Schedule for Affective Disorders and

Schizophrenia for School-Age Children (K-SADS-PL) at screening, and with irritability symptoms defined as: ABC-I subscale score ≥ 18 and Clinical Rated Global Impression-Severity (CGI-S) Irritability score ≥ 4 at Visit 1; and ABC-I subscale score ≥ 18 at Visit 2, with less than 30% decrease in ABC-I subscale score between Visit 1 and Visit 2, and CGI-S Irritability score ≥ 4 at Visit 2 (and no improvement between Visit 1 and Visit 2).

Key exclusion criteria included IQ <25; use of any cannabinoids; treatment with any monoamine oxidase inhibitor within the past 3 months; history of clozapine >50 mg daily or any depot antipsychotic; use of esketamine, electroconvulsive therapy, vagus nerve stimulation, or transcranial magnetic stimulation within the past 6 months or any history of lack of response to these; history of major depressive disorder, bipolar disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, or psychotic disorder due to another medical condition; in subjects with ASD, associated Rett disorder, fragile-X syndrome, or childhood disintegrative disorder; history of substance-related disorder (other than caffeine or tobacco) within the past 3 months; suicide risk as determined by history of suicide attempt in the past year or a “yes” response to Question 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) currently or in the past 6 months; and imminent risk of injuring self or others.

Study Endpoints

The primary efficacy endpoint is the change from baseline to Week 8 (Day 57) in ABC-I subscale score. The Applicant specified key secondary efficacy endpoints as:

- Clinical Rated Global Impression - Change (CGI-C) Irritability responder ("Very much improved" or "Much improved") status at Week 8
- Change from baseline to Week 8 in Parent-Rated Anxiety Scale for Youth with Autism Spectrum Disorder (PRAS-ASD) total score
- Change from baseline to Week 8 in Caregiver Strain Questionnaire Short Form 7-Item (CGSQ SF-7) total score

During the IND review (eCTD 0077, 0078), the clinical team did not agree with the two key secondary endpoints (PRAS-ASD and CGSQSF-7) with the following rationale: (1) the PRAS-ASD and CGSQ SF-7 are exploratory measures because the study was not designed to assess anxiety as an indication and because a caregiver-related instrument is not considered (b) (4) and (2) because (b) (4), any positive outcomes from these endpoints would have to be substantiated with at least two positive studies (b) (4) Therefore, analysis results for these endpoints should be considered exploratory.

Statistical Analysis Plan

Analysis Populations

- Safety Population: included all randomized subjects who were treated with at least 1 dose of study drug.
- Intention-to-Treat (ITT) Population: included all randomized subjects who received at least 1 dose of study drug.
- Modified Intention-to-Treat (mITT) Population: included all randomized subjects who received at least 1 dose of study drug and who had baseline and at least 1 postbaseline observation for the primary efficacy endpoint or the first key secondary efficacy endpoint.

Subjects were summarized according to the study treatment they actually received. The primary and key secondary endpoints were analyzed based on mITT population.

During the IND statistical review (eCTD 0077, 0078), the FDA raised concerns that the mITT population (b) (4) In response, the Applicant updated the mITT definition to include all randomized subjects who received at least one dose and have baseline plus at least one post-baseline observation for the primary or the first key secondary efficacy endpoint. The Applicant clarified the ITT population definition (all randomized subjects receiving at least one dose) and included ITT-based sensitivity analyses.

The mITT population excluded three subjects without post-baseline measurements – one subject in the placebo arm and two subjects in cariprazine arm. In the review, the primary efficacy results based on the mITT were consistent with those based on the ITT.

Intercurrent Events

The plan to deal with intercurrent events during the study was followed as outlined here: Subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits unless subjects decided to discontinue the study participation entirely. Collected postbaseline data from Day 2 will be used regardless of rescue medication use or days relative to the last dose of study drug. Missing data due to a subject discontinuing from study participation will be considered missing at random (MAR).

Primary Efficacy Analysis

The primary efficacy outcomes were evaluated using a Mixed-Effect Model for Repeated Measures (MMRM) approach. Categorical variables were assessed through generalized linear mixed models (GLMM). The parameter calculations assumed that missing data occurred at random (MAR) and employed restrictive maximum likelihood (REML) estimation methods. To account for correlations between repeated measurements within individual subjects, an

unstructured variance-covariance matrix was implemented. The Kenward-Roger method was applied to calculate the appropriate denominator degrees of freedom. If the model failed to converge when using the unstructured covariance matrix structure:

1. For continuous variables, approaches proposed by Lu and Mehrotra will be used in the following order until convergence: (1) Fisher scoring algorithm, (2) no-diagonal factor analytic structure, and (3) successive univariate regression method.

2. If methods introduced above fail to guarantee convergence for MMRM or in the situation of GLMM for binary variable, a structured covariance matrix will be used in combination with empirical variance estimate (i.e., sandwich estimator) to address the potential mis-specification situation. The following sequence of alternative covariance structures will be considered in the MMRM or GLMM until convergence: first-order ante-dependent [ANTE(1)], Toeplitz [TOEP], first-order autoregressive [AR(1)] and compound symmetry [CS].

Multiplicity

To control the familywise error rate at a 2-sided significance level of 0.05 for the entire study, a fixed sequence testing procedure was used for the primary efficacy endpoint and the key secondary efficacy endpoints. Only if success was demonstrated for the primary endpoint of change from baseline to Week 8 in ABC-I subscale score, the testing would proceed to the key secondary endpoints in the following order:

- CGI-C Irritability responder status at Week 8
- Change from baseline to Week 8 in PRAS-ASD total score
- Change from baseline to Week 8 in CGSQ SF-7 total score.

Protocol Amendments

Five protocol amendments occurred after the original protocol on January 13, 2022. Version 4.0 was submitted on July 7, 2023, and separated subjects ages 13 to 17 years into two weight strata, <40 kg and ≥40 kg, to allow for different dosing groups. There were no other major changes.

8.1.2. Study Results

Analysis results of study M21-465 are presented in this section.

Compliance with Good Clinical Practices

The Applicant conducted this study in accordance with Good Clinical Practices principles, the International Conference on Harmonisation E6 guideline, and local regulations. An attestation was included in Section 5 of the clinical study report (CSR).

Financial Disclosure

In pre-sNDA preliminary meeting comments dated March 11, 2025, the Division agreed that the Applicant need not submit financial disclosures on the grounds that Study M21-4654 would not be used to support an efficacy claim.

Patient Disposition

Of the 466 subjects who were screened, 161 were randomized. The treatment arms were reasonably evenly distributed with a similar rate of study completion (placebo 82%, cariprazine 80%) although there was a higher rate of discontinuations due to adverse events (AE) in the cariprazine arm (7%) compared to the placebo arm (1%). The overall rate of study discontinuation and higher rate of discontinuation due to AEs in the active treatment group are consistent with what is expected for psychiatric clinical studies.

Table 15: Analysis Population

Data Analysis Population	Placebo N	Cariprazine N	Total N
Safety population	79	76	155
ITT population	79	76	155
mITT population	78	74	152

Source: Reviewer (ADSL dataset), Applicant page 37, CSR (Table 14.1-3.1)

Table 16. Patient Disposition, Screened Subjects, Study M21-465

Period/Disposition	Placebo n (%)	Cariprazine n (%)	Total n (%)
Screening Period			
Number of Subjects Screened	--	--	466
Number of Subjects Completed	--	--	161 (34.5)
Number of Subjects Who Were Screen Failures	--	--	305 (65.5)
Randomization			
Number of Subjects Randomized	81 (100.0)	80 (100.0)	161 (100.0)
Never Received Any Study Treatment	2 (2.5)	4 (5.0)	6 (3.7)
Received Randomized Study Treatment	79 (97.5)	76 (95.0)	155 (96.3)
Received Study Treatment Other than Randomized	0 (0.0)	0 (0.0)	0 (0.0)
Double-Blind Treatment Period			
Number of Subjects Treated	79 (100.0)	76 (100.0)	155 (100.0)
Number of Subjects Completed	65 (82.3)	61 (80.3)	126 (81.3)
Number of Subjects Discontinued	14 (17.7)	15 (19.7)	29 (18.7)
Reasons for Discontinuation			

Period/Disposition	Placebo n (%)	Cariprazine n (%)	Total n (%)
Adverse Event	1 (1.3)	5 (6.6)	6 (3.9)
Lost to Follow-Up	5 (6.3)	4 (5.3)	9 (5.8)
COVID-19 Infection	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 Logistical Restrictions	0 (0.0)	0 (0.0)	0 (0.0)
Lack of Efficacy	2 (2.5)	1 (1.3)	3 (1.9)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Deviation	0 (0.0)	3 (3.9)	3 (1.9)
Non-compliance with Study Drug	1 (1.3)	1 (1.3)	2 (1.3)
Withdrawal from Treatment by Subject	4 (5.1)	0 (0.0)	4 (2.6)
Study Terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Site Terminated by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.3)	1 (1.3)	2 (1.3)
Safety Follow-up Period			
Number of Subjects Entered	50 (63.3)	49 (64.5)	99 (63.9)

Source: Applicant pages 88-89, CSR (Table 14.1-1.1)
The denominator of 'Total' column is the total number of subjects who are a member of either group
In the DBTP and SFU category, percentages are based on number of subjects treated
DBTP = Double-blind treatment period
SFU = Safety follow-up period
n = Number of subjects within a specific category

Protocol Violations/Deviations

The Applicant identified 43 subjects with protocol deviations (23% placebo, 33% cariprazine). The most frequent type of protocol deviation involved subject enrollment criteria violations, with more occurrence in the cariprazine group (8% placebo, 16% cariprazine). This imbalance did not seem to have impacted the interpretation of study results.

Demographics

Table 17. Demographics, Safety Population, Study M21-465

Parameter	Placebo (N=79)	Cariprazine (N=76)	Total (N=155)
Age (years)			
Mean (SD)	10.5 (3.77)	10.7 (3.30)	10.6 (3.53)
Median	10.0	10.0	10.0
Q1, Q3	7.0, 14.0	8.0, 14.0	8.0, 14.0
Min, Max	5, 18	5, 17	5, 18
Age and Weight Group - n (%)			
5-9 years old	36 (46.2)	32 (42.1)	68 (44.2)
10-12 years old with body weight <40kg	5 (6.4)	7 (9.2)	12 (7.8)

Parameter	Placebo (N=79)	Cariprazine (N=76)	Total (N=155)
10-12 years old with body weight ≥40kg	11 (14.1)	14 (18.4)	25 (16.2)
13-17 years old with body weight <40kg	0 (0.0)	1 (1.3)	1 (0.6)
13-17 years old with body weight ≥40kg	26 (33.3)	22 (28.9)	48 (31.2)
Missing	1	0	1
Sex - n (%)			
Male	51 (64.6)	57 (75.0)	108 (69.7)
Female	28 (35.4)	19 (25.0)	47 (30.3)
Race - n (%)			
White	47 (59.5)	50 (65.8)	97 (62.6)
Black or African American	27 (34.2)	19 (25.0)	46 (29.7)
Asian	3 (3.8)	2 (2.6)	5 (3.2)
American Indian or Alaska Native	0 (0.0)	1 (1.3)	1 (0.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	2 (2.5)	4 (5.3)	6 (3.9)
Ethnicity - n (%)			
Hispanic or Latino	29 (36.7)	34 (44.7)	63 (40.6)
Not Hispanic or Latino	50 (63.3)	42 (55.3)	92 (59.4)
Weight (kg)			
Mean (SD)	47.5 (27.08)	45.8 (21.40)	46.7 (24.40)
Median	42.0	39.7	40.4
Q1, Q3	29.1, 59.9	28.1, 60.8	28.7, 59.9
Min, Max	18, 199	17, 111	17, 199
Height (cm)			
Mean (SD)	143.2 (20.16)	143.9 (20.59)	143.5 (20.31)
Median	143.0	142.1	142.2
Q1, Q3	127.0, 161.0	129.0, 161.5	127.0, 161.0
Min, Max	104, 183	99, 185	99, 185
BMI (kg/m^2)			
Mean (SD)	21.8 (7.32)	21.0 (5.71)	21.5 (6.57)
Median	19.9	19.7	19.8
Q1, Q3	17.0, 26.5	16.7, 24.4	16.8, 24.9
Min, Max	14, 61	11, 43	11, 61

Parameter	Placebo (N=79)	Cariprazine (N=76)	Total (N=155)
Country - n (%)			
US	78 (98.7)	74 (97.4)	152 (98.1)
Puerto Rico	1 (1.3)	2 (2.6)	3 (1.9)
Nicotine Use - n (%)			
Never	79 (100.0)	76 (100.0)	155 (100.0)
Current	0 (0.0)	0 (0.0)	0 (0.0)
Former	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Alcohol Use - n (%)			
Never	79 (100.0)	76 (100.0)	155 (100.0)
Current	0 (0.0)	0 (0.0)	0 (0.0)
Former	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)

Source: Applicant pages 97-99, CSR (Table 14.1-4.1)
Age = Year of informed consent date - Year of Birth.
[1] Subjects who reported multiple races are only included in multiple categories.
BMI = body mass index, weight in kg divided by height in meters squared.

There was a greater proportion of male subjects in the cariprazine group (75%) compared to the placebo group (65%), but this is not expected to have significantly impacted findings from the study. The higher percentage of males overall is typical for a population with ASD. Otherwise, demographic categories and physical characteristics were evenly distributed between the two treatment arms. Age distribution was slightly imbalanced towards a younger age cohort (5 to 9 years) but still comprises a satisfactory distribution overall that is supportive of study findings to the general patient population: 44% of subjects ages 5 to 9 years, 24% ages 10 to 12 years, and 32% ages 13 to 17 years.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease severity was also similar between the two treatment groups with mean ABC-I subscale scores of 31 in the placebo treatment group and 30 in the cariprazine group.

Table 18. Baseline Efficacy Variables, mITT Population, Study M21-465

Parameter	Placebo (N=78)	Cariprazine (N=74)	Total (N=152)
ABC - Total Score			
Mean (SD)	108.9 (22.56)	106.9 (24.43)	107.9 (23.43)
Median	107.5	104.0	106.0
Q1, Q3	93.0, 125.0	90.0, 123.0	91.0, 124.5
Min, Max	57, 167	58, 165	57, 167
n	78	74	152
ABC-I - Subscale Score			

Parameter	Placebo (N=78)	Cariprazine (N=74)	Total (N=152)
Mean (SD)	30.7 (6.43)	30.1 (6.45)	30.4 (6.43)
Median	31.0	29.0	30.0
Q1, Q3	25.0, 35.0	26.0, 35.0	26.0, 35.0
Min, Max	18, 45	18, 45	18, 45
n	78	74	152
CGI-S Irritability - n (%)			
1: Normal, not irritable	0 (0.0)	0 (0.0)	0 (0.0)
2: Borderline irritable	0 (0.0)	0 (0.0)	0 (0.0)
3: Mildly irritable	0 (0.0)	0 (0.0)	0 (0.0)
4: Moderately irritable	14 (17.9)	19 (25.7)	33 (21.7)
5: Markedly irritable	42 (53.8)	38 (51.4)	80 (52.6)
6: Severely irritable	20 (25.6)	16 (21.6)	36 (23.7)
7: Among the most extremely irritable	2 (2.6)	1 (1.4)	3 (2.0)
Missing	0	0	0
CgGI-S Irritability - n (%)			
1: Normal, not irritable	0 (0.0)	0 (0.0)	0 (0.0)
2: Borderline irritable	0 (0.0)	0 (0.0)	0 (0.0)
3: Mildly irritable	1 (1.3)	3 (4.1)	4 (2.6)
4: Moderately irritable	12 (15.4)	12 (16.2)	24 (15.8)
5: Markedly irritable	23 (29.5)	33 (44.6)	56 (36.8)
6: Severely irritable	31 (39.7)	17 (23.0)	48 (31.6)
7: Extremely irritable	11 (14.1)	9 (12.2)	20 (13.2)
Missing	0	0	0

Source: Applicant pages 41-42, CSR (Table 14.1-4.2)
Abbreviations: ABC = Aberrant Behavior Checklist, 2nd edition - Community Version; ABC-I = Aberrant Behavior Checklist, 2nd edition - Community Version - Irritability; CGI-S = Clinical Rated Global Impression - Severity; CgGI-S = Caregiver Rated Global Impression - Severity
Notes: Baseline efficacy variables for safety population is defined as the last non-missing assessment at or prior to the first dose of Double-blind period. N = Number of subjects in the modified intent-to-treat Population. n = Number of subjects within a specific category.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was high in both groups: 99% in the placebo group and 98% in the cariprazine group. There were 90 subjects (58%) who took a concomitant medication during the treatment period: 63% subjects on placebo, 53% on cariprazine. The most common medications used were centrally acting sympathomimetics (e.g., clonidine, methylphenidate): 19% placebo, 20% cariprazine. Other notable concomitant medications included one subject in each treatment group who received lorazepam, one subject in the cariprazine group who received propranolol for anxiolysis, and one subject in the placebo group who received benztropine for akathisia. Few subjects in both treatment groups initiated psychotropic medications after the treatment phase ended: one subject in the placebo group and two in the cariprazine group initiated a second-generation antipsychotic; and one subject in the placebo group initiated an antidepressant.

Efficacy Results – Primary Endpoint

The statistical reviewer confirmed Study M21-465 met its primary objective. Cariprazine demonstrated a statistically significant reduction from baseline in ABC-I subscale score at Week 8 compared to placebo. The LS mean difference (SE) was -3.7 (1.56) (95% CI: -6.75, -0.57; p=0.0205). Because higher ABC-I scores indicate greater severity, this reduction represents improved irritability symptoms.

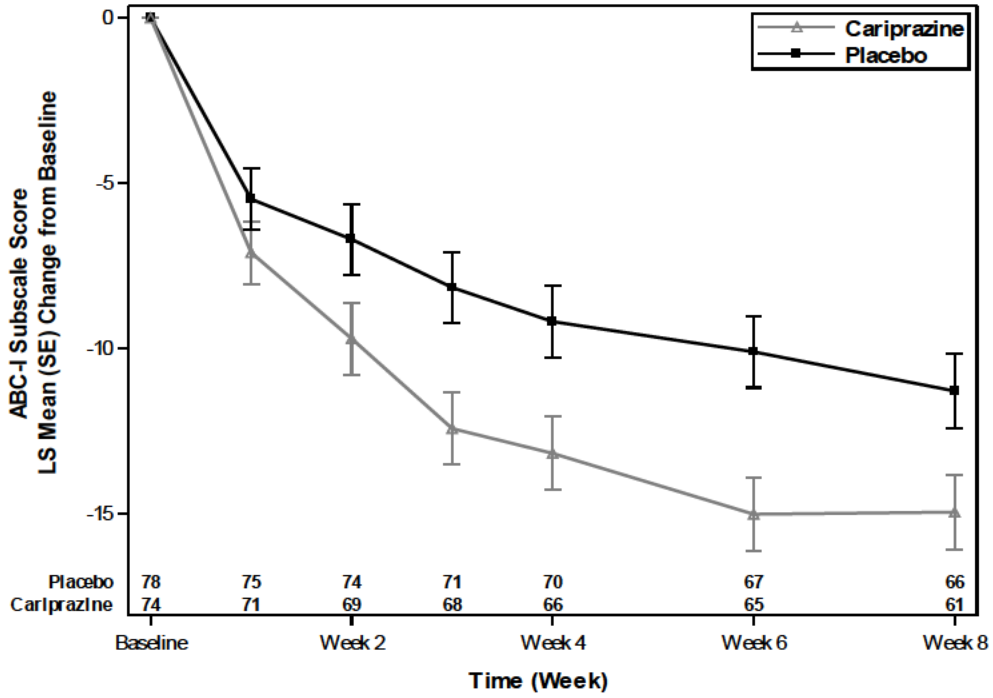
In addition, sensitivity analyses—including MMRM with a J2R (Jump to Reference) MI (multiple imputation) approach and a tipping-point analysis—were performed to assess the missing-data assumptions used in the primary efficacy analysis. Overall, results of these analyses supported the primary efficacy findings.

Table 19. Change From Baseline to Week 8 in ABC-I Subscale Score, mITT Population, Study M21-465

Statistic	Cariprazine (N=74)	Placebo (N=78)
Baseline, mean (SD)	30.1 (6.45)	30.7 (6.43)
Change From Baseline to Week 8		
N	61	66
LS mean (SE)	-14.9 (1.14)	-11.3 (1.11)
LS mean difference (SE)	-3.7 (1.56)	
95% CI	(-6.75, -0.57)	
p-value	0.0205	

Source: Applicant page 49, CSR (Tables 14.2-1.1), verified by FDA statistical reviewer: Dr. Semhar Ogbagaber
Abbreviation: MMRM = Mixed Effect Model for Repeated Measures; ABC-I = Aberrant Behavior Checklist, 2nd edition - Community Version – Irritability; N = Number of subjects in the modified intent-to-treat population; n = Number of subjects in the specific visit with non-missing observation; CFB = Change from Baseline, LS = Least Squares, SE = standard error of the least squares mean, LSMD =least squares mean difference, CI = Confidence Interval; MMRM with treatment group, visit, and treatment group-by-visit interaction, pooled age and weight strata as fixed effects, and the baseline value and baseline by-visit interaction as covariates. An unstructured covariance matrix will be used to model the within-subject covariance.

Figure 5. Least Square Mean of Change from Baseline in ABC-I Subscale Score by Treatment Arm and Study Week, mITT Population

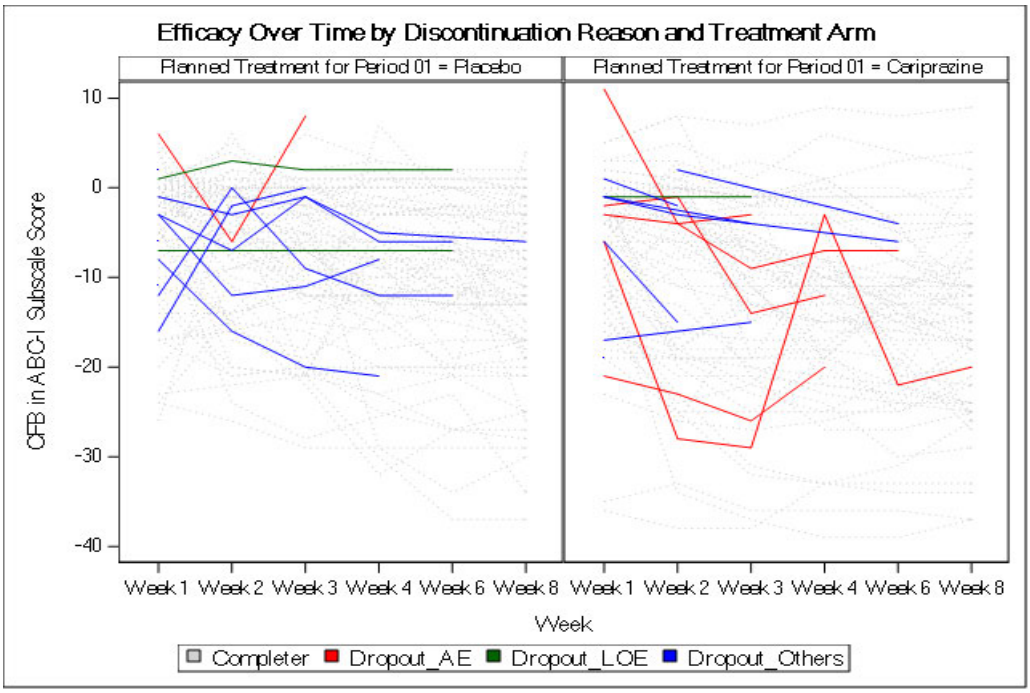


Source: Created by statistical reviewer Dr. Semhar Ogbagaber
Abbreviation: ABC-I = Aberrant Behavior Checklist, 2nd Edition – Community Version – Irritability; MMRM = Mixed Effect Model for Repeated Measures

Graphical Assessment of Dropouts

A graphical examination of longitudinal trajectories was conducted to evaluate the plausibility of the Missing at Random (MAR) assumption in the presence of study dropouts. For each treatment arm, the overall response trajectories of dropouts up to the dropout week do not appear very different from those of the completers, which somewhat provides empirical support for the MAR assumption.

Figure 6. Change from Baseline in ABC-I Subscale Score Over Time by Discontinuation Reason within Treatment Arm



Source: Created by statistical reviewer Dr. Semhar Ogbagaber Abbreviation: CFB = change from baseline

Data Quality and Integrity

Datasets appeared to be of good quality and were complete. The reviewers have no concerns about data integrity.

Efficacy Results – Secondary and Other Relevant Endpoints

The treatment showed statistically significant benefits in CGI-C irritability improvement, where a statistically significantly greater proportion of cariprazine-treated subjects responded compared to placebo (p=0.0012 OR=3.61, 95% CI: 1.68-7.78); cariprazine showed only numerical improvement in anxiety symptoms measured by PRAS-ASD total score compared to placebo (p=0.051). Given that the results for PRAS-ASD did not reach statistical significance, any subsequent analyses should be interpreted as exploratory. Although the mean reduction in CGSQ SF-7 scores versus placebo was nominally statistically significant (p=0.027; LS mean difference=-0.6, 95% CI: -1.2 to -0.07), it did not reach statistical significance after adjusting for multiplicity. See summary results in Table 20 through Table 22 below.

Table 20. CGI-C Irritability Responder Analysis at Week 8, mITT Population, Study M21-465

Treatment	N	Responders n/N_1 (%)	Point Estimate (SE)	95% CI	Odds Ratio vs Placebo	95% CI	P-value
Placebo	78	24/65 (36.9%)	38.0 (6.37)	[26.4, 51.1]	—	—	—
Cariprazine	74	41/61 (67.2%)	68.9 (6.10)	[55.8, 79.5]	3.61	[1.68, 7.78]	0.0012

Source: Applicant page 52, CSR (Tables 14.2-2.1.1), verified by FDA statistical reviewer: Dr. Semhar Ogbagaber
Abbreviation: GLMM = Generalized Linear Mixed Model
CGI-C Irritability = Clinical Rated Global Impression - Change in Irritability
CGI-S Irritability = Clinical Rated Global Impression - Severity in Irritability
CGI-C Irritability responder is defined as having a CGI-C in Irritability score of <=2
N = Number of subjects in the modified intent-to-treat population
N1 = Number of subjects in the modified intent-to-treat population with non-missing postbaseline score at the visit
n = Number of subjects within a specific category.
Percentages are calculated as 100 * (n/N1)
OR = Odds Ratio vs Placebo, CI = Confidence Interval
[1] 95% CI of OR
Analyses are based on GLMM with treatment group, visit, treatment group-by-visit interaction, pooled age-weight stratum as fixed effects, and the baseline CGI-S Irritability score as covariates. An unstructured covariance matrix will be used to model the within-subject covariance

Table 21. Change From Baseline to Week 8 in PRAS-ASD Total Score, mITT Population, Study M21-465

Statistic	**Cariprazine (N=74)**	**Placebo (N=78)**
Baseline, mean (SD)	43.2 (13.98)	43.9 (15.76)
Change From Baseline to Week 8		
n	63	66
LS mean (SE)	-18.2 (1.75)	-13.4 (1.72)
LS mean difference (SE)	-4.7 (2.4)	
95% CI	(-9.5, 0.01)	
p-value	0.051	

Source: Applicant page 54, CSR (Tables 14.2-2.2.1), verified by FDA statistical reviewer: Dr. Semhar Ogbagaber
Abbreviation: PRAS-ASD = Parent-Rated anxiety scale for youth with autism spectrum disorder
N = Number of subjects in the modified intent-to-treat population
n = Number of subjects in the specific visit with non-missing observation
CFB = Change from Baseline, LS = Least Squares, SE = standard error of the least squares mean, LSMD =least squares mean difference, CI = Confidence Interval
MMRM with treatment group, visit, and treatment group-by-visit interaction, pooled age and weight strata as fixed effects, and the baseline value and baseline by-visit interaction as covariates. An unstructured covariance matrix will be used to model the within-subject covariance

Table 22. Change From Baseline to Week 8 in CGSQ SF-7 Total Score, mITT Population, Study M21-465

Statistic	Cariprazine (N=74)	Placebo (N=78)
Baseline, mean (SD)	7.3 (1.74)	7.6 (1.78)
Change From Baseline to Week 8		
n	69	70
LS mean (SE)	-2.1 (0.21)	-1.5 (0.21)
LS mean difference (SE)	-0.6 (0.28)	
95% CI	(-1.2, -0.07)	
p-value	0.027	

Source: Applicant page 56, CSR (Tables 14.2-2.3.1), verified by FDA statistical reviewer: Dr. Semhar Ogbagaber
CGSQ SF-7 = Caregiver Strain Questionnaire Short Form 7-Item
N = Number of subjects in the modified intent-to-treat population
n = Number of subjects in the specific visit with non-missing observation
CFB = Change from Baseline, LS = Least Squares, SE = standard error of the least squares mean, LSMD = least squares mean difference, CI = Confidence Interval
ANCOVA with treatment, pooled age and weight stratum as factors, and the baseline value as covariate.

Dose/Dose Response

Characterization of dose response is limited because cariprazine doses were flexibly titrated based upon efficacy and tolerability.

Durability of Response

No efficacy assessments were administered past the last dose administration at Week 8, so overall durability of response has not been assessed beyond 8 weeks in this study.

Persistence of Effect

ABC-I assessment was not systematically conducted after stopping study drug, so the effect of the drug over time after treatment is stopped or withheld is not evaluable for this study.

Additional Analyses Conducted on the Individual Trial

Not applicable.

Integrated Review of Effectiveness

See Section 8.1.4 below.

8.1.3. Assessment of Efficacy Across Trials

Not applicable, see Section 8.1.4.

Subpopulations

The exploratory subgroup analyses of the ABC-I subscale showed that the differences between treatment groups within each stratum were largely in line with the findings from the primary efficacy analysis.

Table 23: Subgroup Analysis, mITT Population

Age subgroup analysis: 5 to 9 Years

Statistic	**Cariprazine (N=35)**	**Placebo (N=37)**
Baseline, mean (SD)	31.1 (6.16)	32.5 (6.53)
Change From Baseline to Week 8		
N	28	32
Mean (SD)	-14.1 (11.30)	-12.0 (9.69)
LS Mean (SE)	-13.77 (1.73)	-11.38 (1.67)

Age subgroup analysis: 10 to 12 Years

Statistic	**Cariprazine (N=16)**	**Placebo (N=15)**
Baseline, mean (SD)	30.5 (7.69)	31.4 (7.75)
Change From Baseline to Week 8		
N	16	13
Mean (SD)	-17.9 (7.94)	-13.3 (11.29)
LS Mean (SE)	-18.08 (2.29)	-13.01 (2.45)

Age subgroup analysis: 13 to 17 Years

Statistic	**Cariprazine (N=23)**	**Placebo (N=26)**
Baseline, mean (SD)	28.8 (5.20)	27.2 (5.45)
Change From Baseline to Week 8		
N	17	21
Mean (SD)	-13.6 (9.82)	-9.1 (8.41)
LS Mean (SE)	-13.76 (1.99)	-8.75 (1.83)

Sex subgroup analysis: Female

Statistic	**Cariprazine (N=19)**	**Placebo (N=28)**
Baseline, mean (SD)	29.1 (5.11)	30.5 (8.07)
Change From Baseline to Week 8		
N	14	24
Mean (SD)	-17.3 (8.98)	-10.5 (7.31)
LS Mean (SE)	-16.40 (2.06)	-10.24 (1.58)

Sex subgroup analysis: Male

Statistic	**Cariprazine (N=55)**	**Placebo (N=50)**
Baseline, mean (SD)	30.6 (6.65)	30.7 (6.05)
Change From Baseline to Week 8		
N	47	42
Mean (SD)	-14.3 (10.41)	-11.8 (10.79)
LS Mean (SE)	-14.38 (1.38)	-11.81 (1.48)

Race subgroup analysis: White

Statistic	Cariprazine (N=49)	Placebo (N=47)
Baseline, mean (SD)	29.3 (6.66)	30.5 (7.40)
Change From Baseline to Week 8		
N	41	38
Mean (SD)	-14.9 (9.34)	-11.9 (9.57)
LS Mean (SE)	-15.01 (1.30)	-11.06 (1.34)

Race subgroup analysis: Other

Statistic	Cariprazine (N=25)	Placebo (N=31)
Baseline, mean (SD)	32.4 (5.10)	30.8 (6.00)
Change From Baseline to Week 8		
N	20	28
Mean (SD)	-15.3 (11.79)	-10.6 (9.83)
LS Mean (SE)	-15.07 (2.30)	-11.01 (2.09)

Source: Applicant pages 188-201, CSR (Tables 14.2-4.1, 14.2-4.2, 14.2-4.3), verified by FDA statistical reviewer: Dr. Semhar Ogbagaber

8.1.4. Integrated Assessment of Effectiveness

In Study M21-465, the primary objective was met, and cariprazine showed statistically significant improvement in irritability symptoms. However, Study M21-465 does not, alone, support substantial evidence of effectiveness for the treatment of irritability in ASD without replication of results in a second positive adequate and well-controlled study; the Applicant has noted they are not planning to conduct a second study at this time and are not seeking an indication for the treatment of irritability associated with ASD.

Substantial evidence for the other requested pediatric efficacy indications of treatment in schizophrenia and bipolar I disorder is provided by extrapolation of effectiveness from the adult registrational studies for those indications. Extrapolation is supported by population PK report RD241815 showing that the proposed dosing regimens in pediatric patients provided exposures within the efficacious exposure range in the corresponding adult patient populations. Extrapolation was also supported by two PK studies: Study RGH-PK-18, a two-part, dose-escalation, multiple dose study in pediatric subjects ages 13 to 17 years with schizophrenia and ages 10 to 17 years with bipolar I disorder, and Study RGH-188-201, an open-label, multiple dose study in subjects ages 13 to 17 years and adults with schizophrenia, schizoaffective disorder, or schizophreniform disorder.

8.2. Review of Safety

8.2.1. Safety Review Approach

This safety review examines the pediatric population ages 13 years and older with schizophrenia, 10 years and older with bipolar I disorder, and 5 years and older with ASD in the cariprazine pediatric clinical development program. Because of differences in study design, the short-term controlled study, M21-465, in pediatric subjects with ASD and the long-term, open-label study, 3070-301-001, in pediatric subjects with either schizophrenia, bipolar I disorder, or ASD will be analyzed separately. Review of the long-term study is brief and limited to pertinent information as it lacks controlled safety data.

8.2.2. Review of the Safety Database

Overall Exposure

A total of five clinical studies evaluating cariprazine in pediatric subjects ages 13 years and older with schizophrenia, 10 years and older with bipolar I disorder, or 5 years and older with ASD are completed or ongoing. As of June 27, 2025, a total of 520 pediatric subjects received at least one dose of cariprazine. In three phase 1 multiple-dose PK studies, 126 pediatric subjects received at least one dose of cariprazine. In Study M21-465, 76 subjects received at least one dose of cariprazine. Per the Applicant's 120-Day Safety Update for Study 3070-301-001, a total of 306 subjects received at least one dose of cariprazine.

Adequacy of the Safety Database

In Study 3070-301-001, 180 subjects were treated for >26 weeks. As agreed upon within the pediatric written request, a combined total of at least 100 patients with schizophrenia, ASD, and bipolar disorder together and exposed to cariprazine for at least 6 months, would be a minimum requirement to characterize long-term safety.

8.2.3. Study 3070-301-001 (Open-Label Pediatric Safety Study)

This study is an ongoing 52-week, multicenter, open-label, study of the safety of age-, weight-, and diagnosis-dependent flexible doses of cariprazine (0.75 mg to 4.5 mg) in the treatment of pediatric subjects with schizophrenia, bipolar I disorder, or ASD. The study comprises an up to 21-day screening period, a 52-week open-label treatment period, and a 30-day follow-up period. Of note, prior to Protocol Amendment 6, the study treatment duration was 26 weeks then modified to 52 weeks to meet an international medical agency's requirement. The study has a planned enrollment of 325 subjects. As of the interim data cut, 306 subjects have received at least one dose of cariprazine, 180 subjects (59%) have completed at least 26 weeks of treatment, 56 subjects (18%) have completed at least 364 days of treatment, 146 subjects (48%) have completed the open-label treatment period, and 123 subjects (43%) have discontinued during the open-label treatment period. Below is the dosing regimen.

Table 24: Cariprazine Dosing Regimen

Schizophrenia	Subjects 13 to 17 years of age and < 40 kg body weight: Cariprazine 1.5 to 4.5 mg/d[a]
	Subject 13 to 17 years of age and ≥ 40 kg body weight: Cariprazine 3.0 to 4.5 mg/d[a]
Bipolar I Disorder	Subject 10 to 12 years of age and < 40 kg body weight: Cariprazine 1.5 to 3.0 mg/d[a]
	Subject 10 to 12 years of age and ≥ 40 kg in body weight: Cariprazine 3.0 to 4.5 mg/d[a]
	Subject 13 to 17 years of age and < 40 kg body weight: Cariprazine 1.5 to 4.5 mg/d[a]
	Subject 13 to 17 years of age and ≥ 40 kg body weight: Cariprazine 3.0 to 4.5 mg/d[a]
ASD	Subject 5 to 9 years of age Cariprazine 0.75 to 1.5 mg/d[a]
	Subject 10 to 12 years of age and < 40 kg body weight: Cariprazine 0.75 to 1.5 mg/d[a]
	Subject 10 to 12 years of age and ≥ 40 kg in body weight: Cariprazine 1.5 to 3.0 mg/d[a]
	Subject 13 to 17 years of age and < 40 kg body weight: Cariprazine 0.75 to 3.0 mg/d[a]
	Subject 13 to 17 years of age and ≥ 40 kg body weight: Cariprazine 1.5 to 3.0 mg/d[a]

Source: Applicant CSR for Study 3070-301-001, Table 2, page 27

Notably, an oral solution formulation of cariprazine was used for the younger age cohort, subjects with ASD ages 5 to 9 years. The study enrolled pediatric subjects ages 13 to 17 years with schizophrenia, 10 to 17 years with bipolar I disorder, or 5 to 17 years with ASD. These subjects could have been de novo or rolled over from parent studies—3112-301-001, a randomized, controlled study in subjects with bipolar depression; or M21-465, a randomized, controlled, 8-week study in subjects ages 5 to 17 years with irritability associated with ASD.

The primary diagnosis was confirmed by structured diagnostic interview using the K-SADS-PL. Key exclusion criteria included: major depressive disorder, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, or psychotic disorder due to another medical condition; in subjects with ASD, associated Rett disorder, fragile-X syndrome, or childhood disintegrative disorder; substance related disorder (except caffeine or tobacco) within the past 3 months; for subjects with schizophrenia or bipolar I disorder, IQ <70 or for subjects with ASD, IQ <25; antipsychotic depot within 2 cycles of the respective dosing interval or electroconvulsive therapy within the past month; history of or current homicidal risk or behavior that resulted in hospitalization within the past 6 months; and history of suicide attempt within the past year or significant suicidal ideation (SI) currently or within the past 6 months as evidenced by a “yes” response to Question 4 or 5 on the C-SSRS.

The primary study objective was to assess the long-term safety and tolerability of cariprazine in the respective schizophrenia, bipolar I disorder, and ASD populations.

Table 25: Demographics, Safety Population, Study 3070-301-001

Parameter	Schizophrenia (N=21)	Bipolar I Disorder (N=146)	Autism Spectrum Disorder (N=139)	All Subjects (N=306)
Age (years)				
Mean (SD)	15.4 (1.16)	13.5 (2.14)	11.8 (3.61)	12.8 (3.05)
Median	15.0	13.5	12.0	13.0
Q1, Q3	15.0, 16.0	12.0, 15.0	9.0, 15.0	11.0, 15.0
Min, Max	13, 17	10, 17	5, 17	5, 17
n	21	146	139	306
Age Group (years), n (%)				
< 13		52 (35.6)	73 (52.5)	125 (40.8)
5-9 years old			41 (29.5)	41 (13.4)
10-12 years old		52 (35.6)	32 (23.0)	84 (27.5)
>= 13	21 (100.0)	94 (64.4)	66 (47.5)	181 (59.2)
Sex, n (%)				
Male	13 (61.9)	54 (37.0)	104 (74.8)	171 (55.9)
Female	8 (38.1)	92 (63.0)	35 (25.2)	135 (44.1)
Race, n (%)				
White	7 (33.3)	84 (57.5)	93 (66.9)	184 (60.1)
Black or African American	10 (47.6)	57 (39.0)	34 (24.5)	101 (33.0)
Asian	3 (14.3)	0	5 (3.6)	8 (2.6)
American Indian or Alaska Native	0	1 (0.7)	0	1 (0.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.7)	0	1 (0.3)
Multiple [1]	1 (4.8)	3 (2.1)	7 (5.0)	11 (3.6)
Missing	0	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	4 (19.0)	31 (21.2)	56 (40.3)	91 (29.7)
Not Hispanic or Latino	17 (81.0)	115 (78.8)	83 (59.7)	215 (70.3)

Source: Applicant 4-Month Safety Update Report for Study 3070-301-001, Table 14.1-4.1

There were far fewer subjects with schizophrenia enrolled in the study compared to subjects with bipolar I disorder and ASD. However, the safety profile and benefit:risk assessment of subjects ages 13 years and older with schizophrenia is not expected to be meaningfully different from subjects ages 10 years and older with bipolar I disorder, so the safety data from this study is sufficient to characterize the long-term safety of all three patient populations.

In subjects with bipolar I disorder, there was a greater proportion of female subjects compared to male subjects. In subjects with ASD, there was a greater proportion of male subjects compared to female subjects. This ratio mirrors the parent study, M21-465, and the higher percentage of males overall is typical for a population with ASD. Age distribution was imbalanced towards the older age cohort (≥13 years) in contrast to the parent study.

Overall, given the limitations of the study design (i.e., open-label, uncontrolled) and that the safety data does not indicate a new safety signal relative to the known safety profile of cariprazine based on adult study data, the demographic imbalances are not expected to be clinically meaningful.

8.2.4. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No major concerns about data integrity were noted.

Categorization of Adverse Events

Both Studies M21-465 and 3070-301-001 used Medical Dictionary for Regulatory Activities

(MedDRA) Version 27.0 to code adverse events (AE). AEs were recorded at each study visit for both studies. The primary clinical reviewer assessed available data and narratives for AE adjudication. In addition to the groupings identified by the Applicant, the reviewer grouped the following terms:

Somnolence: somnolence, sedation, hypersomnia, and sedation complication
Fatigue: fatigue and lethargy
Akathisia: akathisia and restlessness
Blood pressure increased: blood pressure increased and blood pressure systolic increased
Blood triglycerides increased: blood triglycerides abnormal (specific AE was verified as increased) and blood triglycerides increased
Hallucination: hallucination and hallucination auditory
Muscle contractions involuntary: muscle contractions involuntary and muscle spasms
Bradycardia: bradycardia and sinus bradycardia
Bradykinesia: bradykinesia and psychomotor retardation
Rash: rash and pruritic rash

Based upon the known risk of cataracts as described in cariprazine labeling, the study protocols include ocular AEs as AEs of special interest. Additionally, there were some safety assessment scales administered in the studies to evaluate for suicidal ideation/behavior (C-SSRS), depression (Calgary Depression Scale for Schizophrenia and Children's Depression Rating Scale), and extrapyramidal symptoms (Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scales (AIMS), and Simpson-Angus Scales (SAS).

Routine Clinical Tests

Both studies included a standard array of serum chemistry, hematology and metabolic (i.e., hemoglobin A1c and lipid profile) laboratory assessments along with vital sign and electrocardiogram (ECG) assessments. Additionally, based upon the known risk of cataracts with cariprazine, best corrected visual acuity, color fundus photography, and optical coherence tomography were included in the long-term study, 3070-301-001.

8.2.5. Safety Results

Deaths

No deaths occurred in the cariprazine pediatric development program.

Serious Adverse Events

In Study M21-465, the only two observed serious adverse events (SAEs) (irritability and fecaloma) occurred in subjects who were taking placebo treatment. In Study 3070-301-001,

observed SAEs in the subjects taking cariprazine were bipolar I disorder (in two subjects), SI (in three subjects), aggression (in three subjects), schizophrenia, mental status changes, and anaphylactic reaction.

The clinical narratives for SAEs in subjects taking cariprazine follow:

> **Subject** (b) (6): An 11-year-old female with bipolar I disorder experienced moderate aggression and irritability that worsened to severe, and serious and severe bipolar I disorder. No other AEs were reported. Medical history included allergies, abdominal pain, dyspepsia, and nausea with associated concomitant medications. Psychiatric history included insomnia, anxiety, attention deficit hyperactivity disorder (ADHD), adjustment disorder, and bipolar I disorder, all ongoing and with melatonin as a concomitant medication. Prior medication included aripiprazole for bipolar I disorder. The subject initiated cariprazine 0.5 mg daily with the dose titrated up over 1 week to 4.5 mg daily. Approximately 1 month after initiation of cariprazine and 3 weeks after titration to the maintenance dose, the subject experienced increasing irritability and aggressive behavior without other manic or depressed symptoms. As a result, 1.5 weeks later, she began a taper off of cariprazine and, 2 weeks later, initiated lithium. Approximately 2 weeks after discontinuation of cariprazine, irritability, anger outbursts, and aggressive behaviors worsened, then the subject reported auditory and visual hallucinations. Subsequently, 2 months after initiation of cariprazine and 3 weeks after discontinuation, the subject was hospitalized for bipolar I disorder and psychosis. During the admission, the subject exhibited separation anxiety and complained of hallucinations with separation from her parents; she received single doses of haloperidol and benztropine and initiated quetiapine. She was discharged after 5 days in stable and improved condition.
>
> *Reviewer Comment: Assessment of a causal relationship between this SAE of bipolar I disorder and cariprazine is challenging as symptoms worsened even after study treatment discontinuation. It is also very plausible that symptom exacerbation occurred as a result of study treatment inefficacy, due to the natural course of illness, or secondary to psychosocial factors not detailed.*
>
> **Subject** (b) (6): A 15-year-old female with bipolar I disorder experienced serious and severe SI without plan. Other AEs during treatment included mild nausea and COVID-19. Medical history included headaches, obesity, dysmenorrhea, and allergic rhinitis with associated concomitant medications. Psychiatric history included ADHD, panic disorder, nightmares, and bipolar I disorder with concomitant medications doxylamine, melatonin, and hydroxyzine. Prior medication included lithium. Of note, the Applicant's case narrative describes use of "atarax [alprazolam] for anxiety," but this is expected to be an error as hydroxyzine (brand name atarax) is described numerous instances elsewhere in the narrative. The subject initiated cariprazine 0.5 mg daily with the dose titrated up over 1 week to 3 mg daily. Approximately 5 months after initiation

of cariprazine, the subject reported worsening of depressed mood along with hypersomnia, decreased energy, anhedonia, feeling of worthlessness, and irritability over 2 weeks along with persistent, intense SI with mild intent but no specific plan. There were no associated suicidal behaviors, psychotic symptoms, or manic symptoms. The subject was hospitalized during which cariprazine was discontinued with initiation of Invega. The subject was discharged in stable condition.

Reviewer Comment: Assessment of a causal relationship between this SAE of SI and cariprazine is challenging as the SI was associated with symptoms of depression. It is also very plausible that symptom exacerbation occurred as a result of another study treatment adverse reaction (i.e., depression), related to study treatment inefficacy, due to the natural course of illness, or secondary to psychosocial factors not detailed. SI risk is already included in current cariprazine drug labeling.

Subject (b) (6): A 16-year-old female with bipolar I disorder experienced serious and severe aggression. She also experienced a mild AE of insomnia. Medical history included seasonal allergies, food allergies, asthma, and eczema with associated concomitant medication. No further psychiatric history was described. The subject initiated cariprazine 0.5 mg daily with the dose titrated up over 1 week to 3 mg daily. Approximately 3 months after initiation of cariprazine, she ran away from home twice, during which she abused opioids and cannabis. The second runaway incident lasted for 2 weeks during which she did not take cariprazine, and upon return, the subject threatened self-harm and was aggressive towards her mother leading to hospitalization. Details of the admission were not provided.

Reviewer Comment: Assessment of a causal relationship between this SAE of aggression and cariprazine is challenging as the subject was non-compliant with study treatment and given the additional confounders of substance abuse and behavioral symptoms. Additional psychiatric and behavioral history would be useful in further review of this event.

Subject (b) (6): A 12-year-old female with bipolar I disorder experienced serious and severe SI. No other AEs were reported. Medical history included eczema, arthralgia, gait disturbance, acne, and iron deficiency anemia with associated concomitant medication. Psychiatric history included insomnia and bipolar I disorder; prior medication included melatonin, diphenhydramine, prazosin, trazodone, and lamotrigine. The subject initiated cariprazine 0.5 mg daily with the dose titrated up over 1 week to 3 mg daily then 4 months later to 4.5 mg daily. Approximately 7 months after initiation but 3 weeks after treatment discontinuation, the subject experienced SI with intent and exhibited aggressive behavior for which she was hospitalized for 1 week. Details of the admission were not provided. The subject's medication list details that approximately 1 week after cariprazine treatment completion and 2 weeks prior to hospitalization, the subject initiated aripiprazole and lamotrigine.

Reviewer Comment: Assessment of a causal relationship between this SAE of SI and cariprazine is challenging as the SI occurred 3 weeks after study treatment discontinuation and with aripiprazole and lamotrigine initiation. It is also very plausible that symptom exacerbation occurred as a reaction to one of the other psychiatric medications that was initiated, as a result of the natural course of illness, or secondary to psychosocial factors not detailed. SI risk is already included in current cariprazine drug labeling.

Subject (b) (6): A 13-year-old female experienced severe and serious exacerbation of bipolar I disorder. She also experienced a mild AE of akathisia. Medical history included seasonal allergies with associated concomitant medication. Psychiatric history included ADHD, major depressive disorder, and bipolar I disorder with prior medications methylphenidate, sertraline, and oxcarbazepine. The subject initiated cariprazine 0.5 mg daily with the dose titrated up over 1 week to 3 mg daily. Approximately 3 weeks after initiation and 2 weeks after titration to maintenance dose of cariprazine, the subject experienced exacerbation of bipolar I disorder, described as aggression towards parent. She was hospitalized for 1 week and discontinued cariprazine. Details of the admission were not provided.

Reviewer Comment: Assessment of a causal relationship between this SAE of exacerbation of bipolar I disorder and cariprazine is challenging. It is also very plausible that symptom exacerbation occurred due to study treatment inefficacy, the natural course of illness, or psychosocial factors not detailed.

Subject (b) (6): A 16-year-old male experienced a serious and severe AE of exacerbation of schizophrenia. No other AEs were reported. Medical history included acne and eczema with associated concomitant medication. Psychiatric history included ADHD, major depressive disorder, and schizophrenia. Concomitant medication included mixed amphetamine salt; prior medication included clozapine. The subject initiated cariprazine 0.5 mg daily with the dose titrated up over 2 weeks to 4.5 mg daily. Approximately 1 month after initiation of cariprazine and 2 weeks after titration to maintenance dose, the subject was observed to be pacing, not sleeping, standing over parents at nighttime, smiling and laughing without cause, and attempting to exit a moving vehicle. He was hospitalized for 1 week; cariprazine was discontinued and risperidone, clozapine, and propranolol were initiated. No details of the admission were provided.

Reviewer Comment: Assessment of a causal relationship between this SAE of exacerbation of schizophrenia and cariprazine is challenging. It is also very plausible that symptom exacerbation occurred as a result of study treatment inefficacy or due to the natural course of illness. Notably, the subject's prior use of clozapine implies treatment-resistant illness, which is considered a distinct, more severe indication.

Subject (b) (6): A 17-year-old male with ASD experienced severe and serious aggression. Other AEs included moderate weight increased, mild hyperbilirubinemia, moderate skin laceration, moderate toothache, mild vomiting, and mild agitation and head banging. Psychiatric history included ADHD and ASD; concomitant medications included methylphenidate and clonidine. Note that the Applicant's narrative states that alternative etiology for aggression was risk factor of underlying schizophrenia/bipolar I disorder, but neither of these diagnoses is described elsewhere in the subject's narrative history. The subject initiated cariprazine 0.5 mg daily with the dose titrated up over 1 week to 1.5 mg daily then after 5 weeks to 3 mg daily. Nearly 1 year after initiation of cariprazine, the subject was agitated and hit himself in school. He was hospitalized overnight and received prn haloperidol and lorazepam then discharged. He became agitated again at home and was re-hospitalized 3 days later. During the second hospitalization, he received chlorpromazine, valproate, and clonazepam. Cariprazine was paused during hospitalization but resumed upon discharge. After cariprazine treatment completion, the subject reinitiated chlorpromazine, valproate, and clonazepam.

Reviewer Comment: Assessment of a causal relationship between this SAE of aggression and cariprazine is challenging given occurrence after 1 year on treatment. Alternative etiologies include natural course of illness or psychosocial factors not detailed.

Subject (b) (6): A 7-year-old female with ASD experienced moderate muscle rigidity, leg pain, and pyrexia and serious and severe mental status changes. Other reported AEs included mild ADHD, mild urinary incontinence, mild abdominal pain upper, and mild bradykinesia. Medical history included asthma, speech issues, and retinal pigmentation with associated concomitant medication. Psychiatric history included ASD. The subject initiated cariprazine 0.5 mg daily and only received three doses. After three doses of cariprazine, the subject was hospitalized for altered mental status, muscle rigidity, and fever along with stomachache, leg pain, and slow movements. Creatine kinase (CK) levels were normal, and rhinovirus testing was positive. The subject improved after discontinuation of cariprazine and was discharged home. Of note, it appears that the hospital neurological examination describes the subject exhibiting excellent eye contact and to be very social and talkative leading to a low suspicion of ASD and perhaps undiagnosed behavioral disorder versus ADHD. The AE of ADHD was documented on Day 1 of cariprazine and described as ongoing, but ADHD is not included in the medical or psychiatric history.

Reviewer Comment: This SAE of mental status change appears consistent with neuroleptic malignant syndrome (NMS), despite the normal CK level. CK levels may be normal early or with mild disease; however, concomitant rhinovirus infection is a confounding factor. Notably, an oral solution formulation of cariprazine was used for younger subjects, ages 5 to 9 years. NMS risk is already included in current cariprazine

drug labeling.

Three SAEs were included in the 120-day Safety Update but did not include case narratives. All three occurred in subjects with ASD. Anaphylactic reaction and aggression occurred in subjects during the open-label treatment period, and SI occurred in a subject during the safety follow-up period.

Notably, the majority of the SAEs occurred in subjects with bipolar I disorder. Given the absence of a control group in this open-label study, the meaningfulness of this trend is uncertain. None of the SAEs described indicates a new safety signal.

Dropouts and/or Discontinuations Due to Adverse Effects

In Study M21-465, six subjects reported AEs leading to drug discontinuation (AEDC):

In the cariprazine treatment group—somnolence (in two subjects), headache, insomnia, and fatigue.

In the placebo treatment group—irritability.

Notably, the majority of AEDCs occurred in younger subjects with ASD, ages 5 to 9 years, compared to older subjects with ASD, ages 10 years and older. However, an oral solution formulation of cariprazine was used for this younger age cohort. It is possible the higher exposures plus a more sensitive age group led to poorer tolerability.

In Study 3070-301-001, the following AEDCs were reported: somnolence (in four subjects); aggression (in three subjects); akathisia (in two subjects); irritability (in two subjects); tremor (in two subjects); weight increased (in two subjects); alanine aminotransferase (ALT) increased; SI; hallucination; bipolar I disorder; social problem; flat affect; schizophrenia; myopia; abdominal pain; dizziness; temperature intolerance; anxiety; pyrexia, muscle rigidity, and mental status changes (all in the same subject); and blood creatine phosphokinase increased.

None of the AEDCs described indicates a new safety signal.

Significant Adverse Events

In Study M21-465, three severe AEs were reported: one in a subject taking cariprazine (insomnia) and two in subjects taking placebo (irritability and fecaloma). In Study 3070-301-001, observed severe AEs in the subjects taking cariprazine were aggression (in four subjects), bipolar I disorder (in two subjects), irritability (in two subjects), weight increased (in two subjects), dental caries, dizziness, SI, tremor, schizophrenia, insomnia, UTI, migraine, and mental status changes.

None of the severe AEs described indicates a new safety signal.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent AE summary tables follow.

In the placebo-controlled Study M21-465, the most common AEs (occurring in ≥5% of subjects on cariprazine and greater than placebo) were somnolence, headache, vomiting, and nausea. Notably, somnolence was observed at a higher rate (18%) than reported with other cariprazine studies evaluating adult patients (5 to 10%). However, nearly half of these subjects (6/14) were younger than 10 years old and thus received an oral solution formulation of cariprazine rather than the approved capsule formulation.

Table 26: Study M21-465 Adverse Events Occurring in More Than One Subject on Cariprazine

	Cariprazine (N=76)		Placebo (N=79)	
PT	Number of Subjects	Proportion (%)	Number of Subjects	Proportion (%)
Somnolence	14	18.4	1	1.3
Headache	8	10.5	5	6.3
Vomiting	8	10.5	4	5.1
Nausea	5	6.6	5	6.3
Weight increased	4	5.3	4	5.1
Fatigue	3	3.9	1	1.3
Insomnia	3	3.9	2	2.5
Pyrexia	3	3.9	2	2.5
Rash	3	3.9	0	0
Anxiety	2	2.6	0	0
Salivary hypersecretion	2	2.6	0	0
Skin abrasion	2	2.6	0	0
Tachycardia	2	2.6	0	0

Source: Study M21-465 adae.xpt output via MAED

In the open-label Study 3070-301-001, the most common AEs (≥5% of subjects) were weight increased, somnolence, nausea, headache, fatigue, vomiting, akathisia, and agitation.

Table 27: Study 3070-301-001 Adverse Events Occurring in ≥2% of Subjects

PT	Number of Subjects (N=303)	Proportion (%)
Weight increased	37	12.2
Somnolence	29	9.6
Nausea	24	7.9
Headache	21	6.9

PT	Number of Subjects (N=303)	Proportion (%)
Fatigue	21	6.9
Vomiting	18	5.9
Akathisia	18	5.9
Agitation	15	5
Nasopharyngitis	13	4.3
Insomnia	12	4
Anxiety	9	3
Irritability	9	3
Tremor	9	3
COVID-19	8	2.6
Constipation	7	2.3
Decreased appetite	7	2.3
Dizziness	7	2.3
Aggression	6	2
Diarrhea	6	2
Influenza	6	2
Pharyngitis streptococcal	6	2
Tachycardia	6	2
Upper respiratory tract infection	6	2
Urinary tract infection	6	2
Vision blurred	6	2

Source: Study 3070-301-001 adae.xpt output via MAED

The rate of somnolence reported in subjects with ASD taking cariprazine in Study M21-465 was markedly higher than that reported in adult subjects in clinical cariprazine studies. However, the impact of the younger subgroup of subjects receiving an unapproved oral solution formulation of cariprazine is uncertain. Overall, the reported AEs in both Studies M21-465 and 3070-301-001 do not indicate a new safety signal, but there may be more sensitivity in the child subgroup to certain AEs such as somnolence.

Laboratory Findings

Overall, laboratory results did not show any new safety signals. Laboratory findings in the current cariprazine label include known risks for metabolic laboratory changes, leukopenia, neutropenia, agranulocytosis, transaminase elevation, and creatine phosphokinase elevation. See Section 8.2.6 regarding metabolic laboratory changes, which are a known antipsychotic drug class effect. Otherwise, in both studies, M21-465 and 3070-301-001, serum chemistry and hematology did not show major concerning clinical trends, and no subjects met criteria for Hy's law. AEs during the treatment period from abnormal chemistry and hematology results were as follows:

In Study M21-464,

- ALT increased in 1 subject on cariprazine (1%) compared to no subjects on placebo.
- Blood potassium increased in 1 subject on cariprazine (1%) compared to no subjects on placebo.
- Neutrophil count decreased in no subjects on cariprazine compared to 1 subject on placebo (1%).
- White blood cell count decreased in no subjects on cariprazine compared to 1 subject on placebo (1%).

In Study 3070-301-001, in which all subjects received cariprazine treatment,

- ALT increased in 4 subjects (1%).
- Aspartate aminotransferase (AST) increased in 1 subject (<1%).
- Hyperbilirubinemia occurred in 1 subject (<1%).
- Monocyte count decreased in 2 subjects (1%).
- Blood bicarbonate decreased in 1 subject (<1%).
- Blood creatine phosphokinase increased in 1 subject (<1%).
- Blood prolactin increased in 1 subject (<1%).
- Blood thyroid stimulating hormone decreased in 1 subject (<1%).
- Hypothyroidism occurred in 1 subject (<1%).
- Tri-iodothyronine free increased in 1 subject (<1%).
- Urine ketone body present occurred in 1 subject (<1%).

Given the non-clinically significant changes in laboratory assessments and few AEs reported across different laboratory parameters, there does not appear to be a new safety signal for this category.

Vital Signs

Vital sign changes in the current cariprazine label include known risks for weight gain, orthostatic hypotension and syncope, body temperature dysregulation, and blood pressure changes. See Section 8.2.6 regarding weight gain, which is a known antipsychotic drug class effect.

In Study M21-465, vital sign measurements did not show major concerning clinical trends. In Study 3070-301-001, 5% of subjects with ASD (7/138) were observed to have a potentially clinically significant post-baseline value for increased systolic blood pressure; 6% of all subjects (18/299) met criteria for orthostatic systolic hypotension; and 11% of all subjects (33/299) met criteria for orthostatic diastolic hypotension. AEs during the treatment period from abnormal vital sign measurements were as follows:

In Study M21-465,

- Pyrexia occurred in 3 subjects on cariprazine (4%) compared to 2 subjects on

placebo (3%).
- Tachycardia occurred in 2 subjects on cariprazine (3%) compared to no subjects on placebo.
- Orthostatic hypotension occurred in 1 subject on cariprazine (1%) compared to no subjects on placebo.

In Study 3070-301-001,
- Tachycardia occurred in 6 subjects (2%).
- Bradycardia occurred in 3 subjects (1%).
- Pyrexia occurred in 5 subjects (2%).
- Orthostatic hypotension occurred in 2 subjects (1%).
- Blood pressure increased in 2 subjects (1%).
- Additionally, syncope was reported in 1 subject (<1%).

In Study 3070-301-001, increased systolic blood pressure and orthostatic hypotension were both noted. These findings are difficult to assess in the absence of a control arm and are already known risks with cariprazine. Given the non-clinically significant changes in laboratory assessments in controlled study, M21-465, and few AEs reported across different laboratory parameters in both studies, there does not appear to be a new safety signal.

Electrocardiograms (ECGs)

In both Studies M21-465 and 3070-301-001, there were no notable ECG changes, and no ECG-related AEs were reported.

QT

In both Studies M21-465 and 3070-301-001, there were no notable QT changes, and no QT-related AEs were reported.

Immunogenicity

In Study M21-465, three subjects on cariprazine (4%) compared to no subjects on placebo had an AE of rash and no subjects on cariprazine compared to one subject on placebo (1%) had an AE of hypersensitivity. In Study 3070-301-001, 1 subject (<1%) had an AE of anaphylactic reaction, 1 subject (<1%) had an AE of lip swelling, and two subjects (1%) had AEs of rash. Due to the non-specific nature of rashes and in uncontrolled study, 3070-301-001, the single AEs of anaphylactic reaction and lip swelling with cariprazine, these AEs do not indicate a major signal for hypersensitivity reaction.

8.2.6. Analysis of Submission-Specific Safety Issues

Metabolic Changes

Metabolic changes are a known antipsychotic drug class effect; in the current cariprazine label,

described risks include hyperglycemia and diabetes mellitus, dyslipidemia, and weight gain. Additionally, the adolescent population has been identified as particularly at risk for SGA-induced weight gain and dyslipidemia.

In Study M21-465, metabolic laboratory results did not show major concerning clinical trends. As described in labeling, the mean change in weight z-score from baseline to last available visit was +0.2 SD in subjects on cariprazine compared to <0.1 SD in subjects on placebo. Change in body weight z-score ≥0.5 SD occurred in 19% of subjects on cariprazine compared to 1% of subjects on placebo.

In Study 3070-301-001, metabolic laboratory results also did not show major concerning clinical trends. (b) (4), the following shifts from normal to abnormal laboratory values and weight were observed:

- Glucose <100 mg/dL to ≥126 mg/dL: subjects with schizophrenia = 0, subjects with bipolar disorder = 5% (4/87)
- Total cholesterol <170 mg/dL to ≥200 mg/dL: subjects with schizophrenia = 0, subjects with bipolar disorder = 1% (1/83)
- HDL cholesterol >45 mg/dL to <40 mg/dL: subjects with schizophrenia = 9% (1/11), subjects with bipolar disorder = 10% (9/93)
- Triglycerides (TG) <190 mg/dL to ≥130 mg/dL: subjects with schizophrenia = 13% (1/8), subjects with bipolar disorder = 18% (11/60)
- Change in body weight z-score ≥0.5 SD: subjects with schizophrenia = 0, subjects with bipolar disorder = 15% (21/144), subjects with ASD = 32% (44/139).

The mean change in weight from baseline to last available visit (range 7 to 419 days, mean 144 days) was +2.4 kg in subjects with schizophrenia, +3.1 kg in subjects with bipolar I disorder, and +5.3 kg in subjects with ASD. The mean change in weight z-score from baseline to last available visit was +0.1 SD in subjects with schizophrenia, +0.2 SD in subjects with bipolar I disorder, and +0.4 SD in subjects with ASD.

AEs during the treatment period from abnormal metabolic laboratory and weight results were as follows:

In Study M21-465,

- Hypertriglyceridemia occurred in 1 subject on cariprazine (1%) compared to no subjects on placebo.
- Weight increased in 4 subjects (5%) each in both the cariprazine and placebo groups

In Study 3070-301-001,

- Weight increased in 37 subjects (12%).
- Weight decreased in 3 subjects (1%).

- Waist circumference increased in 2 subjects (1%).
- Blood triglycerides increased in 2 subjects (1%).
- Hyperlipidemia occurred in 1 subject on cariprazine (<1%).

Overall, per the data above in both Studies M21-465 and 3070-301-001, the increase in weight was particularly marked in subjects with ASD on cariprazine. However, the impact of the younger subgroup of subjects receiving an unapproved oral solution formulation of cariprazine is uncertain. Metabolic changes, including increase in weight, are a known antipsychotic drug class effect. Furthermore, the adolescent population has been identified as particularly at risk for SGA-induced weight gain and dyslipidemia.

Extrapyramidal Symptoms

Extrapyramidal symptoms (EPS) are also a known antipsychotic drug class effect; in the current cariprazine label, described risks include dystonia, extrapyramidal symptoms, and akathisia. In Study M21-465, AIMS, BARS, and SAS assessments did not show major concerning clinical trends. In Study 3070-301-001, 2% of subjects experienced parkinsonism, and 5% experienced akathisia per EPS assessment scales. AEs during the treatment period related to EPS were as follows:

In Study M21-465,

- Akathisia occurred in no subjects on cariprazine compared to 1 subject on placebo (1%).

In Study 3070-301-001,

- Tremor occurred in 9 subjects (3%).
- Dyskinesia occurred in 3 subjects (1%).
- Muscle rigidity occurred in 3 subjects (1%).
- Extrapyramidal disorder occurred in 2 subjects (1%).
- Bradykinesia occurred in 2 subjects (1%).
- Muscle contractions involuntary occurred in 2 subjects (1%).
- Musculoskeletal stiffness occurred in 1 subject (<1%).
- Oculogyric crisis occurred in 1 subject (<1%).
- Parkinsonian gait occurred in 1 subject (<1%).

There were no new safety data from Studies M21-465 and 3070-301-001 to add to the characterization of the already known antipsychotic drug class effect of EPS.

Suicidal Ideation/Behavior

Risk for suicidal thoughts and behaviors in children, adolescents, and young adults are a known antidepressant drug class effect and are included in antipsychotic drug labels that carry an indication for the treatment of depression, such as cariprazine. In Study M21-465, C-SSRS

responses did not show major concerning clinical trends. In Study 3070-301-001, 10% of subjects with schizophrenia (2/20), 7% of subjects with bipolar I disorder (10/141), and 1% of subjects with ASD (2/138) reported SI on the C-SSRS; no subjects with schizophrenia, 2% of subjects with bipolar I disorder (3/141), and 1% of subjects with ASD (2/138) reported non-suicidal self-injurious behavior on the C-SSRS. One subject with bipolar I disorder reported a suicide attempt on the C-SSRS that was documented as a non-serious AE of SI and on audit trail, described as the subject not expecting to end their life. AEs during the treatment period related to SI/B were as follows:

In Study M21-465, there were no reports of SI/B-related AEs.

In Study 3070-301-001,

- SI occurred in 4 subjects (1%).
- Self-destructive behavior occurred in 2 subjects (1%).

There were no safety data from Studies M21-465 and 3070-301-001 indicating any new or increased risk for suicidal ideation and behavior in this population relative to adults.

Cataracts

The development of cataracts was observed in nonclinical studies. Although cataracts were reported in premarketing adult clinical trials of cariprazine, the trials were too short to attribute a direct risk of cataract development to cariprazine usage. A general note about the nonclinical cataract signal and results from two longer-term open-label safety studies (where the incidence of cataracts was 0.1 and 0.2% in patients with schizophrenia [48-week study] and bipolar mania [16-week study] respectively) was still included in Section 6 of the cariprazine label.

As cataracts are therefore still included in the current cariprazine label as a potential risk, the pediatric study protocols included ocular AEs as AEs of special interest and Study 3070-301-001 included specific ocular safety monitoring. (In Type D Meeting- Written Responses Only on November 3, 2023, the Agency was in agreement with the Applicant's proposal to remove ocular assessments from the short-term pediatric studies with a duration of 8 weeks or less.) Overall, 76.6% of subjects with $\geq$ 26 weeks of exposure to cariprazine had ophthalmologic examination data (BCVA, OCT, or color fundus photography) at Week 26 (Study 3070-301-001 Post hoc Table 14.3-1.1a).

One ocular SAE was reported as follows: on (b) (6), relevant laboratory and diagnostics tests included color vision tests, intraocular pressure, lens status, ophthalmologist consultation, optical coherence tomography, retinal photography, slit-lamp examination, and visual acuity tests. The color vision tests results were: normal OS and OD, type of color plates used HRR (Hardy Rand and Rittler), not clinically significant. The intraocular pressure results were: 10 mm Hg (OS left), 12 mm Hg (OD right). The lens status results were: OS (left eye) abnormal, trace nuclear sclerosis, opacification: yes, location: nuclear, OD normal. The ophthalmologist

consultation results were: trace nuclear sclerosis left eye. The optical coherence tomography results were: no separation of the retinal layers was noted, retinal layer separation was normal for both eyes, Zeiss OCT machine was used. The retinal photography results were: normal OS and OD, no blurred images, fundus camera used was Clarus. The slit-lamp examination results were: lid, conjunctiva (palpebral and bulbar), anterior chamber, cornea, vitreous pathology, iris/pupil pathology, optic disc/cup, retinal vessels, macula, and other pathology results were normal for both eyes. The visual acuity tests results were: +0.10 OS (left), 0.00 OD (right) (assessed at a lane distance of 2 meters). Action taken with the suspect drug CARIPRAZINE HCL 3mg CAP was not changed due to the event. The study drug administration was completed on (b) (6). Subject did not receive treatment for cataract nuclear. On (b) (6), the subject recovered without sequelae from cataract nuclear. Follow-up was performed for this case and the required information was obtained.

The Division of Ophthalmology's assessment is that the SAE report does not provide information regarding the subject's visual acuity. The results reported for visual acuity are a refraction (glasses prescription), not visual acuity. Additionally, it is reported that the subject recovered from the cataract, but cataracts do not resolve without surgical intervention.

Two ocular AESIs were reported, both in the bipolar I disorder population (Listing 14.3-3.4):

- One subject had an AE of cataract nuclear (investigator term: trace nuclear sclerosis left eye) reported on Day 168 (mild, treatment-related, nonserious, dose not changed, reported as resolved on Day 209). The investigator indicated that this observation was not clinically significant.

- One subject with a history of myopia had an AE of myopia (investigator term: worsening myopia, bilateral) reported on Day 23 (moderate, not treatment related, nonserious, drug withdrawn, reported as resolved on Day 37).

The Division of Ophthalmology agrees with the Applicant that the AE of trace nuclear sclerosis is likely treatment related but not clinically significant and that worsening myopia is likely not treatment related and is non-serious.

There were no new safety data from Studies M21-465 and 3070-301-001 to add to the characterization of the already known risk of cataracts with cariprazine.

8.2.7. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable; no new COA safety analyses were conducted for these studies.

8.2.8. Safety Analyses by Demographic Subgroups

Not applicable; studies are too small to provide interpretable subgroup data.

8.2.9. Specific Safety Studies/Clinical Trials

Not applicable; no additional special safety studies were conducted.

8.2.10. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new human carcinogenicity studies were submitted with this application.

Human Reproduction and Pregnancy

No new information regarding human reproduction was submitted with this application. No pregnancies were reported in the pediatric cariprazine program.

Pediatrics and Assessment of Effects on Growth

Please reference Section 8.2.6 regarding the effect of cariprazine on weight increase.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No relevant overdose or abuse potential assessments were conducted. Understanding of these areas is informed by Sections 9 and 10 of the current cariprazine label.

8.2.11. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The cariprazine adverse reactions identified through postmarketing experience and described in the label are: Skin and Subcutaneous Tissue Disorders, Stevens-Johnson syndrome. No cases of Stevens-Johnson syndrome were reported in the pediatric studies. The Applicant submitted a Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Report on January 2, 2025, reporting period October 6, 2022, through October 5, 2024, which did not indicate any new safety signals.

Expectations on Safety in the Postmarket Setting

The Applicant has demonstrated acceptable safety of cariprazine in pediatric subjects with schizophrenia and bipolar I disorder, and the postmarket safety profile is anticipated to be consistent with what is known for cariprazine.

8.2.12. Integrated Assessment of Safety

The safety assessment for cariprazine for the treatment of schizophrenia in subjects ages 13 to 17 years and bipolar I disorder in subjects ages 10 to 17 years is adequate. The safety findings from Study 3070-301-001 are generally consistent with the known safety profile of cariprazine, including risks for metabolic changes and weight gain, EPS, and cataracts– these are adequately described in current labeling. There are no new safety issues that preclude the approval of this sNDA.

The safety assessment for cariprazine for the treatment of irritability associated with ASD in patients ages 5 to 17 years is adequate. The safety findings from Study M21-465 are generally consistent with the known safety profile of cariprazine as described in current labeling. However, the reported rate of somnolence was higher in pediatric subjects with ASD compared to adult subjects in the cariprazine pivotal studies. The impact of the younger subgroup of subjects receiving an unapproved oral solution formulation of cariprazine is uncertain. Because Study M21-465 does not, alone, support substantial evidence of effectiveness for an indication for the treatment of irritability associated with ASD, this indication will not be approved, but safety data from this study will be included in Section 8.4.

8.3. Statistical Issues

No major statistical issues were identified.

8.4. Conclusions and Recommendations

Substantial evidence of effectiveness for the treatment of schizophrenia in pediatric patients 13 through 17 years of age and acute manic or mixed episodes associated with bipolar I disorder in pediatric patients 10 through 17 years of age is based upon extrapolation from cariprazine's known efficacy in the treatment of adult schizophrenia and bipolar I disorder, which is supported by a population PK report and two PK studies.

In the placebo-controlled study M21-465 for the treatment of irritability in autism, the primary objective was met, and cariprazine showed statistically significant improvement in irritability symptoms based on both the primary and secondary endpoints. However, Study M21-465 does not, alone, support substantial evidence of effectiveness without a second positive study; and the Applicant has informed us that they are not currently pursuing further studies of irritability associated with ASD. As such, this indication will not be approved. Because this study was conducted in response to a PWR, the resultant safety data will be included in the label under Section 8.4.

9 Advisory Committee Meeting and Other External Consultations

Not applicable; per FDA recommendations and standards on advisory committee (AC) input, this review did not require an AC Meeting or other major external consultations other than what was noted earlier for pediatric requirements from the Division of Pediatric and Maternal Health (see also next section).

10 Pediatrics

Study 3070-301-001 fulfills PREA PMR 2947-6: deferred long-term, open-label safety study in pediatric patients with schizophrenia (ages 13 to 17) and bipolar I disorder, recent manic episodes (ages 10 to 17).

The following studies fulfill the pediatric written request:

- Studies RGH-PK-18 and 2000-103-009 fulfill Study 1, a 12-week pediatric pharmacokinetic study in two populations: 1) ages 13 to 17 years, and 2) ages 5 to 12 years.

- Study M21-465 fulfills Study 2, adequate and well-controlled pediatric efficacy and safety study in patients with irritability associated with ASD.

- Study 3070-301-001 fulfills Study 3, pediatric long-term safety study.

Respective pediatric data will be added to the cariprazine label:

- The expanded indications for the treatment of schizophrenia in pediatric patients 13 years and older and acute treatment of manic or mixed episodes associated with bipolar I disorder in pediatric patients 10 years and older

- Dosage information in Section 2 (Dosage and Administration)

- Safety data in Sections 5 (Warnings and Precautions), 6 (Adverse Reactions) and 8 (Use in Specific Populations, Pediatric Use.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

This updated prescribing information (PI) for cariprazine is generally consistent with the previous version with the additions described below. This PI review also includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI submitted on June 18, 2025.

Boxed Warning: The risk discussed in the W&P is relevant to adolescents and young adult patients. Therefore, the following statement is unnecessary to include and was deleted:

> Safety and effectiveness of VRAYLAR have not been established in pediatric patients (b) (4) (5.2, 8.4).

Section 1 Indications and Usage

> Expanded indications:
>
> - Treatment of schizophrenia in adults and pediatric patients ages 13 years and older
> - Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults and pediatric patients ages 10 years and older.

Section 2 Dosage and Administration

> Section 2.2 Recommended Dosage in Schizophrenia: Dosage in pediatric patients 13 to 17 years of age was added.
> Section 2.3 Recommended Dosage in Manic or Mixed Episodes Associatd with Bipolar I Disorder: dosage in pediatric patients 10-17 years of age was added.
>
> Section 2.6 Dosage Modifications for CYP3A4 Inhibitors and Inducers: Revised the dosage adjustment recommendation based on the newly available dosage strengths, 0.5 mg and 0.75.

Section 3 Dosage Forms and Strengths: New 0.5 and 0.75 mg dosage strengths

5 Warnings and Precautions

> 5.2 Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults: as

above (see Boxed Warning)

5.7 Metabolic Changes, Dyslipidemia: Metabolic data from the clinical study in pediatric patients ages 13 years and older with schizophrenia and pediatric patients ages 10 years and older with bipolar I disorder. This information was edited so that the data reflects normal and abnormal pediatric laboratory ranges:

Cholesterol normal <170 and high >/= 200
HDL normal >45 and low <40r
Triglycerides normal <90 high >/=130.

5.7 Metabolic Changes, Weight Gain: Data was edited per the 120-day Safety Update.

Section 6 Adverse Reactions

6.1: Description of the safety database for the expanded pediatric indications and statement that adverse reactions reported in these pediatric populations were generally similar to those observed in adult patients

8 Use in Specific Populations

8.4 Pediatric Use

Details of the extrapolation of efficacy for the expanded pediatric populations in schizophrenia and bipolar I disorder

(b) (4)
.

Information regarding the different formulation used in one subgroup of subjects in this study is detailed.

Notable safety findings regarding somnolence adverse events and weight changes are described.

(b) (4) in this open-label study (b) (4)
.
However, notable safety findings regarding weight changes are described.

Weight data was edited per the 120-day Safety Update.

Section 12 Clinical Pharmacology

12.3 Pharmacokinetics: pediatric data in the approved age groups was added.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable; no REMS was required for the approved indications with this drug. No new safety issues necessitating a REMS were identified.

13 Postmarketing Requirements and Commitment

The Applicant conducted Study 3070-301-001 to address PREA PMR 2947-6: deferred long-term, open-label safety study in pediatric patients with schizophrenia (ages 13 to 17) and bipolar I disorder, recent manic episodes (ages 10 to 17). The PMR is now considered fulfilled.

14 Division Director Comments

The content of this Unireview reflects the issues discussed in the marketing application assessment and regulatory decisions and actions taken. My feedback and edits have been incorporated above. I agree with the findings as documented by the primary review team.

15 Appendices

15.1. References

None

15.2. Financial Disclosure

In pre-sNDA preliminary meeting comments dated March 11, 2025, the Division agreed that the Applicant need not submit financial disclosures.

15.3. Nonclinical Pharmacology/Toxicology

Not applicable.

15.4. Clinical Pharmacology

Bioanalysis methods

Cariprazine and its metabolites, DCAR and DDCAR were quantitated in human plasma using validated liquid-chromatography and tandem mass spectrometry method (b) (4).

Table 28. Validation Report for Method M(b) (4) for the Quantification of Cariprazine, Desmethylcariprazine and Didesmethylcariprazine by LC-MS/MS

Bioanalytical method validation report name, amendments and hyperlinks	Validation Report on an Analytical Procedure for the Quantification of Cariprazine, Desmethyl Cariprazine and Didesmethyl Cariprazine in K2EDTA Human Plasma by LC/MS/MS (c-da-val-lcms-cariprazine-pla(b) (4) v(b) (4))	
Method description	Cariprazine, Desmethyl Cariprazine and Didesmethyl Cariprazine and their internal standards were extracted from plasma using MTBE. Following evaporation of the organic layer, the reconstituted sample is subjected to LC-MS/MS quantitation.	
Materials used for standard calibration curve and concentration (% purity) (V(b) (4).04, Section 2)	Cariprazine HCl: Batches FMD-RGH-038 (99.7%), and L37092N (99.9%) Desmethyl Cariprazine HCl: Batch FMD-RGH-077 (96.3%) Didesmethyl Cariprazine HCl: Batches FMD-RGH-075 (97.7%), and R590010 (99.8%)	
Validated assay range	Cariprazine (CAR): 20 – 20,000 pg/mL Desmethyl Cariprazine (DCAR): 20 – 20,000 pg/mL Didesmethyl Cariprazine (DDCAR): 50 – 50,000 pg/mL	
Material used for QCs and concentration (% purity) (V(b) (4).04, Section 2)	Cariprazine HCl: Batches FMD-RGH-038 (99.7%), and L37092N (99.9%) Desmethyl Cariprazine HCl: Batch FMD-RGH-077 (96.3%) Didesmethyl Cariprazine HCl: Batches FMD-RGH-075 (97.7%), and R590010 (99.8%)	
Regression model and weighting	Linear, $1/x^2$ for all analytes of interest	
Validation parameters	**Method Validation Summary**	**Cariprazine**
Standard calibration curve performance during accuracy and precision runs	# std calibrators from LLOQ to ULOQ (V(b) (4).00, Table 5)	CAR: 9; DCAR: 9; DDCAR: 9
	% Bias from LLOQ to ULOQ (V(b) (4).00, Table 5)	CAR: -2.74% to 1.91% DCAR: -1.19% to 1.80% DDCAR: -2.86% to 3.19%

	% CV from LLOQ to ULOQ (V (b) (4) .00, Table 5)	CAR: 0.56% to 4.12% DCAR: 1.88% to 8.60% DDCAR: 0.74% to 4.25%
Selectivity (V (b) (4) .00, Section 5) **Matrix Factor (MF)** (V (b) (4) .00, Table-17)	CAR: Selectivity; 6 Lots; no peaks were found MF: 6 Lots: 2 Concentrations; Low 4.87% CV, High 1.16% CV DCAR: Selectivity; 6 Lots; no peaks were found MF: 6 Lots: 2 Concentrations; Low 5.98% CV, High 1.63% CV DDCAR: Selectivity; 6 Lots; no peaks were found MF: 6 Lots: 2 Concentrations; Low 4.52% CV, High 1.44% CV	
Interference & Specificity	CAR: Not Performed DCAR: Not Performed DDCAR: Not Performed	
Hemolysis effect (V (b) (4) .00, Table 15)	CAR: 1 lot at two concentrations: -4.90 to -0.89% Bias DCAR: 1 lot at two concentrations: 0.38 to 0.67% Bias DDCAR: 1 lot at two concentrations: 2.71 to 2.95%Bias	
Lipemic effect (V (b) (4) .00, Table 16)	CAR: 1 lot at two concentrations: -0.98 to -0.07% Bias DCAR: 1 lot at two concentrations: -9.99 to -1.62% Bias DDCAR: 1 lot at two concentrations: -0.11 to 0.82% Bias	
Dilution linearity (V (b) (4) .00, Table 14)	CAR: a DF4 at 40,000 pg/mL: 4.72% Bias DCAR: DF4 at 40,000 pg/mL: 7.83% Bias DDCAR: DF4 at 100,000 pg/mL: 5.42% Bias	
Bench-top stability (V (b) (4) .00, Table 10, LQC and HQC, respectively **Process stability** (V (b) (4) .00, Table 9, LQC, MQC and HQC)	CAR: Bench-Top: Stable up to 24 hours at Room Temperature: -10.45 and 0.73% Bias, 5.31 and 2.82 %CV Post Preparative: Stable up to 93.8 hours refrigerated: between -7.75 and –0.51% Bias, between 1.70 and 6.56 %CV DCAR: Bench-Top: Stable up to 24 hours at Room Temperature: -1.64 and 1.07% Bias, 5.63 and 3.85 %CV Post Preparative: Stable up to 93.8 hours refrigerated: between –13.05 and -1.94% Bias, between 1.54 and 6.63 %CV DDCAR: Bench-Top: Stable up to 24 hours at Room Temperature: -1.23 and 2.86% Bias, 5.39 and 2.50 %CV Post Preparative: Stable up to 93.8 hours refrigerated: between -2.96 and –0.68% Bias, between 2.50 and 4.57 %CV	

Freeze-Thaw stability (V(b) (4).00, Table 11, LQC and HQC, respectively)	CAR: 4 cycles, from both -20ºC (-0.97 and –1.88% Bias, 4.90 and 3.87 %CV) and -70ºC (-7.12 and –3.48% Bias, 6.86 and 1.21% CV) to RT DCAR: 4 cycles, from both -20ºC (-12.94 and 0.80% Bias, 3.86 and 3.09% CV) and -70ºC (-3.92 and –1.55% Bias, 14.75 and 2.36% CV) to RT DDCAR: 4 cycles, from both -20ºC (-4.70 and 2.34% Bias, 3.03 and 2.54 %CV) and -70ºC (2.30 and –0.34% Bias, 5.79 and 2.30% CV) to RT
Long-term storage (V(b) (4).00, Table 12, LQC and HQC, respectively)	CAR: 605 days at -20ºC (-0.95 and –8.87% Bias, 4.91 and 2.31% CV) and 605 days at -70ºC (-4.11 and -9.10% Bias, 3.12 and 1.87% CV) DCAR: 605 days at -20ºC (1.13 and –6.57% Bias, 6.56 and 1.40% CV) and 605 days at -70ºC (-5.41 and -6.25% Bias, 5.07 and 2.21% CV) DDCAR: 605 days at -20ºC (1.57 and –0.98% Bias, 3.82 and 1.15% CV) and 605 days at -70ºC (1.03 and -0.86% Bias, 3.12 and 1.69% CV)
Carry over (V(b) (4).00, Section 15)	CAR: No significant carryover observed DCAR: No significant carryover observed DDCAR: No significant carryover observed
LLOQ Inclusive Intra-Batch Accuracy (% Bias) and Precision (% CV) (V(b) (4).00, Table 7)	CAR: 6 Lots, -0.29% Bias; 9.06% CV DCAR: 6 Lots, 10.75% Bias; 9.46% CV DDCAR: 6 Lots, -4.28% Bias; 6.31% CV

MTBE: Methyl tert-butyl ether; CAR: Cariprazine; CV: Coefficient of variation; DCAR: Desmethyl Cariprazine; DDCAR: Didesmethyl Cariprazine; DF: Dilution Factor; HQC: High QC; LLOQ: lower limit of quantitation; LQC: Low QC; N/A: not applicable; MQC: mid-level QC; P&A: Precision & Accuracy; PA: Peak area; RT: room temperature; ULOQ: upper limit of quantitation
Source: Appendix B in Biopharmaceutic Studies and Analytical Methods

Table 29. Summary of Method Performance: Clinical Study Reports

Method Performance in Study:		**RGH-188-201**	**RGH-PK-18**
Study Report ID		rgh188201-analytical-pla	rghpk18-analytical-pla
Analytes	**Parameter**	RGH-188, D RGH-188, DD RGH-188	CAR, DCAR, DDCAR
Assay passing rate	accepted runs /total runs	RGH-188: 13/13 D RGH-188: 13/13 DD RGH-188: 13/13 (Table A1.1)	CAR: 37/37 DCAR: 37/37 DDCAR: 37/37 (Attachment 3)
Standard curve performance	x to y% bias ≤ x% CV	RGH-188: -3.5 to 4.0% Bias, ≤ 4.7% CV D RGH-188: -3.7 to 4.3%Bias, ≤ 3.1% CV DD RGH-188: -2.1 to 3.0% Bias, ≤ 4.5 % CV (Table A1.2, Table A1.3, and Table 1.4)	CAR: -2.96 to 2.37% Bias, ≤ 6.38% CV DCAR: -2.75 to 3.08% Bias, ≤ 6.98% CV DDCAR: -2.41 to 3.55%Bias, ≤ 5.70 %CV (Table 3)
QC Performance	x to y% bias; ≤ x% CV	RGH-188: -2.2 to 3.0% Bias, ≤ 4.8% CV D RGH-188: -1.4 to 3.7% Bias, ≤ 4.0% CV DD RGH-188: -3.5 to 1.6% Bias, ≤ 5.3% CV (Table A1.8, Table A1.9, and Table A1.10)	CAR: -3.65 to 4.06%Bias, ≤ 7.76% CV DCAR: -0.34 to 4.83% Bias, ≤ 7.31% CV DDCAR: -2.26 to 1.74% Bias, ≤ 6.53% CV (Table 4, QCs Low to High)
Method reproducibility / ISR	# study samples analyzed; % study samples;# Passed / Assessed	RGH-188: 728; 10.4%; 76 of 76 D RGH-188: 728; 10.4%; 74 of 76 DD RGH-188: 728; 10.4%; 76 of 76 (Sections A1.2, A1.3.4, A1.4.18; Table A1.14, Table A1.15, Table A1.16)	CAR: 1314; 10.05%; 128 of 132 DCAR: 1314; 10.05%; 127 of 132 DDCAR: 1314; 10.05%; 132 of 132 (Section 6.2.2, Table 6)
Study sample analysis /stability	Maximum calibrators/QCs storage maximum sample storage validated LTS	Calibrant STDs & QCs: 161 Days at -20ºC (Section A1.4.8) Maximum Sample Storage: 211 days at -20ºC (Excluding Subject 44-13). Maximum Subject 44-13 Sample Storage: 206 Days at -20 °C (Sections 8.5 and A1.2) LTS of 221 Days at -20ºC (GLP1213, Section 8.2.4)	Calibrant STDs & QCs: Not Specified Stored at -70ºC (Sections 3.3 and 3.4) Maximum Sample Storage: 331 Days at -70ºC (Section 4.1) LTS of 769 Days at -70ºC (Section 4.1, Attachment 2)
Validation Standard calibration curve performance in accuracy and precision runs	# calibrators; % Bias %CV	RGH-188: 8; -2.9 to 1.5% Bias; ≤ 4.6% CV D RGH-188: 8; -4.7 to 2.3% Bias; ≤ 3.6% CV DD RGH-188: 8; -0.9 to 1.7% Bias; ≤ 5.1% CV (GLP1213, Table 4A, Table 4B, Table 4C)	CAR: 9; -2.74% to 1.91% Bias; ≤ 4.12% CV DCAR: 9; -1.19 to 1.80% Bias; ≤ 8.60% CV DDCAR: 9; -2.86% to 3.19% Bias; ≤ 4.25% CV (V (b) (4).00, Table 5)

Summary Method Performance: Clinical Study Reports (continued)

Method Performance in Study:		2000-103-009	2000-101-009
Study Report ID		2000-103-009 ((b) (4)) Final BA Report 22Feb2022.pdf	2000101009-analytical-pla
Analytes	**Parameter**	CAR, DCAR, DDCAR	CAR, DCAR, DDCAR
Assay Passing Rate	accepted runs / total runs	CAR: 22/22 DCAR: 22/22 DDCAR:22/22 Attachment 4)	CAR: 31/31 DCAR: 31/31 DDCAR: 31/31 (Attachment 4)
Standard curve performance	x to y% bias ≤ x% CV	CAR: -2.19 to 2.13% Bias, ≤ 4.68% CV DCAR: -2.62 to 1.67% Bias, ≤ 3.83 % CV DDCAR: -2.88 to 3.71% Bias, ≤ 5.72% CV (Table 3)	CAR: -3.89 to 3.25% Bias, ≤ 7.00% CV DCAR: -3.27 to 2.84% Bias, ≤ 5.65% CV DDCAR: -3.74 to 2.51% Bias, ≤ 5.66% CV (Table 3)
QC performance	x to y% bias; ≤ x% CV	CAR: -3.28 to 4.09% Bias, ≤ 4.53% CV DCAR: -2.09 to 3.24% Bias, ≤ 5.42% CV DDCAR: -3.19 to 4.12% Bias, ≤ 5.93% CV (Table 4)	CAR: -2.71 to 2.63% Bias, ≤ 7.30% CV DCAR: -1.88 to 6.24% Bias, ≤ 7.03% CV DDCAR: -0.41 to 4.52% Bias, ≤ 6.12% CV (Table 4)
Method reproducibility / ISR	# study samples analyzed; % study samples; # Passed / Assessed	CAR: 570; 10.53%; 60 of 60 DCAR: 570; 10.53%; 60 of 60 DDCAR: 570; 10.53%; 60 of 60 (Section 6.2.2, Table 6)	CAR: 1333; 11.70%; 155/156 DCAR: 1333; 11.70%; 130/156 DDCAR: Not Conducted (Section 6.2.2, Table 6)
Study sample analysis / stability	Maximum calibrators/QCs storage maximum	Calibrant STDs & QCs: 437 Days at -70ºC (Sections 3.3 and 3.4; Attachment 4) Maximum Sample Storage: 540 Days at -70ºC (Section 4.1) LTS of 769 Days at -70ºC (Section 4.1, Attachment 3)	Calibrant STDs & QCs: Not Specified 4 Stored at -70ºC (Sections 3.3 and 3.4) Maximum Sample Storage: 75 Days at -70ºC (Section 6) LTS of 605 Days at -70ºC (Section 6, Attachment 3)
Validation Standard calibration curve performance in accuracy and precision runs	# calibrators; % bias, %CV	CAR: 9; -2.74% to 1.91% Bias, ≤ 4.12% CV DCAR: 9; -1.19 to 1.80% Bias, ≤ 8.60% CV DDCAR: 9; -2.86% to 3.19% Bias, ≤ 4.25% CV (V (b) (4) .00, Table 5)	CAR: 9; -2.74% to 1.91% Bias; ≤ 4.12% CV DCAR: 9; -1.19 to 1.80% Bias; ≤ 8.60% CV DDCAR: 9; -2.86% to 3.19% Bias; ≤ 4.25% CV (V (b) (4) .00, Table 5)

CAR = Cariprazine; CV = Coefficient of variation; DCAR = Desmethyl Cariprazine; DDCAR = Didesmethyl Cariprazine; ID = Identification; ISR = Incurred Sample Reproducibility; LTS = Long-Term Stability; QC = Quality Control; STD = Standard
Source: Biopharmaceutic Studies and Associated Analytical Methods, Appendix C.

Incurred Sample Reanalysis (ISR): The number of samples reanalyzed to test the reproducibility of the method in studies RGH-188-201, RGH-PK-108, 2000-101-009, and 2000-103-009 was 76, 132, 156, and 60 samples, respectively. Greater than 67% of the repeat results were found to be within ±20% of the mean of repeat and original values for all three active analytes in each study, and ISR passing rates were within the acceptance criteria.

Reviewer's Comments: The bioanalysis of samples for studies RGH-188-201, RGH-PK-108, 2000-101-009, and 2000-103-009 are acceptable.

Individual studies

Study RGH-PK-18

This was a two-part, phase 1, multicenter, open-label, dose-escalation, parallel-group, multiple-dose study to evaluate the pharmacokinetics, safety, and tolerability of cariprazine capsule in pediatric patients with schizophrenia (13 to 17 years), or bipolar I disorder (10 to 17 years) for 6 weeks. The study enrolled 50 patients with 24 patients aged 13 to 17 years (Part A, cohorts 1-4) and 26 patients aged 10-12 years (Part B, cohort 5-8). Each cohort enrolled at least 6 patients. Study treatments were administered by cohort:

- Cohorts 1 and 5: gradual titration from 0.5 mg QD, target dose at 1.5 mg QD
- Cohorts 2 and 6: gradual titration from 0.5 mg QD, target dose at 3.0 mg QD
- Cohorts 3 and 7: gradual titration from 0.5 mg QD, target dose at 4.5 mg QD
- Cohorts 4 and 8: fast titration from 1.5 mg QD, target dose at 4.5 mg QD

Reviewer's Comments:
This study was previously reviewed. Refer to the clinical pharmacology review for NDA204370 (Post Marketing Requirement/Commitment-1) archived on 01/08/2021 for additional information. The review concluded that the PK characteristics of cariprazine and its two active metabolites (DCAR and DDCAR) are relatively similar between pediatric patients aged 10 to12 years and 13 to17 years. From a safety perspective, there were no clinically meaningful imbalances in the nature, number, or severity of the reported treatment emergent adverse events (TEAEs) between pediatric participants aged 13 to 17 years (Part A) and pediatric participants aged 10 to 12 years (Part B), except that the reported incidence of increased weight as a TEAE was higher for participants aged 10 to 12 years in Part B (38.5%; 10/26) versus participants aged 13 to 17 years in Part A (12.5%; 3/24). There was no significant difference between the safety profile between gradual titration and fast titration as well. However, given the small sample size, safety profile of titration regimen needs further evaluation.

Additionally, after multiple dose administration, Cmax,ss and AUCtau,ss for CAR, DCAR and DDCAR showed approximately dose proportional PK characteristics over the dose range of 1.5 mg to 4.5 mg in pediatric patients aged 10 to 17 years old.

Study RGH-188-201

Title: An open-label, multicenter, multiple dose study to evaluate pharmacokinetics, safety and tolerability of cariprazine in adolescent subjects with schizophrenia, schizoaffective and schizophreniform disorders compared to adults

Clinical sample collection period: 12 Mar 2017- 19 June 2018

Bioanalysis study period: 19 June 2017 and 09 July 2018

The passing rate of incurred sample reanalysis (ISR) was 100%, 98.7% and 100% for CAR, DCAR and DDCAR, respectively.

EDR: \\Cdsesub1\evsprod\NDA204370\0168\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\rgh-188-201

Study design
This was a multiple-dose study includes 3 cohorts (1, 2, and 3) who received different doses of cariprazine for a treatment period of 28 days. Each cohort consisted of 3 age-groups (A, B, and C) with at least 6 patients in each of the following age ranges: 13 to < 15 years (Subgroup 1A, 2A, and 3A), 15 to < 18 years (Subgroup 1B, 2B, and 3B), and 18 to 40 years (Subgroup 1C, 2C, and 3C).

All adolescent patients were hospitalized for at least the first 5 days of their treatment and were discharged no earlier than Day 5. The first adolescent patient in each adolescent subgroup had to complete the 5-day hospitalization (up-titration phase) without any tolerability concerns or major safety findings before the next patient in the same subgroup was dosed. All patients were hospitalized for at least 2 days for PK sampling (Day 28-Day 29/Early Termination [ET]).

Cohort 1: 0.5 mg on Day 1, 1.0 mg on Day 2, and 1.5 mg on Day 3, followed by stable doses of 1.5 mg/day for the remaining period

Cohort 2: 1.5 mg on Day 1 and 3 mg on Day 2, followed by stable doses of 3 mg/day for the remaining period

Cohort 3: 1.5 mg on Day 1, 3 mg on Day 2, 4.5 mg on Day 3, and 6 mg on Day 4, followed by stable doses of 6 mg/day for the remaining period

Overview of the study design with treatment allocations

Cohorts based on dosage	Subgroups based on age		
	A (13-<15 years)	B (15-<18 years)	C (18-40 years)
1 (1.5 mg/day)	Subgroup 1A	Subgroup 1B	Subgroup 1C
2 (3 mg/day)	Subgroup 2A	Subgroup 2B	Subgroup 2C
3 (6 mg/day)	Subgroup 3A	Subgroup 3B	Subgroup 3C

Pharmacokinetic (PK) sampling and analysis: PK blood samples were collected at predose on days 14, 21, day 28 predose and at 1, 2, 3, 4, 8, 24, 72, 168 and 336 hours. Plasma concentrations of all active moieties (i.e., cariprazine (CAR), desmethylcariprazine (DCAR), didesmethylcariprazine (DDCAR)

Results

Demographic profile

Randomized (cohort)/Completed/Discontinued	63/ 61/2*
Mean (±SD) Age (median (range)) years	Cohort 1A: 13.5 (±0.55) (13.5 (13,14)) Cohort 2A: 13.4 (±0.52) (13.0 (13,14)) Cohort 3A: 13.3 (±0.52) (13.0 (13,14)) Cohort 1B: 16.7 (±0.52) (17.0 (16,17)) Cohort 2B: 15.8 (±0.67) (16.0 (15, 17)) Cohort 3B: 15.8 (±0.41) (16.0 (15, 16)) Cohort 1C: 28.8 (±8.61) (29.5 (18, 38)) Cohort 2B: 27.8 (±9.00) (23.5 (18, 39)) Cohort 3C: 30.8 (±7.70) (32.5 (18, 38))
Male/Female	Cohort 1A: 5/1; Cohort 2A: 9/1; Cohort 3A: 4/2 Cohort 1B: 2/4; Cohort 2B: 5/4; Cohort 3B: 5/1 Cohort 1C: 4/2; Cohort 2C: 6/2; Cohort 3C: 4/2
Race (White/Asian)	Cohort 1A: 6/0; Cohort 2A: 9/0; Cohort 3A: 6/0 Cohort 1B: 6/0; Cohort 2B: 9/0; Cohort 3B: 5/1 Cohort 1C: 6/0; Cohort 2B: 8/0; Cohort 3C: 6/0

*Subject (b) (6) (2A) discontinued due to acute tonsillitis on Day 14; subject (b) (6) (2B) withdraw consent.

Pharmacokinetic summary

The PK parameters of cariprazine (CAR) and its metabolites (DCAR and DDCAR) in pediatric patients 13 to <15 years old, 15 to <18 years old and adults 18 to 40 years are shown in Table 30. The PK parameters of total CAR is shown in Table 6 in Section 6, and comparison of the total cariprazine PK parameters between adolescents and adults are presented in Table 7. PK parameters (Cmax, AUCtau, Cmin and Cavg at steady state) for all three analytes and total CAR were similar between age groups at 1.5 mg/day and 3 mg/day.

Table 30. Geometric Mean of Pharmacokinetic Parameters of CAR, DCAR and DDCAR on Day 28 after Multiple Oral Administration to Patients in Study RGH-188-201 (PK Population)

Dose	Age Group	CAR		DCAR		DDCAR	
		AUCtau (ng*h/mL)	Cmax (ng/mL)	AUCtau (ng*h/mL)	Cmax (ng/mL)	AUCtau (ng*h/mL)	Cmax (ng/mL)
1.5 mg/day	13 to < 15	70.4 (41.9)	4.39 (48.2)	18.06 (45.3)	0.91 (47.6)	140.2 (51.8)	6.15 (54.9)
	15 to < 18	67.7 (34.1)	4.33 (26.9)	20.28 (55.5)	1.09 (59.2)	157.4 (59.5)	7.03 (57.8)
	18 to 40	68.2 (33.1)	3.91 (30.0)	19.58 (34.4)	1.01 (43.3)	153.6 (39.3)	6.66 (40.4)
3.0 mg/day	13 to < 15	123.1 (37.1)	8.43 (28.7)	46.47 (75.9)	2.62 (75.0)	381.3 (64.0)	17.12 (61.9)
	15 to < 18	143.0 (27.4)	9.12 (20.8)	46.07 (54.1)	2.33 (57.5)	338.2 (33.2)	15.00 (30.8)
	18 to 40	124.6 (36.6)	7.65 (29.6)	39.70 (4.7)	2.01 (5.6)	333.3 (30.3)	15.18 (29.9)
6.0 mg/day	13 to < 15	242.3 (31.9)	16.02 (40.1)	94.12 (31.4)	5.11 (39.8)	726.7 (52.0)	33.49 (51.1)
	15 to < 18	318.1 (28.9)	18.67 (18.5)	77.20 (27.1)	3.85 (30.0)	502.8 (85.2)	23.78 (81.9)
	18 to 40	262.7 (19.3)	16.60 (17.8)	90.67 (40.2)	4.67 (34.7)	529.4 (50.0)	24.02 (50.0)

AUCtau: area under the curve during one dosing interval; Cmax: peak plasma concentration
Source: Reviewer adapted from study RGH-188-201 report, pages 88-90.

Apparent clearance and volume of distribution were similar between the pediatric age groups and adults, and the results are presented in Table 31 for total cariprazine.

Table 31. Geometric Mean Ratios for Clearance and Volume of Distribution for Total Cariprazine in Study RGH-188-201 (PK Population)

Analyte	PK parameter	Comparison	Geometric Mean Ratio (90%CI)
Total (CAR, DCAR AND DDCAR)	CLss/F	A/C	92.8 (69.5, 123.8)
		B/C	96.9 (75.0, 125.2)
	Vz/F	A/C	84.3 (61.0, 116.6)
		B/C	90.1 (67.4, 120.5)

A: 13-<15 years of age; B: 15-<18 years of age, C: 18-40 years of age; CLss/F; apparent oral clearance at steady state; Vz/F: apparent volume of distribution; t1/2: elimination half-life
Source: Reviewer adapted from Study RGH-188-201 Bioanalysis and PK Evaluation Report, page 33.

Reviewer's Comments
The GMRs of CL/F are similar between pediatric patients (13 to <15 years and 15 <18 years) and adults. The confidence intervals for the geometric mean ratios (GMRs) between the age groups were wide, which may be due to the small sample size of the study and PK variability of cariprazine.

Study 2000-103-009

Title: Pharmacokinetics, Safety, and Tolerability of Cariprazine in Pediatric Participants with Autism Spectrum Disorder Aged 5 – 17 Years

Clinical sample collection period: 26 June 2020 - 10 December 2021

Bioanalysis study period: 23 November 2020 – 31 December 2021

EDR: \\CDSESUB1\evsprod\NDA204370\0245\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\2000-103-009

Study design

This is a phase 1, multicenter, open-label, parallel-group, multiple-dose study to evaluate the PK of cariprazine and its metabolites, desmethylcariprazine (DCAR) and didesmethylcariprazine (DDCAR) after administration of another unapproved cariprazine oral solution formulation. The duration was up to 118 days, including the following: Up to a 28-day screening period, 42-day intervention period and 42-day post-intervention PK and safety follow-up. Twenty-five participants were enrolled into one of the following four cohorts:

	10-12 Years of age	**13-17 Years of age**	**5-9 Years of age**
Cohort 1	0.5 mg titrate to 0.75 mg QD	0.5 mg titrate to 1.5 mg QD	-
Cohort 2	0.5 mg titrate to 1.5 mg QD	0.5 mg titrate to 3 mg QD	-
Cohort 3	-	-	0.5 mg QD
Cohort 4	-	-	0.5 mg titrate to 1.5 mg QD

QD: once daily

Pharmacokinetic (PK) sampling and analysis: PK blood samples were collected starting on Day 1 at predose, and at 2, 3, 4, 6, 8, and 24 hours postdose; Days 7, 14, 21, 28, and 35 at predose; and starting on Day 42 at predose and at 2, 3, 4, 6, 8, 24, 48 (Day 44), 168 (Day 49), 336 (Day 56), 672 (Day 70), and 1008 (Day 84) hours postdose.

Results

Demographic profile

Randomized (cohort 1 to 4)/Completed Treatment Period/Discontinued due to AE	25 (7/6/6/6)/24*
Mean (±SD) Age (median (range)) years	Cohort 1: 14.3 (±2.36) (14.0 (12, 17)) Cohort 2: 12.5 (±2.26) (12.0 (10, 16)) Cohort 3: 7.8 (±1.2) (8.0 (6, 9)) Cohort 4: 7.3 (±1.63) (7.5 (5, 9))
Male/Female	Cohort 1: 4/3 Cohort 2: 2/4 Cohort 3: 3/3 Cohort 4: 4/2
Race (White/Black)	Cohort 1: 2/5 Cohort 2: 1/5 Cohort 3: 2/4 Cohort 4: 2/4

* Subject (b) (6) (16 years of age) in cohort 1 discontinued the study on Day 41 due to withdrawal consent by parent/guardian.

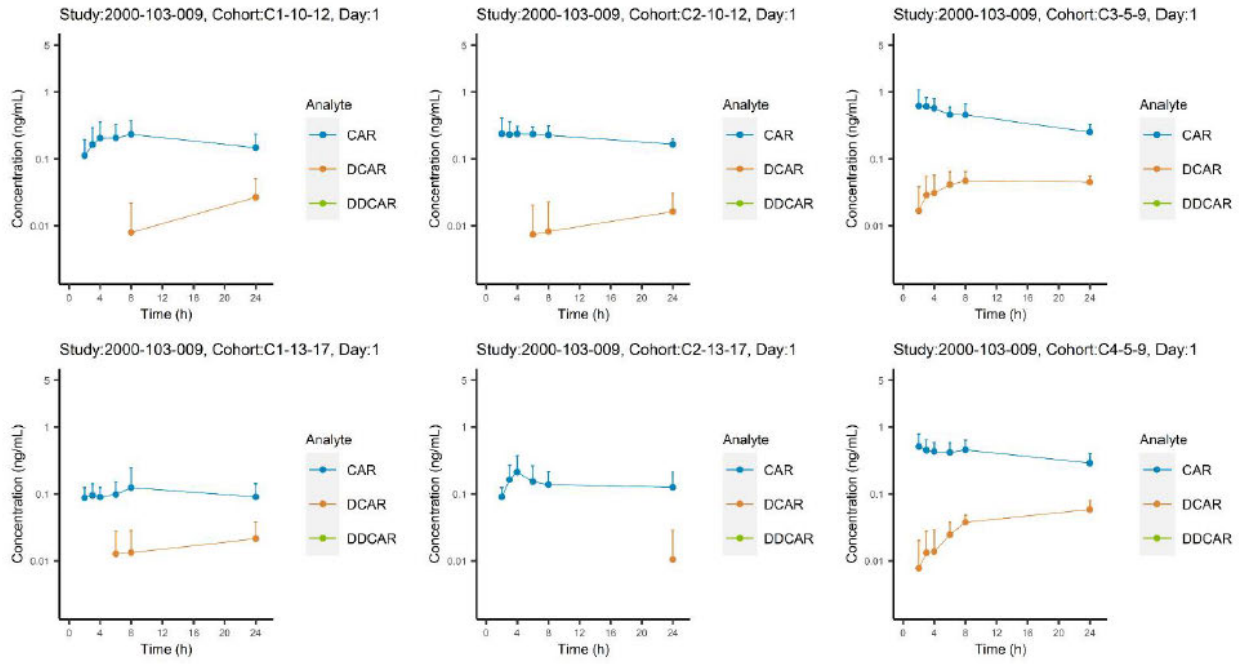
Pharmacokinetic summary

The Day 1 and Day 42 mean plasma concentration-time profiles for cariprazine, DCAR and DDCAR are presented for each cohort in Figure 7 and Figure 8. PK summaries are presented in Table 32, Table 33, and Table 34.

Oral cariprazine treatments were started at 0.5 mg once daily on Day 1 in all cohorts. Though with high variability, exposures of cariprazine on Day 1 increased in younger patients, Cmax and

AUCt increased approximately 1.8 folds in the 10-to-12-year-old group, Cmax and AUCt increased approximately 4 folds in the 5-to-9-year-old group, as compared to the adolescent group (13-17 years of age). Within 24 hours after treatment initiation, DCAR were detectable in some patients between 10-17 years of age and all patients between 5 to 9 years of age, DDCAR were not observed in any individual. Exposures of DCAR in the younger age group are also expected to be higher than that in the adolescent group.

Figure 7. Mean (+SD) Plasma Concentrations of Cariprazine and Metabolites after Dosing on Day 1 in Study 2000-103-009.



Source: Study 2000-103-009 clinical report, page 49.

Table 32. Geometric Mean (Mean, % CV) Pharmacokinetic Parameters of Cariprazine (Day 1) in Study 2000-103-009.

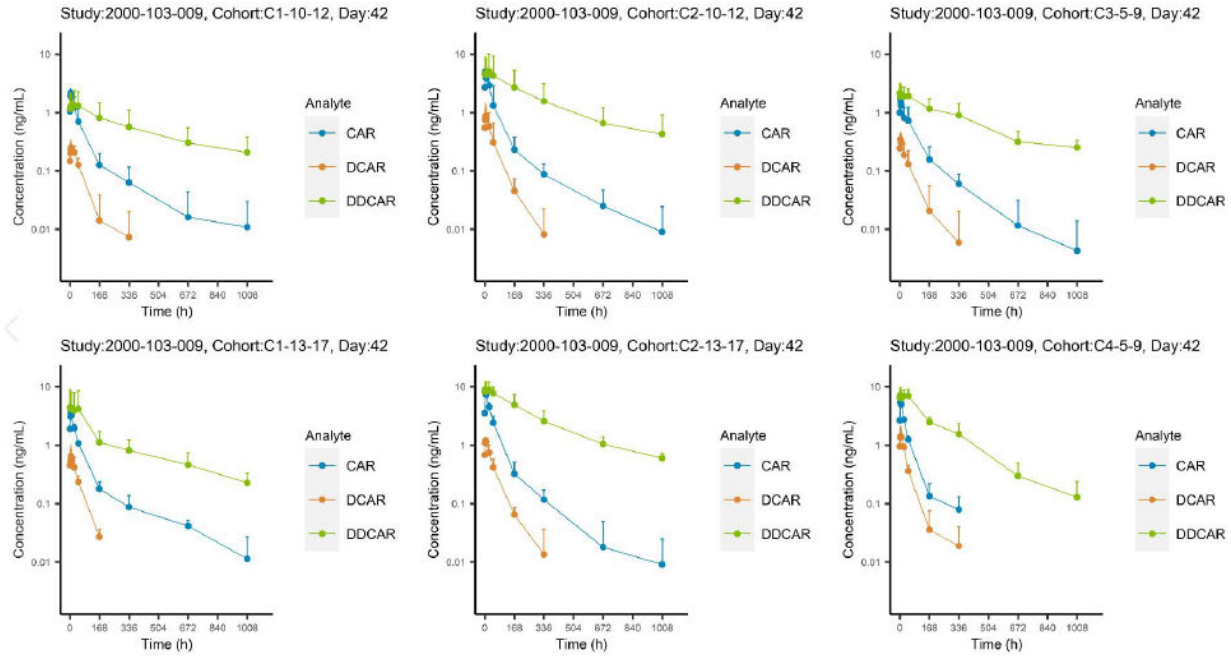
Parameter	Cohort 1		Cohort 2		Cohort 3	Cohort 4
Age (years)	10-12	13-17	10-12	13-17	5-9	5-9
Day 1 Dose (mg)	0.5	0.5	0.5	0.5	0.5	0.5
N	3	4	3	3	6	6
Cmax (ng/mL)	0.207 (0.252, 60.3)	0.129 (0.153, 68.4)	0.329 (0.331, 15.0)	0.175 (0.221, 66.7)	0.681 (0.738, 45.8)	0.522 (0.564, 38.1)
Tmax (hr)[1]	8 (4-8)	4 (3-8)	4 (2-8)	3 (2-4)	3 (2-6)	2 (2-6)
AUCt (ng*hr/mL)	3.62 (4.29, 57.9)	1.96 (2.37, 68.7)	4.71 (4.74, 12.5)	2.60 (3.16, 60.1)	8.79 (9.29, 38.4)	8.40 (9.01, 37.9)

[1]Reported as median (range)
AUCt: area under the curve from time 0 to t (24 hrs); Tmax: median time to reach peak plasma concentration; Cmax: peak plasma concentration; N: number of subjects
Source: Study 2000-103-009 clinical study report, page 52.

Following the assigned dosing regimens, cariprazine and DCAR are expected to attain steady state within 1-2 weeks per the USPI of VRAYLAR, predose plasma concentrations for DDCAR were evaluated between days 7 and 42, and steady state were attained in all cohorts between 21 to 28 days. On Day 42, all the moieties were detectable, and the rank of exposure based on AUCtau,ss was DDCAR > cariprazine > DCAR, which is consistent with data from adults.

On Day 42, exposures of each active moiety (cariprazine, DCAR and DDCAR) in patients 10-12 years of age were comparable to those in adolescents, in patients 5-9 years of age, Cmax,ss and AUCtau,ss of cariprazine were approximately 38% and 27% higher, respectively, Cmax,ss and AUCtau,ss of DCAR were approximately 100% higher, and Cmax,ss and AUCtau,ss of DDCAR were approximately 70% higher, compared to that in adolescents.

Figure 8. Mean (+SD) Plasma Concentrations of Cariprazine and Metabolites after Dosing on Day 42 in Study 2000-103-009.



Source: Study 2000-103-009 clinical report, page 50.

Table 33. Geometric Mean (Mean, % CV) Pharmacokinetic Parameters of Cariprazine and Metabolites (Day 42) in Study 2000-103-009.

Parameter	Cohort 1 (10-12 years)	Cohort 1 (13-17 years)	Cohort 2 (10-12 years)	Cohort 2 (13-17 years)	Cohort 3 (5-9 years)	Cohort 4 (5-9 years)
Day 42 Dose (mg)	0.75	1.5	1.5	3.0	0.5	1.5
N	3	3	3	3	6	6
Cariprazine						
Tmax,ss (hr)[1]	3 (3-4)	6 (3-6)	3 (2-4)	2 (2-3)	4 (2-4)	3 (2-8)
T1/2 (hr)	96.9 (52.3)	61.5 (170)	122 (95.9)	69.6 (46.4)	97.1 (45.0)	63.1 (16.1)
Cmax,ss/Dose (ng/mL/mg)	2.84 (2.89, 21.4)	2.44 (2.51, 28.5)	3.36 (3.61, 48.7)	3.14 (3.15, 7.15)	3.48 (3.68, 39.2)	4.26 (4.33, 19.2)
AUCtau,ss/Dose (ng*h/mL/mg)	50.3 (51.9, 30.5)	43.1 (43.9, 23.8)	52.8 (58.9, 56.0)	50.9 (51.0, 4.06)	54.4 (58.0, 42.7)	65.8 (66.1, 9.48)
CLss/F (L/hr)	19.9 (20.6, 31.5)	23.2 (23.7, 26.0)	18.9 (21.1, 55.1)	19.6 (19.6, 4.15)	18.4 (19.5, 33.8)	15.2 (15.3, 10.1)
Vz/F (L)	3360 (3820, 62.8)	3640 (5090, 98.9)	3720 (3870, 34.6)	2610 (3760, 106)	2940 (3050, 30.0)	1410 (1430, 18.1)
Desmethyl Cariprazine (DCAR)						
Tmax,ss (hr)[1]	6 (6-8)	6 (6-6)	4 (3-4)	4 (4-8)	3 (2-4)	6 (2-24)
T1/2 (h)	48.1 (38.5)	32.5 (12.8)	50.6 (9.19)	46.1 (22.0)	31.0 (17.3)	59.8 (16.9)
Cmax,ss/Dose (ng/mL/mg)	0.336 (0.349, 32.0)	0.388 (0.436, 56.4)	0.542 (0.611, 60.0)	0.423 (0.425, 13.4)	0.705 (0.737, 31.0)	0.972 (1.04, 43.3)
AUCtau,ss/Dose (ng*h/mL/mg)	6.86 (7.09, 29.2)	7.69 (8.43, 51.3)	9.96 (11.3, 63.6)	7.76 (7.87, 21.2)	12.0 (12.8, 38.2)	18.5 (19.0, 27.2)
Didesmethyl Cariprazine (DDCAR)						
Tmax,ss (hr)[1]	3 (3-24)	3 (0-24)	24 (4-24)	4 (2-24)	1 (0-24)	24 (2-24)
T1/2 (hr)	467 (50.4)	371 (14.0)	290 (69)	285 (75.7)	298 (79.7)	199 (41.9)
Cmax,ss/Dose (ng/mL/mg)	1.26 (1.80, 77.2)	2.04 (3.03, 102)	2.82 (3.61, 87.5)	3.08 (3.17, 30.3)	4.11 (4.56, 46.9)	4.78 (5.00, 37.2)
AUCtau,ss/Dose (ng*h/mL/mg)	28.2 (39.8, 76.3)	43.8 (65.6, 103)	57.0 (75.3, 92.9)	66.9 (69.7, 36.6)	84.6 (94.4, 46.5)	103 (106, 30.9)

[1]Reported as median (range)
N: number of subjects, subject (b) (6) (16 years of age) in cohort 1 discontinued the study on Day 41.
; Cmax,ss: peak plasma concentration at steady state; Tmax,ss: time to reach peak plasma concentration at steady state; AUCtau,ss: area under the curve from time during one dosing interval at steady state; t1/2: half-life during the elimination phase; CLss/F: apparent clearance at steady state; Vz/F: apparent volume of distribution
Source: Reviewer adapted from study 2000-103-009 clinical report, pages 53-55.

Because cariprazine, DCAR and DDCAR are pharmacologically equipotent, total molar cariprazine were also evaluated in all cohorts. Similar to cariprazine on Day 1, exposures of total molar cariprazine on Day 1 increased in younger patients. Cmax and AUCt increased approximately 1.7 folds in the 10-12-year-old group, Cmax and AUCt increased approximately 4 folds in the 5-9-year-old group, as compared to the adolescent group (13-17 years of age). The exposure difference between the age groups were smaller at steady state on Day 42 for total cariprazine compared to that on Day 1. In patients 10-12 years of age, dose normalized Cmax,ss and AUCtau,ss were comparable to that in adolescents. In patients 5-9 years of age, both Cmax,ss and AUCtau,ss were approximately 50% higher, compared to that in adolescents.

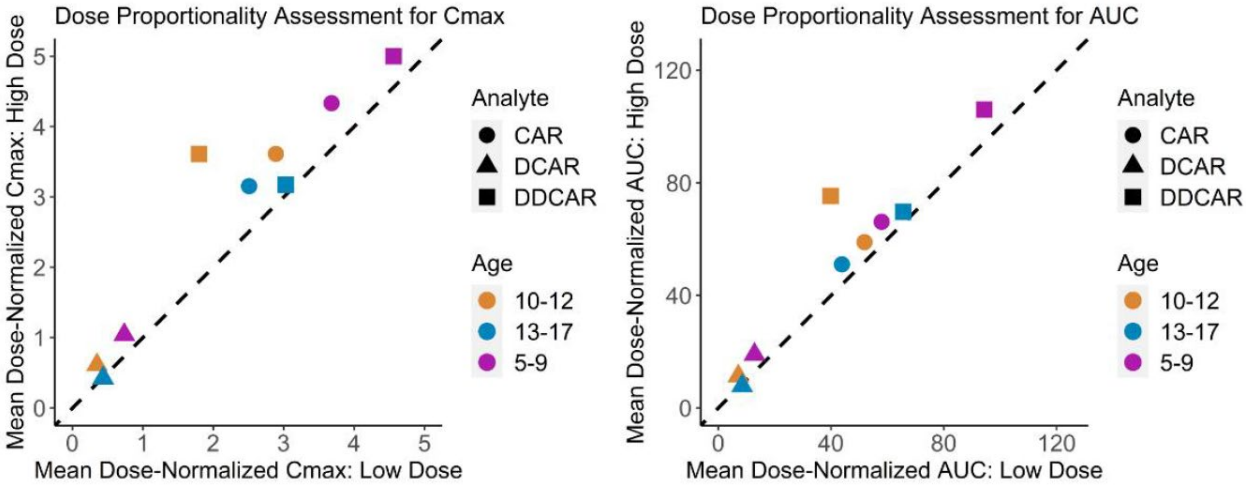
Table 34. Geometric Mean (Mean, % CV) Pharmacokinetic Parameters of Total Molar Cariprazine (Day 1, Day 42) in Study 2000-103-009.

	Cohort 1		Cohort 2		Cohort 3	Cohort 4
Age (years)	10-12	13-17	10-12	13-17	5-9	5-9
Day 1 Dose (mg)	0.5	0.5	0.5	0.5	0.5	0.5
Day 42 Dose (mg)	0.75	1.5	1.5	3.0	0.5	1.5
N	3	4 (3 Day 42)	3	3	6	6
Day 1						
Cmax (nM/L)	0.484 (0.590, 60.3)	0.335 (0.379, 60.3)	0.769 (0.775, 15.0)	0.405 (0.516, 66.7)	1.67 (1.80, 43.8)	1.25 (1.36, 38.5)
Tmax (h)[1]	8 (4-8)	7 (3-24)	4 (2-8)	3 (2-4)	3 (2-6)	2 (2-6)
AUCt (hr*nM/L)	8.93 (10.8, 59.6)	5.65 (6.35, 57.0)	11.6 (11.6, 7.99)	6.19 (7.58, 60.9)	23.1 (24.1, 34.9)	21.8 (23.3, 37.3)
Day 42						
Tmax,ss (h)[1]	4 (3-6)	6 (3-6)	4 (3-4)	3 (2-4)	4 (2-4)	2 (2-8)
$t_{1/2}$ (h)	425 (38.2)	347 (4.29)	266 (46.6)	325 (76.8)	262 (79.1)	164 (47.7)
Cmax,ss/Dose (nM/L/mg)	11.0 (11.8, 41.3)	13.2 (14.1, 46.2)	15.7 (18.0, 68.0)	15.7 (15.9, 17.4)	20.1 (21.2, 32.2)	23.3 (24.2, 33.0)
AUCtau,ss/Dose (hh*nM/L/mg)	217 (239, 49.0)	260 (288, 55.2)	299 (354, 74.5)	310 (314, 20.1)	378 (404, 36.0)	462 (470, 21.9)

[1]Reported as median (range)
N: number of subjects; Cmax: peak plasma concentration; Tmax: time to reach peak plasma concentration; AUCtau: area under the curve from time during one dosing interval; Cmax,ss: peak plasma concentration at steady state; Tmax,ss: time to reach peak plasma concentration at steady state; AUCtau,ss: area under the curve from time during one dosing interval at steady state; t1/2: half-life during the elimination phase
Source: Study 2000-103-009 clinical report, page 56.

Cariprazine, DCAR, and DDCAR steady-state exposures (Cmax,ss and AUC0-τ,ss) following the last dose on Day 42 appeared to increase approximately in proportion to dose within each of the three age groups (0.5 mg versus 1.5 mg for ages 5 to 9 years; 0.75 mg versus 1.5 mg for ages 10 to 12 years; 1.5 mg versus 3.0 mg for ages 13 to 17 years) across Cohorts 1 through 4 (Figure 9).

Figure 9. Dose Proportionality Assessment for Steady State Pharmacokinetic Parameters (Cmax and AUC) of Cariprazine and Its Metabolites in Study 2000-103-009.



Source: Study 2000-103-009 clinical report, page 57.

Reviewer's Comments:
Exposures in pediatric patients 5-9 years, 10-12 years and 13-17 years were evaluated in this PK study. The small size of this study may contribute to the large variability and information derived from study should be interpreted with caution.

- CAR, DCAR and DDCAR are dose proportional over the dose range of 1.5 to 3 mg/day in patients 13 to 17 years of age, 0.75 to 1.5 mg in patients 10 to 12 years of age, 0.5 mg to 1.5 mg in patients 5 to 9 years of age.
- On day 1, Cmax and AUC0-24h of CAR were approximately 1.8-fold in the 10-to-12-year-old age group, Cmax and AUC0-24h were approximately 4-fold in the 5-to-9-year-old age group, as compared to the patients 13 to 17 years of age. DCAR were detectable in some patients 10 to 17 years of age and all patients 5 to 9 years of age, DDCAR were not detectable in any individual.
- After prolonged use (42 days), patients 5 to 9 years of age are 50% higher while patients 10 to 12 years of age have similar exposures to that of the adolescents.

Study 2000-101-009

Title: A Single-Center, Randomized, Open-Label, Parallel-Group Study to Assess the Relative Bioavailability of Cariprazine Oral Solution and Capsule Formulations Following a Single Dose in Healthy Human Adult Participants

Clinical sample collection period: 27 Apr 2019 - 01 Jul 2019

Bioanalysis study period: 6 Jun 2019 – 11 Jul 2019

EDR: \\CDSESUB1\EVSPROD\nda204370\0224\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\2000-101-009

Study design

This study was a Phase 1, single-center, randomized, open-label, parallel-group, single-dose study in healthy male and female participants. Participants were admitted on Day -1 and remained in the study center until 48 hours following dose administration. Rest of PK samplings and AE assessments were conducted as outpatient visits.

Intervention A (reference product): A single 1.5 mg oral cariprazine capsule under fasted conditions on Day 1. Bulk Lot Number: W02280.

Intervention B (test product): A single dose of (b) (4) mL of cariprazine oral solution (containing 1.5 mg cariprazine) under fasted conditions on Day 1. Bulk Lot Number: 3915-01.

Pharmacokinetic (PK) sampling and analysis: PK blood samples were collected for Day 1 at 0 hour (predose) and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 24, 36, 48, 72, 96, 168, 336, 504, and 672 hours postdose, for a total of 21 blood samples per study participant

Results

Demographic profile

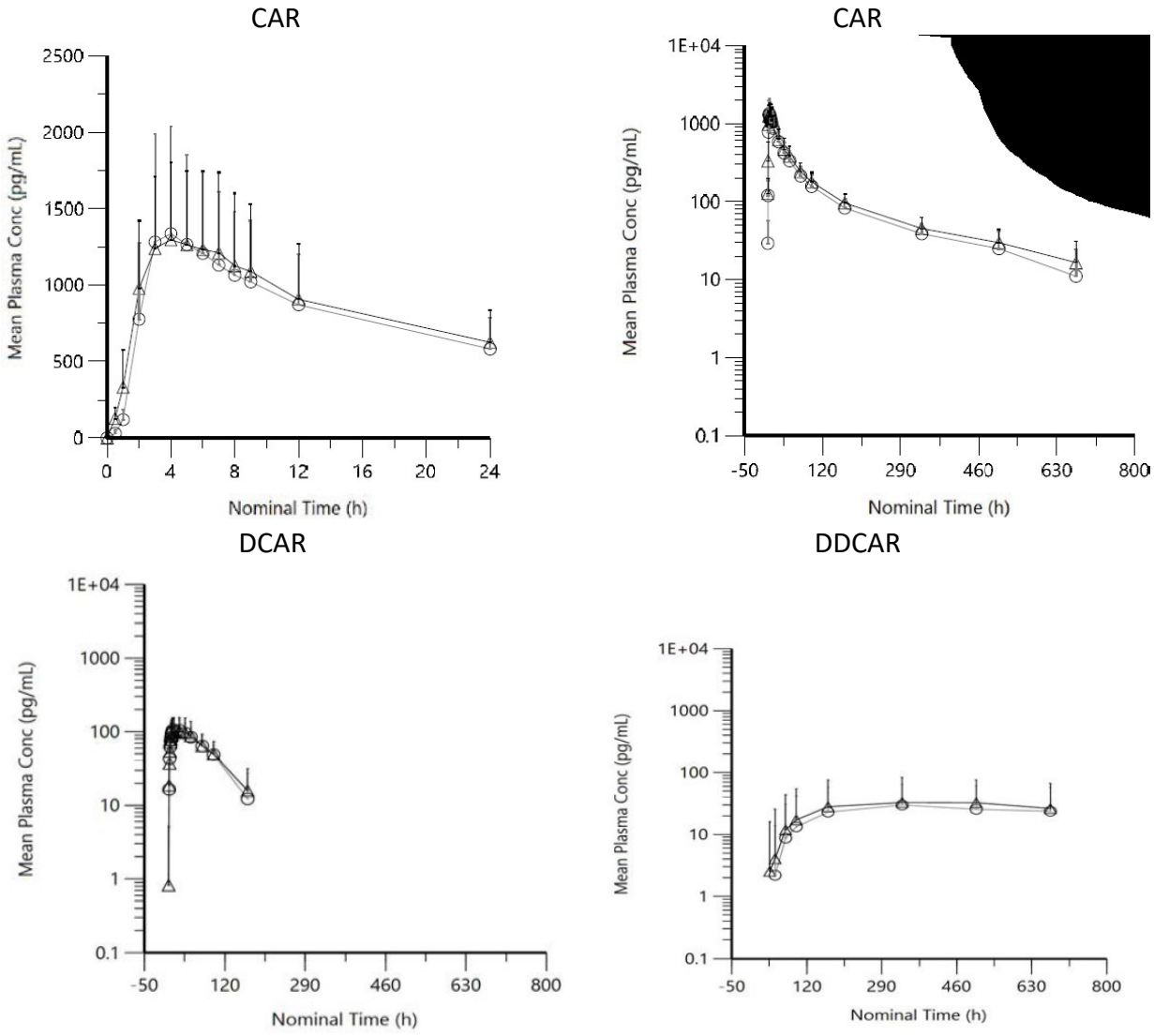
Randomized (A:B)/Completed (A:B)/Discontinued due to AE (A:B)	31:33/31:31/0:0
Mean (±SD) Age (median (range)) years	A: 34.0 (6.18) (35.0 (19, 43)) B: 33.2 (7.79) (34.0 (19, 45))
Male/Female	A: 17/14 B: 20/13
Race (White/Black)	A: 15/16 B:24/9

A: oral capsule; B: oral solution

Pharmacokinetic summary

The mean plasma cariprazine, DCAR, and DDCAR concentration-time profiles are presented in Figure 10. Statistical comparisons of cariprazine Cmax and AUC values between the solution (test formulation) vs the capsule (reference formulation), including the ratio of geometric means and 90% CI are presented in Table 35. In the comparison of a single oral dose of cariprazine 1.5 mg administered as a solution (Test) versus a single oral dose of cariprazine 1.5 mg administered as a capsule (Reference), the geometric mean ratios (GMR; 90% CI) for cariprazine Cmax, AUCt, and AUCinf were 101.15 (80.59-126.96), 114.77 (97.57- 135.02), and 114.80 (96.89- 136.03), respectively.

Figure 10: Mean Plasma Concentration-Time Profiles of CAR, DCAR and DDCAR Following Single Oral Administration a Capsule (Intervention A – Open Circle) or a Solution (Intervention B – Open Triangle) to Fasted Healthy Participants in Study 2000-101-009.



Source: Study 2000-101-009 clinical report, pages 56-57.

Table 35. Summary of Statistical Analysis Results of Plasma Cariprazine Pharmacokinetic Parameters Following Single Dose Administration of 1.5 mg Oral Solution (Intervention B, Test) in Comparison to Single Dose administration of 1.5 mg Oral Capsule (Intervention A, Reference) in Healthy Adult Participants in Study 2000-101-009 (N=56, PK Population).

PK Parameter	Geometric LSM		Geomean Ratio (%)	90% Lower CI	90% Upper CI
	Test	Reference	Test/Reference		
Cmax (pg/mL)	1287.89	1273.21	101.15	80.59	126.96
AUC0-24 (pg*h/mL)	19692.25	18294.64	107.64	87.97	131.71
AUC0-72 (pg*h/mL)	37722.42	34265.04	110.09	92.17	131.49
AUC0-t (pg*h/mL)	71220.50	62052.88	114.77	97.57	135.02
AUCinf (pg*h/mL)	81749.11	71207.11	114.80	96.89	136.03
Tmax (h)**	4 (2, 7)	4 (2, 9)	-	-	-

CI = confidence interval; LSM = least squares mean
*N=50, only AUCinf with % extrapolated area (AUC%) <20% were included in the statistical analysis
**Median (min, max)
Source: Study 2000-101-009 clinical report, page 61.

Reviewer's Comments:
Oral solution appears to have a comparable Cmax, 15% higher AUCinf compared to the approved formulation, oral capsule, with similar time to reach peak plasma concentration. These minor increases in cariprazine AUCinf after administration of the solution compared to capsule are not anticipated to be clinically significant.

Physiologically based Pharmacokinetic (PBPK) Analyses Review

Executive Summary
The objective of this review is to evaluate the adequacy of the Applicant's Physiologically based Pharmacokinetic (PBPK) modeling analyses to support dose adjustment scenarios of cariprazine for patients who are co-administered strong or moderate CYP3A4 inhibitors.

The Division of Pharmacometrics has reviewed the PBPK submission (Report R&D/22/0201 Version 3 and associated modeling and simulation files) to conclude the following:

- PBPK analysis supported changes to the approved DDI dosing adjustments from cariprazine 1.5 mg every three days (Q3D) to 0.5 mg once daily (QD) and 1.5 mg every other day (Q2D) to 0.75 mg QD, when use concomitantly with CYP3A4 inhibitors.

1. Background

Cariprazine is metabolized by CYP3A4 and, to a lesser extent, by CYP2D6 to desmethyl cariprazine (DCAR). DCAR is further metabolized into didesmethyl cariprazine (DDCAR) by CYP3A4 and CYP2D6. DDCAR is then metabolized by CYP3A4 to a hydroxylated metabolite.

Dosing modifications for cariprazine when concomitant use with strong and moderate CYP3A4 inhibitors were updated in a prior labeling supplement (NDA204370-S-012, submitted on March

06, 2024, seq0224, Ref ID 5484584), based on the results of a new drug-drug interaction (DDI) study of cariprazine with the moderate CYP3A4 inhibitor, erythromycin and PBPK modeling analyses (Ref ID 5440133). Considering the lowest cariprazine dose strength being 1.5 mg at that time, the dosing regimens of either 1.5 mg Q3D or 1.5 mg Q2D were recommended for DDI management of cariprazine with strong and moderate CYP3A inhibitors, respectively, as described in Table 36 and Table 37.

Table 36. Dosage Modifications for the Starting Dosage of Cariprazine in Patients Taking a Strong or Moderate CYP3A4 Inhibitor in the Current USPI (Modified 2024)

Indication or Disease being Treated	Cariprazine Starting Dosage	
	When Taking a Strong CYP3A4 Inhibitor	When Taking a Moderate CYP3A4 Inhibitor
Schizophrenia	Start at 1.5 mg orally Q3D; increase to 1.5 mg orally Q2D, if needed.	Start at 1.5 mg orally Q2D; increase to 1.5 mg once daily (QD), if needed.
Bipolar Mania		
Bipolar Depression	1.5 mg Q3D	1.5 mg Q2D
Adjunctive therapy for treatment of MDD		

Table 37. Dosage Modifications for Cariprazine When Initiating a Strong or Moderate CYP3A4 Inhibitor While on a Stable Dose of Cariprazine in the Current USPI (Modified 2024)

Current Cariprazine Dosage	Cariprazine Dosage When Initiating a Strong CYP3A4 Inhibitor	Cariprazine Dosage When Initiating a Moderate CYP3A4 Inhibitor
1.5 or 3 mg QD	1.5 mg Q3D	1.5 mg Q2D
4.5 or 6 mg QD	1.5 mg Q2D	1.5 mg QD

In this supplement, the Applicant submitted PBPK analysis to evaluate alternative daily dosing regimen of cariprazine when use concomitantly with CYP3A4 inhibitors considering the newly lower dose strengths of 0.5 mg and 0.75 mg. Specifically, the simulations aimed to support changes to the approved DDI dosing modifications from cariprazine 1.5 mg Q3D to 0.5 mg QD and 1.5 mg Q2D to 0.75 mg QD.

2. Methods

2.1 PBPK model of cariprazine and active metabolites

The PBPK analyses were performed using the software Simcyp® version 20. A PBPK model for cariprazine and its two active metabolites DCAR and DDCAR was previously reviewed and supported the approval of the current dosing modification for DDI when co-administered with CYP3A4 inhibitors (VRAYLAR® Label Ref ID 5484584). Detailed description of the PBPK model

development and verification for cariprazine and metabolites is presented in the PBPK review of the labeling supplement S-012 (Ref ID 5440133).

2.2 PBPK model application

DDI simulations were conducted with the PBPK model of cariprazine and metabolites DCAR and DDCAR with the strong and moderate CYP3A inhibitors ketoconazole and fluconazole, respectively, considering the proposed lower dose strengths of cariprazine 0.5 mg and 0.75 mg. The software's default virtual population model of healthy subjects (Sim-Healthy) and the default perpetrator models for ketoconazole and fluconazole were used without modifications. Simulations were carried out in a fasted state. As CAR is formulated as cariprazine-HCl, an equivalent amount of cariprazine free base was simulated to be dosed using the conversion: 0.92 × Dose of CAR-HCl. PK parameters for total cariprazine (Total CAR), represent the sum of cariprazine, DCAR and DDCAR exposures at steady state.

3. Results

3.1 Dose modification for patients initiating a CYP3A4 inhibitor while on a stable dose of cariprazine, considering 0.5 mg and 0.75 mg dose strengths

A comparison of the predicted total CAR PK parameters Cmax, Cmin, and Cavg at steady state between the dosing regimens Q2D or Q3D vs QD, in the presence of the strong or moderate CYP3A4 inhibitor ketoconazole or fluconazole, respectively, is listed in Table 38.

Table 38. Comparison of Total CAR PK Parameters for Q3D or Q2D vs. QD Dosing for Patients Initiating a CYP3A4 Inhibitor While on a Stable Dose of Cariprazine

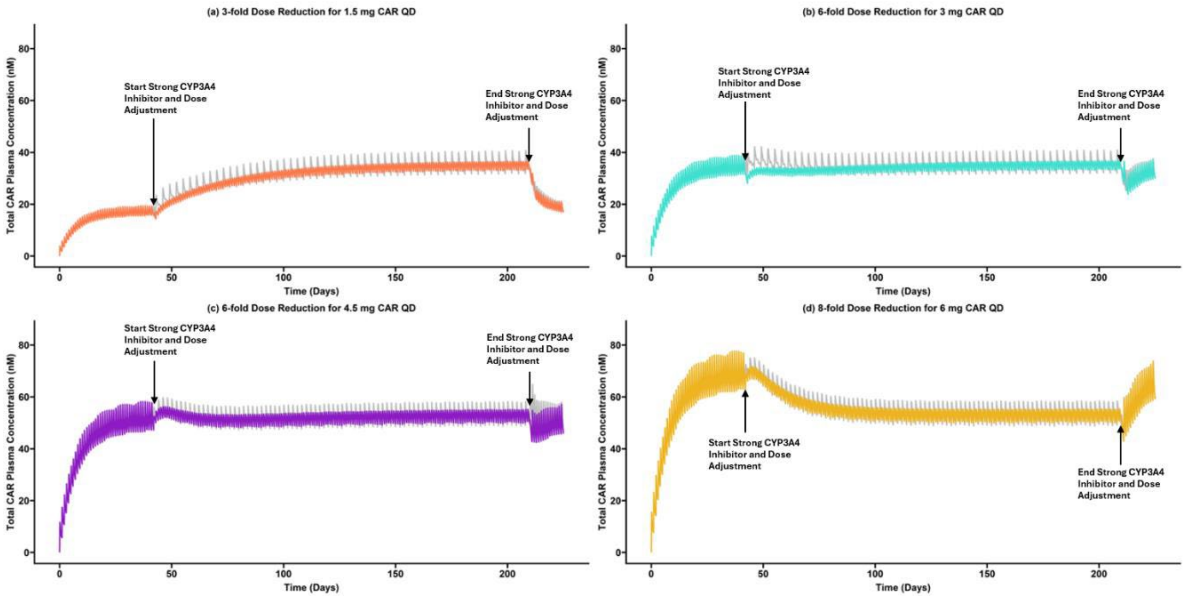
DDI Scenario: Stable dose of cariprazine initiating a strong CYP3A4 inhibitor (ketoconazole)			
Cariprazine	Predicted Total CAR PK at steady state		
DDI modified dosing	Cmax (nM)	Cmin (nM)	Cavg (nM)
1.5 mg Q2D	58.22	49.01	53.56
0.75 mg QD	55.14	50.14	53.53
1.5 mg Q3D	41.16	32.47	34.68
0.5 mg QD	36.73	33.40	35.66
DDI Scenario: Stable dose of cariprazine initiating a moderate CYP3A4 inhibitor (fluconazole)			
Cariprazine	Predicted Total CAR PK at steady state		
DDI modified dosing	Cmax (nM)	Cmin (nM)	Cavg (nM)
1.5 mg Q2D	29.52	23.26	25.75
0.75 mg QD	27.22	24.17	25.78

PK data are geometric means of steady state Total CAR.

Cavg: average concentration of the drug in the central circulation during the dosing interval in steady state; Cmax: observed maximum concentration; Cmin: minimum blood plasma concentration reached by the drug during the dosing interval; QD: once daily; Q2D: every two days; Q3D: every three days.
(Source: Tables 14 and 15 of the PBPK report R&D/22/0201 Version 3).

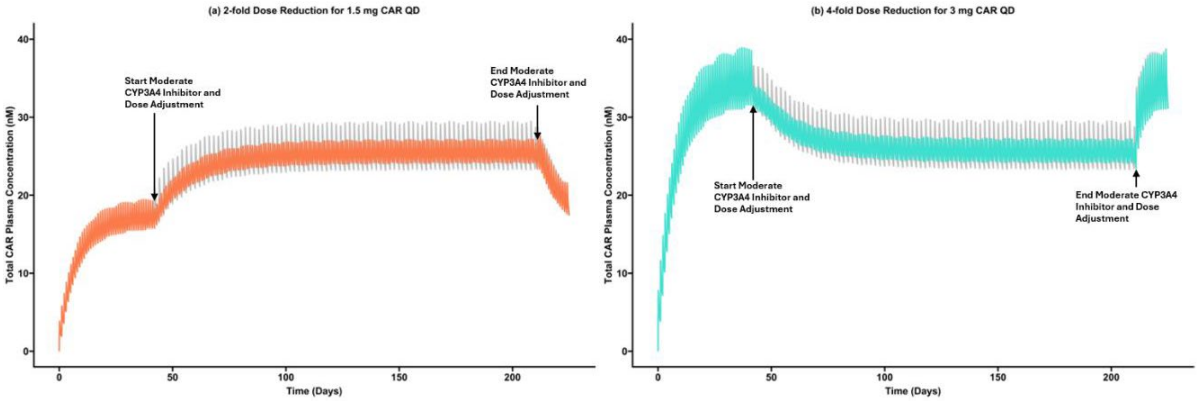
For patients initiating a strong CYP3A4 inhibitor (such as ketoconazole) while on a stable dose of cariprazine, substitution of the current DDI dosing modification of 1.5 mg Q3D to the proposed 0.5 mg QD and 1.5 mg Q2D to 0.75 mg QD resulted in comparable predicted total CAR Cavg (Table 38), with less concentration fluctuation at steady state (Figure 11). Similarly, for patients initiating a moderate CYP3A4 inhibitor (such as fluconazole) while on a stable dose of cariprazine, the current DDI dosing adjustment of 1.5 mg Q2D or the proposed 0.75 mg QD resulted in comparable total CAR Cavg (Table 38 and
Figure 12).

Figure 11: Comparison of Total CAR PK Profiles between QD vs Q2D or Q3D for Patients Initiating a Strong CYP3A4 Inhibitor While on a Stable Dose of Cariprazine



a. Grey line: 1.5 mg QD CAR adjusted to 1.5 mg Q3D; orange line: 1.5 mg QD CAR adjusted to 0.5 mg QD.
b. Grey line: 3 mg QD CAR adjusted to 1.5 mg Q3D; aqua line: 3 mg QD CAR adjusted to 0.5 mg QD.
c. Grey line: 4.5 mg QD CAR adjusted to 1.5 mg Q2D; purple line: 4.5 mg QD CAR adjusted to 0.75 mg QD.
d. Grey line: 6 mg QD CAR adjusted to 1.5 mg Q2D, yellow line: 6 mg QD CAR adjusted to 0.75 mg QD.
Source: Figure 13 of the PBPK report R&D/22/0201 Version 3.

Figure 12: Comparison of Total CAR PK Profiles between 1.5 mg Q2D vs. 0.75mg QD for Patients Initiating a Moderate CYP3A4 Inhibitor While on a Stable Dose of Cariprazine

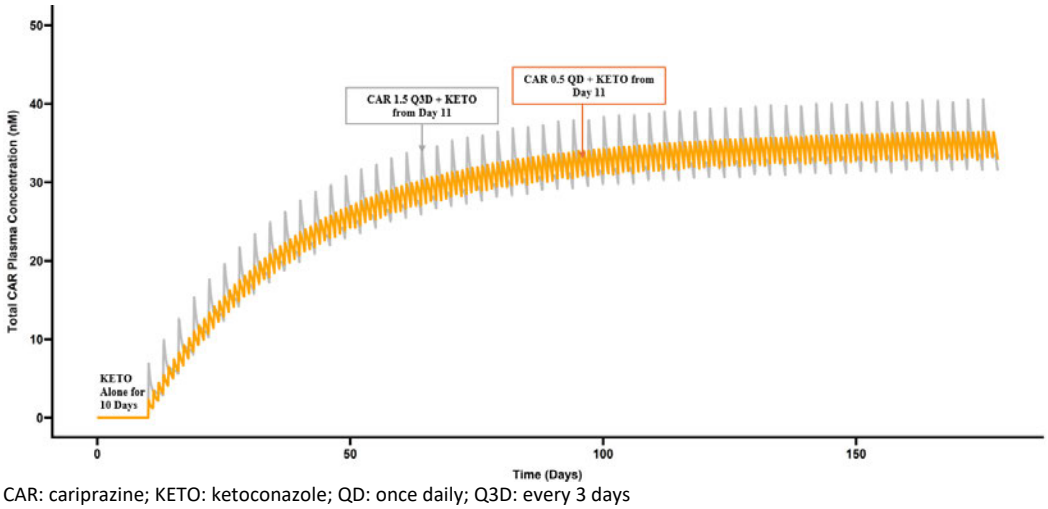


a. Grey line: 1.5 mg QD CAR adjusted to 1.5 mg Q2D; Orange line: 1.5 mg QD CAR adjusted to 0.75 mg QD.
b. Grey line: 3 mg QD CAR adjusted to 1.5 mg Q2D; aqua line: 3 mg QD CAR adjusted to 0.75 mg QD.
Source: Figure 14 of the PBPK report R&D/22/0201 Version 3.

3.2 Dose modification for patients initiating cariprazine while on a stable dose of a CYP3A4 inhibitor, considering 0.5 and 0.75 mg dose strengths

For patients initiating cariprazine treatment while on stable doses of a strong CYP3A4 inhibitor, prior simulations showed that initiating cariprazine at 1.5 mg Q3D on a stable dose of ketoconazole could achieve adequate Total CAR exposure over time, as initiating cariprazine at 1.5 mg QD in the absence of ketoconazole. A comparison of the predicted Total CAR plasma PK profiles at steady state between 1.5 mg Q3D and the proposed 0.5 mg QD dosing is shown in Figure 13. Based on steady-state total CAR exposure, the dosing regimen of 5 mg QD seems to be a suitable alternative to 1.5 mg Q3D, with less concentration fluctuation at steady state.

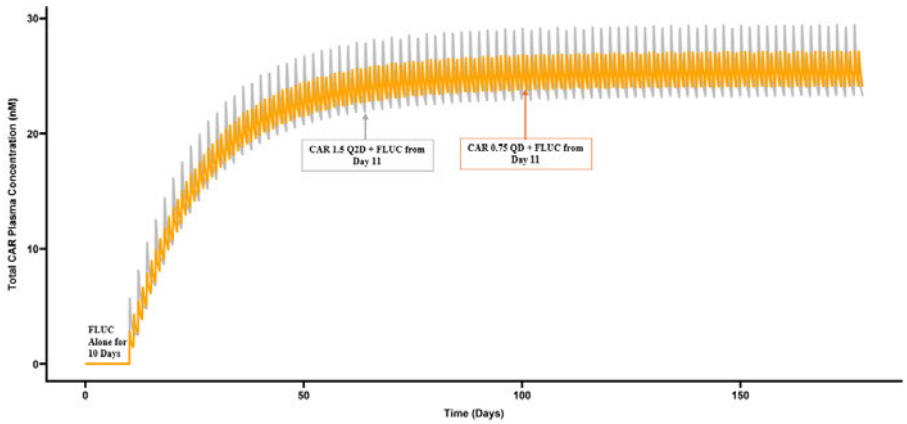
Figure 13: Comparison of Total CAR PK Profiles between 1.5 mg Q3D vs. 0.5 mg QD in Patients Initiating Cariprazine while on a Stable Dose of a Strong CYP3A4 Inhibitor



CAR: cariprazine; KETO: ketoconazole; QD: once daily; Q3D: every 3 days
Grey line: 1.5 mg Q3D CAR starting on stable doses of ketoconazole; yellow line: 1.5 mg Q3D CAR adjusted to 0.5 mg QD.
Source: Figure 15 of the PBPK report R&D/22/0201 Version 3

For patients initiating cariprazine treatment while on stable doses of a moderate CYP3A4 inhibitor, prior simulations showed that initiating cariprazine at 1.5 mg Q2D on a stable dose of fluconazole could achieve adequate Total CAR exposure over time, comparable with initiating cariprazine at 1.5 mg QD in the absence of fluconazole. A comparison of the predicted total CAR plasma PK profiles between 1.5 mg Q2D and the newly proposed 0.75 mg QD dosing is shown in Figure 14. Based on Total CAR exposure at steady state, the dosing regimen 0.75 mg QD seems to be a suitable alternative to 1.5 mg Q2D, with less concentration fluctuation at steady state.

Figure 14: Comparison of Total CAR PK Profiles between 1.5 mg Q2D vs. 0.75 mg QD in Patients Initiating Cariprazine While on a Stable Dose of a Moderate CYP3A4 Inhibitor



CAR: cariprazine; FLUC: fluconazole; QD: once daily; Q2D: every two days.
Grey line: 1.5 mg Q2D CAR starting on stable doses of fluconazole; yellow line: 1.5 mg Q2D CAR adjusted to 0.75 mg QD in the presence of fluconazole.
Source: Figure 16 of the PBPK report R&D/22/0201 Version 3.

4. Conclusions

Based on the newly available dose strengths of cariprazine, the Applicant proposed alternative dosing regimens for DDI management to maintain steady state exposure of total CAR when co-administered with strong and moderate CYP3A4 inhibitors. Simulations supported the following:

- Dosing regimens of cariprazine 0.5 mg QD and 0.75 mg QD are suitable alternatives to 1.5 mg Q3D and 1.5 mg Q2D, respectively, when initiating a strong CYP3A4 inhibitor while on a stable dose of cariprazine.

- Dosing regimen of cariprazine 0.5 mg QD is a suitable alternative to 1.5 mg Q3D, for patients starting cariprazine while on stable doses of a strong CYP3A4 inhibitor.

- Dosing regimen of cariprazine 0.75 mg QD is a suitable alternative to 1.5 mg Q2D, for patients either initiating a moderate CYP3A4 inhibitor while on a stable dose of cariprazine or starting cariprazine while on stable doses of a moderate CYP3A4 inhibitor.

Pharmacometric Review

Applicant submitted report rd241815-poppk.pdf and report rd241924-poppk-report.

rd241815-poppk.pdf

The file rd241815-poppk.pdf was submitted to module 5335 of sequence 0245 and contains a report titled "*Population Pharmacokinetic Analysis of Cariprazine to Support Extrapolation of Efficacy in Treatment of Pediatric Patients with Schizophrenia or Bipolar Mania: Analyses of the Phase 1 Studies RGH-PK-18 and RGH-188-201*". This report describes pharmacokinetic analyses of cariprazine to support pediatric dosing recommendations for schizophrenia and bipolar mania. The primary objectives were to characterize the population pharmacokinetics of cariprazine (CAR), desmethyl cariprazine (DCAR), and didesmethyl cariprazine (DDCAR) in pediatric patients with schizophrenia or bipolar mania, and to simulate pharmacokinetic profiles for proposed pediatric dose regimens.

Modeling

The analysis utilized data from two Phase 1 studies: RGH-PK-18 (N=49 pediatric patients) and RGH-188-201 (N=52 patients including adolescents and adults). A total of 101 patients contributed 4,237 concentration records across the three analytes. The population from which the data were obtained were children (10-12 years, N=25), adolescents (13-17 years, N=60), and adults (18+ years, N=16). There 60% male patients, with racial composition of 58% White, 41% Black, 1% Asian. Body weights ranged from 26.9 to 95.4 kg, with 75% of patients weighing ≥40 kg.

The Applicant updated three existing adult PPK models (for CAR, DCAR, and DDCAR) using the observed PK. The coefficients for body weight effect on apparent clearance (Cl/F) as well as apparent volume of distribution (Vc/F), proportional error, interindividual (IIV) for Cl/F, and IIV for Vc/F were re-estimated for all three models. The IIV term for first order absorption rate constant (Ka) was re-estimated for the parent, CAR. All other parameters were held constant at the final estimates from the previous PPK models for CAR, DCAR, and DDCAR. The final estimates after updating the models are presented in Table 39, Table 40, and Table 41.

Table 39: Updated PPK Model Estimates for CAR PPK Model in Pediatric Patients with SCZ and BPM

Parameter	Population Estimate	%RSE	95% Confidence Interval
Apparent CAR Elimination Clearance (CAR CL/F) (L/h) (fixed)	21.5	--	--
Apparent CAR Central Volume (CAR Vc/F) (L) (fixed)	266	--	--
Apparent CAR First Distribution Clearance (CAR Q3/F) (L/h) (fixed)	0.431	--	--
Apparent CAR First Peripheral Volume (CAR Vp1/F) (L) (fixed)	149	--	--
Duration of Zero-order CAR Absorption Process (DUR/F) (h) (fixed)	2.57	--	--
First-Order CAR Absorption Rate Constant (KA) (1/h) (fixed)	0.352	--	--
Apparent CAR Second Distribution Clearance (CAR Q4/F) (L/h) (fixed)	100	--	--
Apparent CAR Second Peripheral Volume (CAR Vp2/F) (L) (fixed)	501	--	--
CAR Vc/F Prop. Shift for First Dose (fixed)	2.84	--	--
CAR Q3/F Prop. Shift for First Dose (fixed)	39.4	--	--
CAR Vp1/F Prop. Shift for First Dose (fixed)	2.61	--	--
Power of CAR CL/F for WTKG	0.0977	73.4	(-0.0429, 0.238)
Power of CAR Vc/F for WTKG	0.998	28.6	(0.438, 1.56)
Prop. Shift of CAR CL/F for Race=Black (fixed)	-0.0907	--	--
Prop. Shift of CAR CL/F for Race=Asian (fixed)	-0.178	--	--
Prop. Shift of CAR CL/F for Race=Japanese (fixed)	-0.111	--	--
Proportional Error Full Profile Studies CAR	0.107	2.59	(0.102, 0.113)
Proportional Error CAR (fixed)	0.154	--	--
IIV on CAR CL/F	0.0608	25.0	5.34
IIV on CAR Vc/F	1.47	184	18.8
IIV on KA	0.906	121	44.5

%RSE was calculated as the standard error of the estimator divided by the absolute value of the mean of the estimator multiplied by 100. %CV was calculated as SQRT(exp(ω2)-1)*100.
Source: sequence 0245, module 5335, rd241815-poppk.pdf, page 25.

Table 40: Updated PPK Model Estimates for DCAR PPK Model in Pediatric Patients with SCZ and BPM

Parameter	Population Estimate	%RSE	95% Confidence Interval
Apparent DCAR Elimination Clearance (DCAR CL/F) (L/h) (fixed)	77.3	--	--
Apparent DCAR Central Volume (DCAR Vc/F) (L) (fixed)	128	--	--
Apparent DCAR Distribution Clearance (DCAR Q3/F) (L/h) (fixed)	78.5	--	--
Apparent DCAR Peripheral Volume (DCAR Vp/F)(L) (fixed)	347	--	--
DAR Vc/F Prop. Shift for First Dose (fixed)	1.27	--	--
DAR Vp/F Prop. Shift for First Dose (fixed)	0.535	--	--
Power of DCAR CL/F for WTKG	0.0697	121	(-0.0963, 0.236)
Power of DCAR Vc/F for WTKG	0.284	174	(-0.686, 1.25)
Prop. Shift of DCAR CL/F for Race=Black (fixed)	0.249	--	--
Prop. Shift of DCAR CL/F for Race=Asian (fixed)	-0.0861	--	--
Prop. Shift of DCAR CL/F for Race=Japanese (fixed)	-0.145	--	--
Prop. Shift of DCAR CL/F for Sex=Female (fixed)	-0.160	--	--
Proportional Error Full Profile Studies DCAR	0.0688	3.08	(0.0647, 0.0730)
Proportional Error DCAR (fixed)	0.141	--	--
IIV on DCAR CL/F	0.105	33.2	2.90
IIV on DCAR Vc/F	1.56	194	39.3

%RSE was calculated as the standard error of the estimator divided by the absolute value of the mean of the estimator multiplied by 100. %CV was calculated as SQRT(exp(ω2)-1)*100.
Source: sequence 0245, module 5335, rd241815-poppk.pdf, page 32.

Table 41: Updated PPK Model Estimates for DDCAR PPK Model in Pediatric Patients with SCZ and BPM

Parameter	Population Estimate	%RSE	95% Confidence Interval
Apparent DDCAR Elimination Clearance (DDCAR CL/F) (L/h) (fixed)	9.24	--	--
Apparent DDCAR Central Volume (DDCAR Vc/F) (L) (fixed)	1310	--	--
Apparent DDCAR Distribution Clearance (DDCAR Q3/F) (L/h) (fixed)	0.386	--	--
Apparent DDCAR Peripheral Volume (DDCAR Vp/F) (L) (fixed)	258	--	--
Rate Constant Delaying DDCAR Formation (DDKTR/F) (1/h) (fixed)	0.0269	--	--
Power of DDCAR CL/F for WTKG	0.511	20.1	(0.310, 0.712)
Prop. Shift of DDCAR CL/F for Race=Black (fixed)	0.547	--	--
Prop. Shift of DDCAR CL/F for Race=Asian (fixed)	-0.194	--	--
Prop. Shift of DDCAR CL/F for Race=Japanese (fixed)	-0.156	--	--
Power of DDCAR Vc/F for WTKG	0.244	54.7	(-0.0174, 0.506)
Power of DDCAR Vc/F for AGE (fixed)	0	--	--
Prop. Shift of DDCAR Vc/F for Race=Black (fixed)	0.676	--	--
Prop. Shift of DDCAR Vc/F for Race=Asian (fixed)	-0.240	--	--
Prop. Shift of DDCAR Vc/F for Race=Japanese (fixed)	0.0888	--	--
Proportional Error Full Profile Studies DDCAR	0.0470	2.48	(0.0447, 0.0492)
Proportional Error DDCAR (fixed)	0.0875	--	--
IIV on DDCAR CL/F	0.167	42.6	2.09
IIV on DDCAR Vc/F	0.295	58.6	6.07

%RSE was calculated as the standard error of the estimator divided by the absolute value of the mean of the estimator multiplied by 100. %CV was calculated as SQRT(exp(ω2)-1)*100.
Source: sequence 0245, module 5335, rd241815-poppk.pdf, page 41.

The diagnostic plots and VPC are presented in Figure 15, Figure 16, Figure 17, Figure 18, Figure 19, and Figure 20.
Source: sequence 0245, module 5335, rd241815-poppk.pdf, page 36 and 37.

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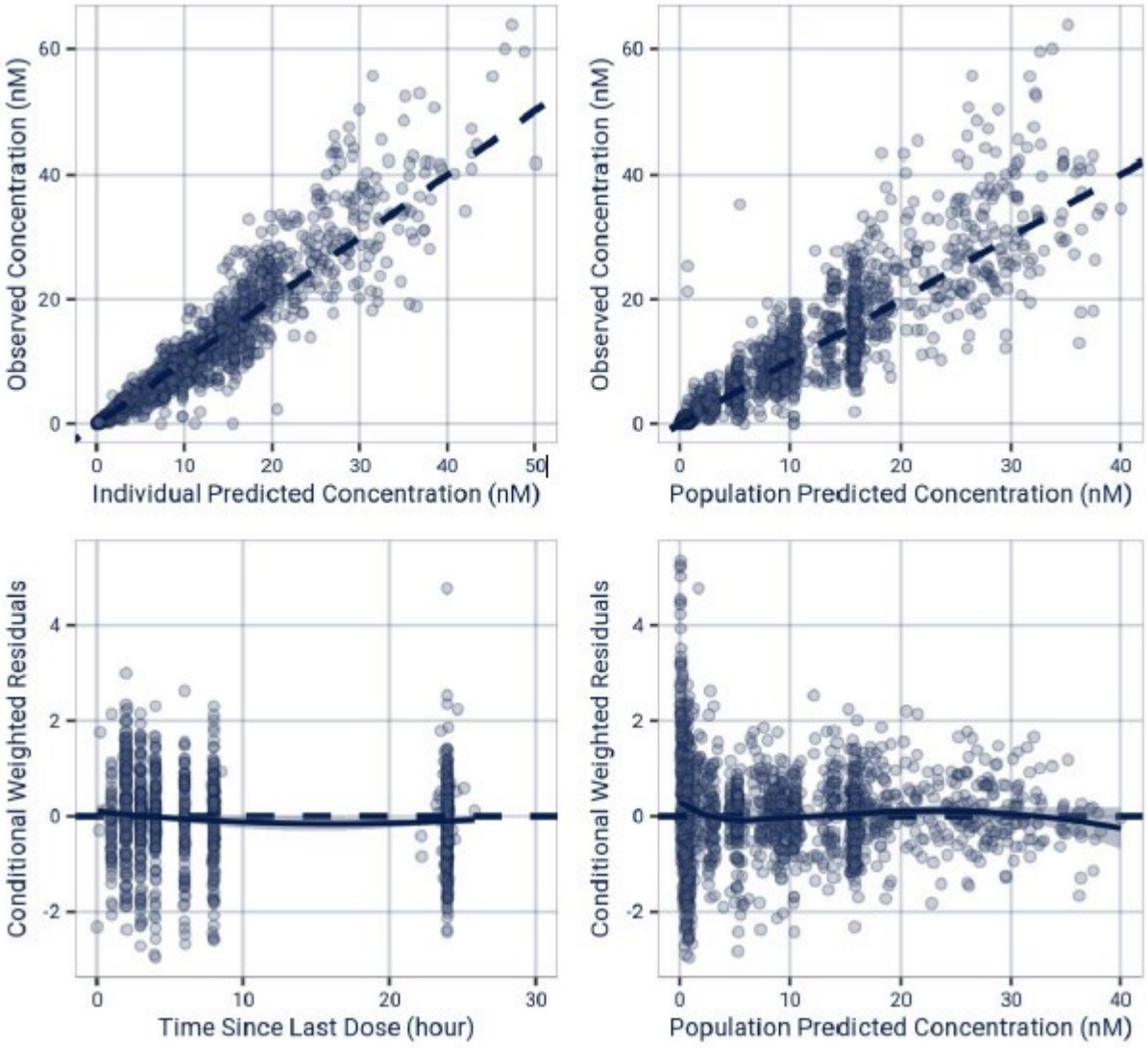
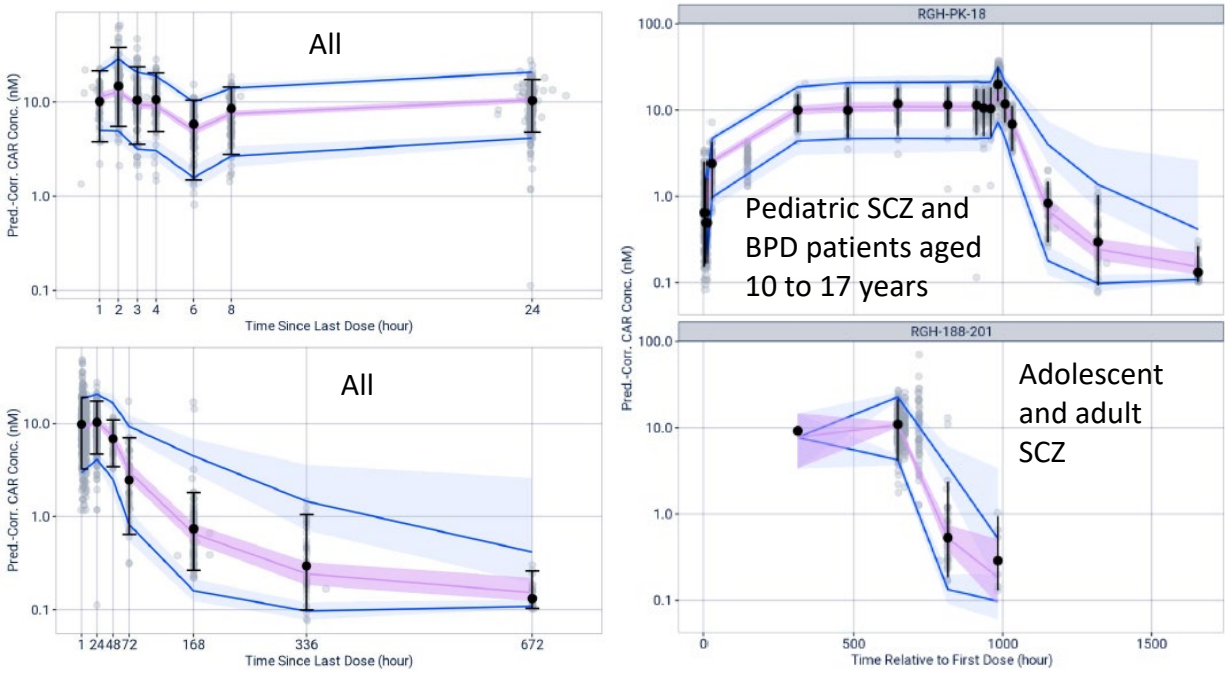
Figure 15: Diagnostic Plots for Final CAR PPK Model



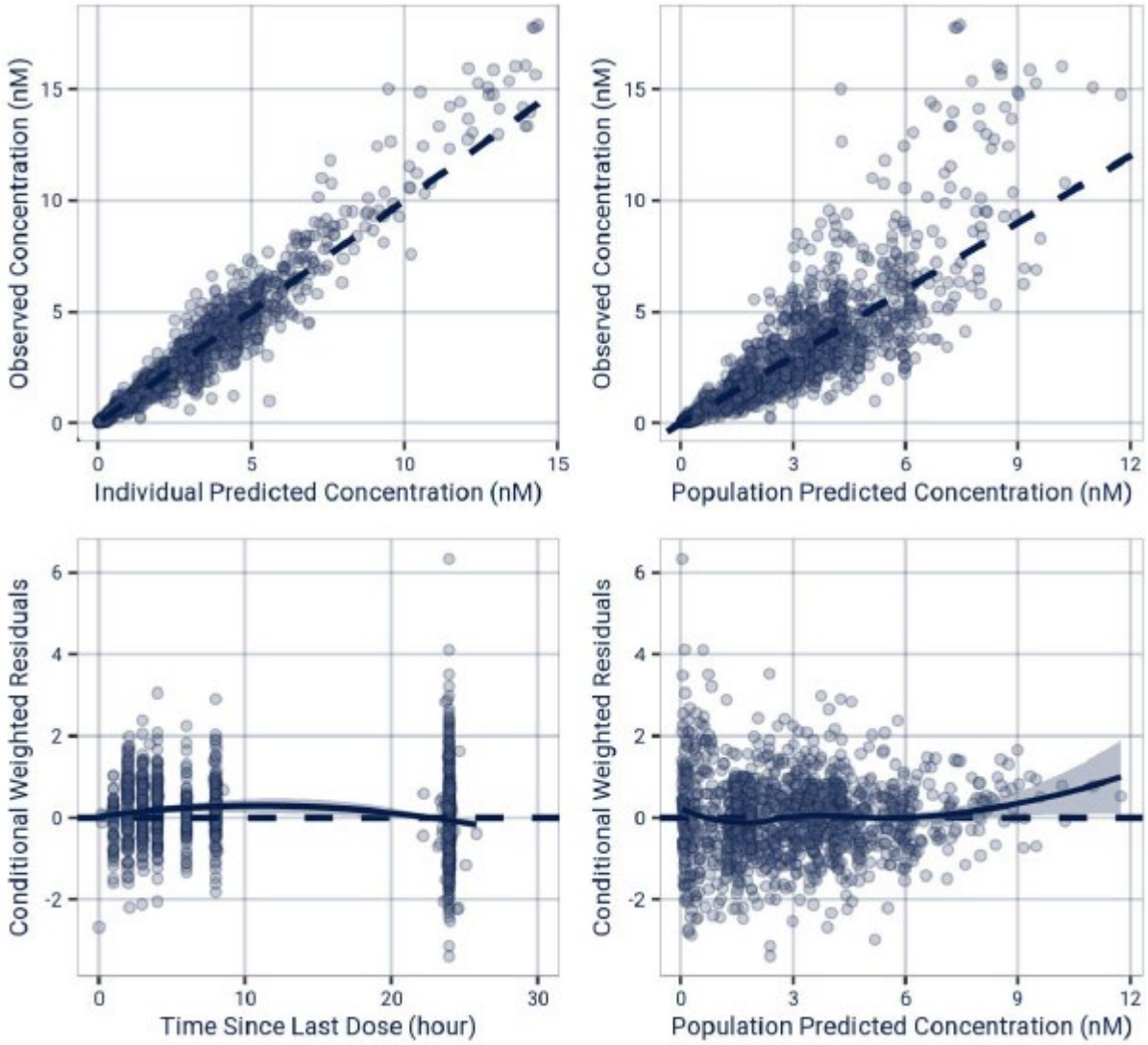
Goodness-of-fit plots for the individual predicted and population predicted versus observed concentrations (top left and right, respectively) and CWRES versus TSLD and population prediction (bottom left and right, respectively) with loess smooth (95% CI).
Source: sequence 0245, module 5335, rd241815-poppk.pdf, page 26.

Figure 16: Prediction-Corrected Visual Predictive Check for Final CAR PPK Model



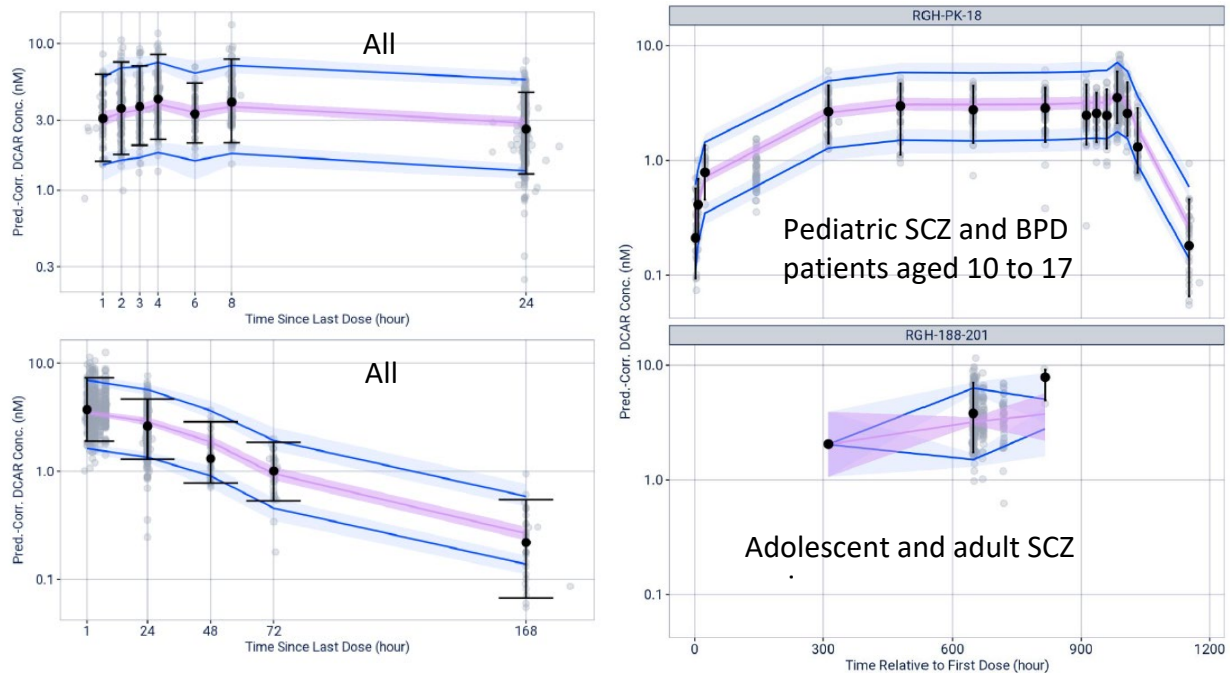
The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. Black dots and error bars represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Gray circles denote observed concentrations. Left Panels: all patients in study RGH-PK-18 (pediatric SCZ and BPD patients aged 10 to 17 years) pooled with patients in RGH-188-201 (adolescent age 13 to 17 and adult SCZ patients). Right Panels: stratified by study (RGH-PK-18 in pediatric patients; RGH-188-201 in adolescents and adults).
Source: sequence 0245, module 5335, rd241815-poppk.pdf, page 28, 29.

Figure 17: Diagnostic Plots for Final DCAR PPK Model



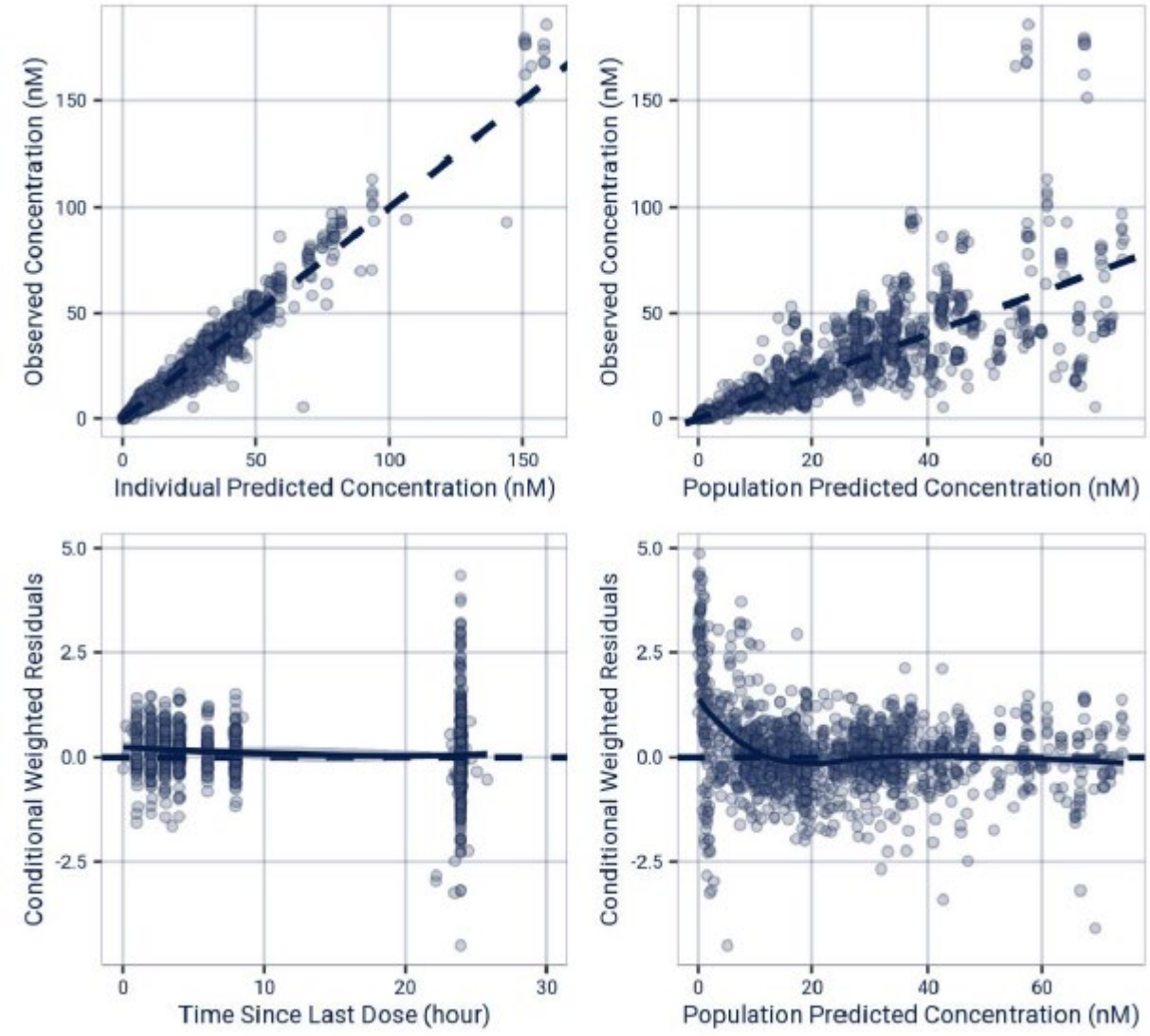
Goodness-of-fit plots for the individual predicted and population predicted versus observed concentrations (top left and right, respectively) and CWRES versus TSLD and population prediction (bottom left and right, respectively) with loess smooth (95% CI).
Source: sequence 0245, module 5335, rd241815-poppk.pdf, page 34.

Figure 18: Prediction-Corrected Visual Predictive Check for Final DCAR PPK Model



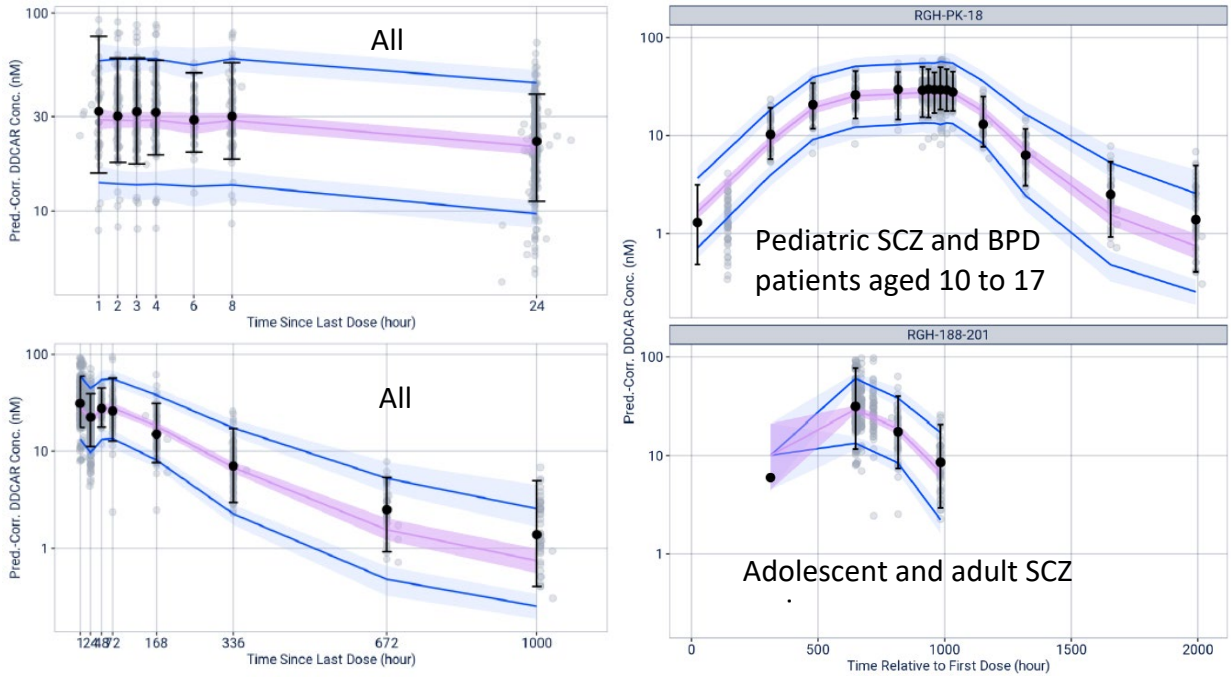
The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. Black dots and error bars represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Gray circles denote observed concentrations. Left Panels: all patients in study RGH-PK-18 (pediatric SCZ and BPD patients aged 10 to 17 years) pooled with patients in RGH-188-201 (adolescent age 13 to 17 and adult SCZ patients). Right Panels: stratified by study (RGH-PK-18 in pediatric patients; RGH-188-201 in adolescents and adults).
Source: sequence 0245, module 5335, rd241815-poppk.pdf, page 36 and 37.

Figure 19. Diagnostic Plots for Final DDCAR PPK Model



Goodness-of-fit plots for the individual predicted and population predicted versus observed concentrations (top left and right, respectively) and CWRES versus TSLD and population prediction (bottom left and right, respectively) with loess smooth (95% CI).
Source: sequence 0245, module 5335, rd241815-poppk.pdf, page 43.

Figure 20. Prediction-Corrected Visual Predictive Check for Final DDCAR PPK Model



The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. Black dots and error bars represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Gray circles denote observed concentrations. Left Panels: all patients in study RGH-PK-18 (pediatric SCZ and BPD patients aged 10 to 17 years) pooled with patients in RGH-188-201 (adolescent age 13 to 17 and adult SCZ patients). Right Panels: stratified by study (RGH-PK-18 in pediatric patients; RGH-188-201 in adolescents and adults).
Source: sequence 0245, module 5335, rd241815-poppk.pdf, page 45 and 46.

The Applicant concludes:

- estimated effects of body weight on the apparent clearance of cariprazine, DCAR, and DDCAR were moderate and markedly less than the allometric scaling relationship assumed in the previous preliminary pediatric PK modeling analysis.
- The pediatric population pharmacokinetic model adequately describes the data obtained from two pediatric PK studies.

Reviewer comment: The estimated allometry coefficient for CL/F terms (0.0977, 0.0697, 0.511 for CAR, DCAR, and DDCAR, respectively) are lower than the previously used values, fixed at 0.75. However, the updated models are able to describe the PK data observed in the pediatric patients from studies RGH-PK-18 and RGH-188-201 reasonably well. Overall, the model is acceptable for performing PK simulations for comparison with adult patients.

Simulations

The Applicant simulated CAR, DCAR, and DDCAR with the three updated population PK models for pediatric patients, and the legacy model for adults. For pediatric patients, a total of n=1000 subjects were generated for children (age 10 to 12 years) and adolescents (13 to 17 years).

Ages were randomly selected assuming a uniform distribution and random weight assigned according to the CDC growth chart[6] weight distribution for the age. The sex and race covariates followed the same proportions as found in the adult legacy population. The demographics for the simulations are presented in Table 42.

Table 42. Demographic and Baseline Characteristics of Populations (Adults, Adolescents, and Children) used for Simulations

Characteristic	Children (< 40 kg) (N = 571)	Children (≥ 40 kg) (N = 429)	Adolescents (N = 1000)	Adults (N = 2199)
Sex, n (%)				
Male	387 (68%)	277 (65%)	664 (66%)	1,461 (66%)
Female	184 (32%)	152 (35%)	336 (34%)	738 (34%)
Race, n (%)				
White	260 (46%)	196 (46%)	456 (46%)	1,003 (46%)
Black	189 (33%)	160 (37%)	349 (35%)	767 (35%)
Asian	86 (15%)	57 (13%)	143 (14%)	314 (14%)
Japanese	13 (2%)	4 (1%)	17 (2%)	37 (2%)
Others	23 (4%)	12 (3%)	35 (4%)	78 (4%)
Age (year)				
Mean (SD)	11 (1)	11 (1)	15 (1)	39 (11)
Median	11	11	15	40
Min, Max	10, 12	10, 12	13, 17	18, 65
Body Weight (kg)				
Mean (SD)	33.7 (3.96)	48.1 (7.66)	58.1 (13.5)	78.9 (18.7)
Median	33.8	46.3	56.4	77.7
Min, Max	23.1, 40.0	40.0, 93.6	31.7, 157	33.1, 155

Note: some of the percentages do not add up to 100% due to rounding.
Source: sequence 0245, module 5335, rd241815-poppk.pdf, page 163.

For each pediatric population and the adult population, PK was simulated for the following dosing regimens with titration (value is amount administered once daily):

1. Children (< 40 kg): Start at 0.5 mg, 1.5 mg on Day 3, 3.0 mg on Day 5, 4.5 mg On Day 8 and beyond
2. Children (>= 40 kg): Start at 0.5 mg, 1.5 mg on Day 3, 3.0 mg on Day 5, 4.5 mg On Day 8 and beyond
3. Adolescents: Start at 0.5 mg, 1.5 mg on Day 3, 3 mg on Day 5, 4.5 mg on Day 8 and beyond
4. Adults (1.5 mg): 1.5 mg dosing daily
5. Adults (3 mg): Start at 1.5 mg, 3 mg on Day 2 and beyond
6. Adults (6 mg): Start at 1.5 mg, 3 mg on Day 2, 4.5 on Day 5, 6 mg on Day 8 and beyond

[6] Centers for Disease Control and Prevention, National Center for Health Statistics. CDC growth charts: United States; 2024. http://www.cdc.gov/growthcharts/clinical_charts.htm

The median and 5th/95th percentiles of predicted CAR, DCAR, DDCAR and total CAR concentrations over time of the dosing regiments for children and adolescents were graphically compared to the adult dosing regiments. Steady-state exposures were evaluated after 42 days of dosing at a single dose level for the following dose levels administered once daily:

- Children < 40 kg: 1.5 mg, 3 mg, 4.5 mg
- Children >= 40 kg: 1.5 mg, 3 mg, 4.5 mg
- Adolescents: 1.5 mg, 3 mg, 4.5 mg
- Adults: 1.5 mg, 3 mg, 4.5 mg, 6 mg

Individual values of Cmax,ss, Ctrough,ss, and AUCtau,ss (where tau is 24 hours) were computed and summarized for CAR, DCAR, DDCAR, and total CAR for comparison between adult and pediatric patients. This review will focus on total CAR.

The results of the simulation during the titration period for children < 40 kg, children ≥40 kg, and adolescents compared to adults over 12 days is shown in
Figure 1 and over 42 days in

Figure 2. The simulated AUCtau,ss, Cmax,ss, and Ctrough,ss are summarized in Table 9 and presented graphically in Figure 3. The percent difference of the median value of simulated AUCtau,ss, Cmax,ss, and Ctrough,ss in pediatric patients from Table 9 versus adults in Table 9 is presented in Table 10.

The Applicant concludes:

- doses of 1.5 to 4.5 mg/day simulated in adolescent patients 13 to 17 years of age yielded exposures that are within the efficacious exposure range simulated in adult patients with SCZ at 1.5 to 6 mg per day.
- doses of 3.0 mg and 4.5 mg/day for pediatric patients 10 to 12 years of age and adolescent patients yielded simulated exposures within the efficacious exposure range in adult patients with BPM at 3 mg to 6 mg per day.

Reviewer comment: The Applicant's PK simulations are acceptable to use to help inform dose selection. Compared to the equivalent dose in adults, the median predicted AUCtau,ss, Cmax,ss, and Ctrough,ss are up to 33% higher in pediatric patients at the proposed dose compared to adults. Overall, the PK simulations support the effectiveness of the proposed dosing from a PK perspective. The proposed dosing in pediatric patients down to 10 years of age is the same as was administered in Study 3070-301-001, which assessed the effect of 0.75 to 4.5 mg once daily in bipolar patients aged 10 to 17 years. Please refer to section 6.3.1 Clinical Pharmacology Questions for additional details on dose selection.

rd241924-poppk-report

Report rd241924-poppk-report.pdf was submitted to module 5335 of sequence 0245 and contains a report titled, "*Population Pharmacokinetic Analysis of Cariprazine in Pediatric Subjects with Schizophrenia, Bipolar I Disorder, or Autism Spectrum Disorder: Analyses of Phase 3 Studies 3070-301-001 and M21-465.*" The report presents PPK analyses to assess the ability of the PPK model from report R&D/24/1815 (which includes PK data from SCZ and BPD subjects down to age 10 years) to describe sparse PK data collected in two Phase 3 studies conducted in SCZ, BPD, and ASD subjects aged 5 to 17 years of age. A summary of the Phase 3 study details is shown in Table 43.

Table 43: Summary of Studies and Data Included in the Population PK Analyses

Study (N)	Phase/Population	Cariprazine Regimen(s), Formulation	PK Assessment Time Points
3070-301-001 (N= 168)	Phase 3/pediatric subjects with SCZ, BPD or ASD	0.5, 0.75, 1.5, 3.0, 4.5 mg QD, oral capsule [redacted] (b) (4) mg/mL QD, oral solution	Days 29, 127, 183, 365, 395 (follow-up)
M21-465 (N=57)	Phase 3/pediatric subjects with ASD	0.5, 0.75, 1.5, 3.0 mg QD, oral capsule [redacted] (b) (4) mg/mL QD, oral solution	Days 15, 29, 57 and premature discontinuation

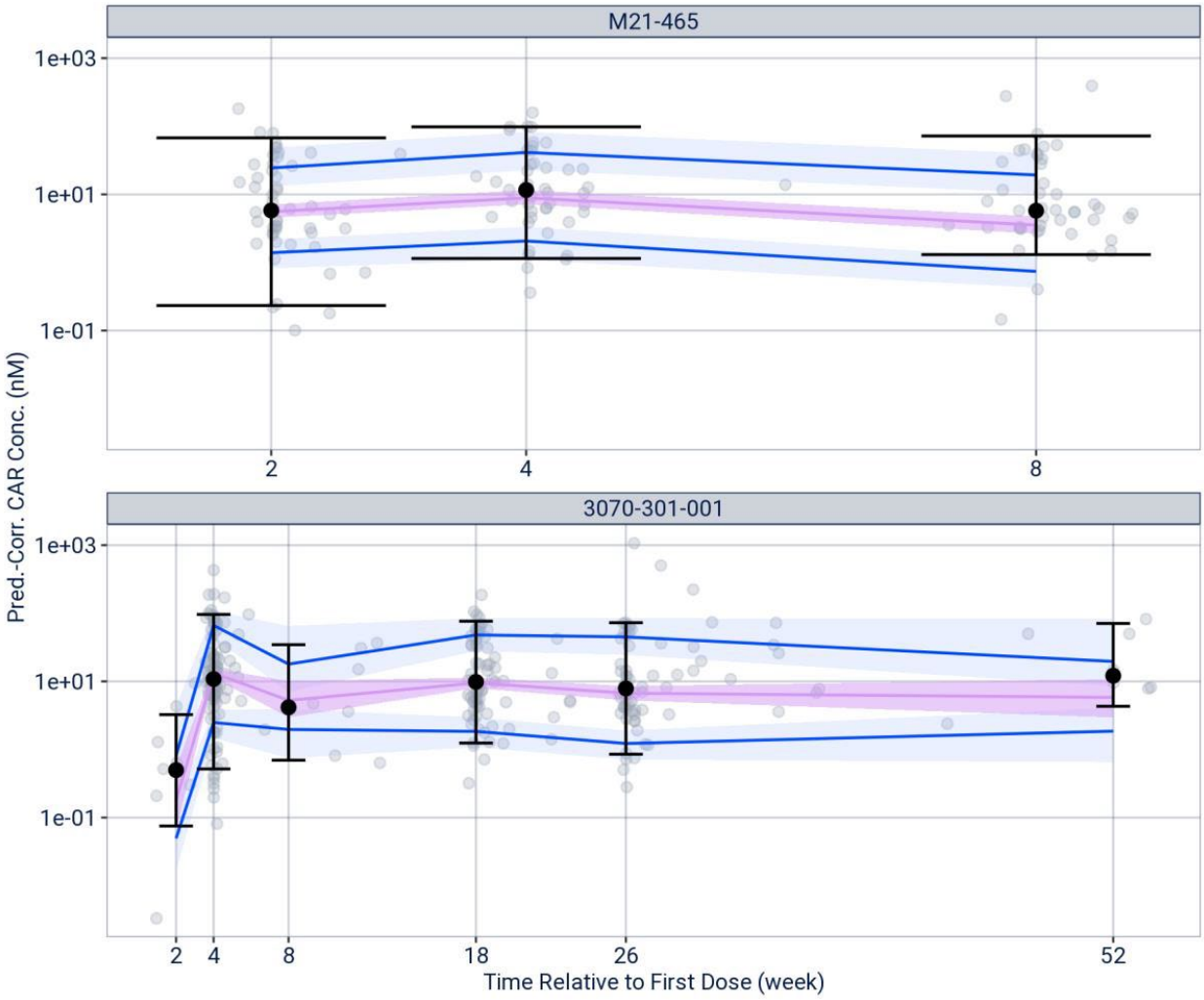
Source: sequence 0245, module 5335, rd241924-poppk.pdf, page 10.

The population was 55% male, 58% White, and 33% Black. Age distribution included 15% aged 5-9 years, 30% aged 10-12 years, and 55% aged 13-17 years. Body weight ranged from 17.3 to 147 kg, with 22% of subjects weighing less than 40 kg. A total of 1,376 concentration records were included in the analyses (463 for CAR, 417 for DCAR, and 496 for DDCAR).

The analysis utilized the previously developed population pharmacokinetic model from report R&D/24/1815, which described CAR, DCAR, and DDCAR pharmacokinetics in pediatric subjects with schizophrenia and bipolar mania, as a starting point. The Applicant notes a subset of patients have unexpectedly low exposures. A mixture model approach was implemented the characterize this phenomenon. This approach classified subjects into one of two sub-populations: those with normal bioavailability (69.9% of subjects) and those with reduced bioavailability (30.1% of subjects, with an estimated bioavailability reduction to 12.9% of the normal bioavailability). It should be noted that the model is parameterized in terms of apparent clearance terms (e.g., Cl/F) and apparent volume terms (e.g., V/F) as the absolute bioavailability F is not known. For the parent CAR, the mixture parameter (that is, the assignment of subjects belonging to normal bioavailability group or reduced bioavailability group) and inter-individual variability on clearance were estimated, while other parameters remained fixed. For the metabolites DCAR and DDCAR, only the inter-individual variability on clearance was re-estimated, with all other parameters fixed to previously established values. The Applicant

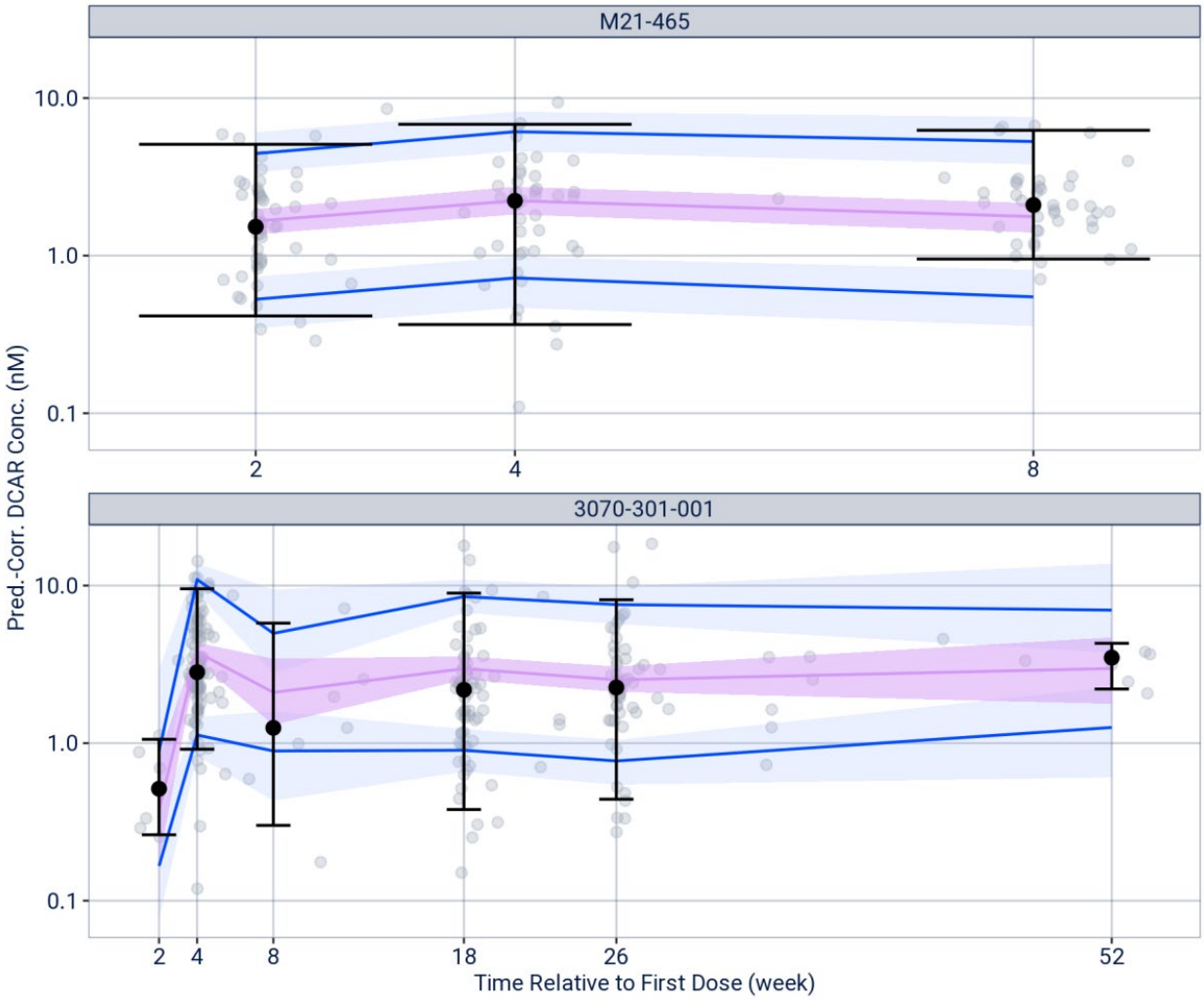
generated diagnostic plots, prediction-corrected (pc) visual predictive checks (VPCs). The pcVPCs for the updated model are presented in Figure 21, Figure 22, and Figure 23.

Figure 21: Prediction-Corrected Visual Predictive Checks of CAR Concentration in Subjects with SCZ, BPD and ASD Stratified by Study



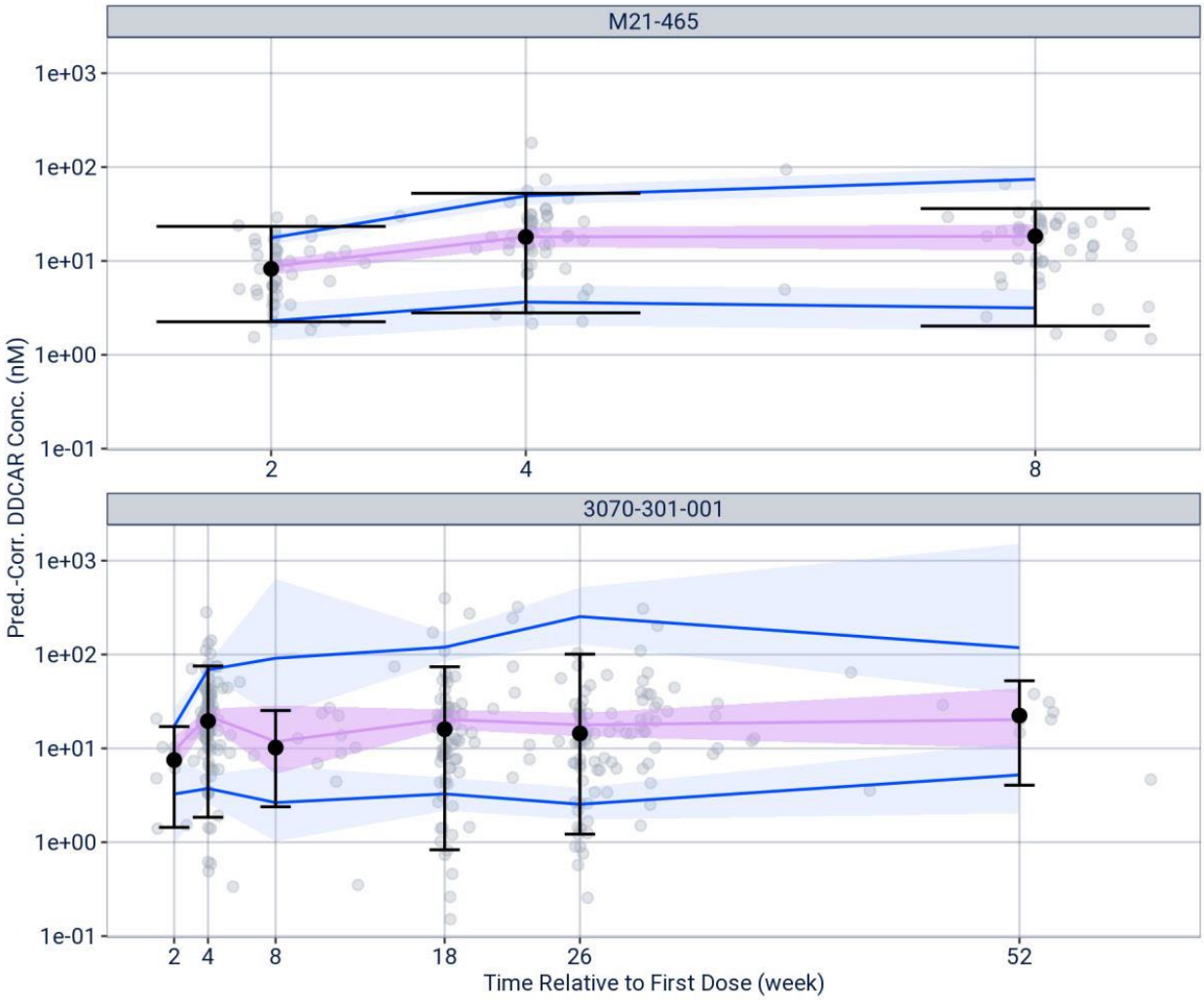
The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. Black dots and error bars represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Circles denote observed concentrations.
Note: Time bins were chosen at 2, 4, 8, 18, 26, and 52 weeks since first dose.
Source: sequence 0245, module 5335, rd241924-poppk-report.pdf, page 25.

Figure 22: Prediction-Corrected Visual Predictive Checks of DCAR Concentration in Subjects with SCZ, BPD and ASD Stratified by Study



The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. Black dots and error bars represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Circles denote observed concentrations.
Note: Time bins were chosen at 2, 4, 8, 18, 26, and 52 weeks since first dose.
Source: sequence 0245, module 5335, rd241924-poppk-report.pdf, page 32

Figure 23: Prediction-Corrected Visual Predictive Checks of DDCAR Concentration in Subjects with SCZ, BPD and ASD Stratified by Study



The blue lines represent the 90% PI of the model, the shaded blue areas are the associated 90% CIs of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% CI. Black dots and error bars represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Circles denote observed concentrations.
Note: Time bins were chosen at 2, 4, 8, 18, 26, and 52 weeks since first dose.
Source: sequence 0245, module 5335, rd241924-poppk-report.pdf, page 39

The pcVPCs (Figure 21, Figure 22, and Figure 23) and diagnostic plots (not shown here) suggest that the model is able to describe the observed data well, where the observed data are the same data used to generate the model (wherein the assignment of the “normal bioavailability” or “reduced bioavailability” status is known).

Individual exposure predictions were generated for subjects who remained on treatment until Week 8 (Study M21-465) or Week 18 (Study 3070-301-001). Among included subjects, 48.7% in M21-465 and 83.6% in 3070-301-001 remained on the same dose for at least 42 days post-titration.

The Applicant concludes:

- Large variability was seen in the model-predicted dose-normalized exposure parameters which possibly resulted from differences in compliance to treatment
- no major differences in total CAR model-predicted exposures were observed across the different age groups (5 to 9 years of age, 10 to 12 years of age weighing less than 40 kg, 10 to 12 years of age and weighing 40 kg or more, and 13 to 17 years of age.)

Reviewer comment: Due to optional dose increases and optional dose decreases allowed in both Study M21-465 and Week 18 Study 3070-301-001, the dose levels administered over time vary across subjects in these studies. Thus, it difficult to make meaningful direct comparisons of the sparse observed PK data (e.g. comparing observed PK for normal bioavailability versus observed PK for reduced bioavailability subjects). As such, these PPK analyses are a useful way to describe the observed PK in this scenario.

The PPK analyses indicate that 30% of the subject had unexpectedly low PK, quantified as having bioavailability approximately 87% lower than the bioavailability for the remaining 70% of subjects. For example, in study M21-465, out of five subjects aged 5 to 9 years receiving 0.75 mg QD, the predicted steady-state total Cmax for the subject assigned the "low bioavailability" designation is 0.394 nM in yet the steady-state total Cmax ranges from 7.8 nM to 39.2 nM in the four subjects assigned the "normal bioavailability" designation.

Though the updated PPK model described in report rd241924 can predict the observed PK reasonably well, the diagnostic assessments focus on describing the dataset used to build the model. As such, the model performs best in subjects that have already been pre-designated in the estimation procedure as having "normal bioavailability" or "reduced bioavailability". The PPK model described in report rd241924 would be more useful if there was a clear understanding of the cause of the low bioavailability, and ultimately if the model could provide a reliable way to prospectively identify whether pediatric subjects can be expected to experience the low bioavailability. Though the specific cause of the low PK It is unclear, it is plausible that non-adherence contributed to this phenomenon.

This PPK model described in report rd241924 was not used for PK simulations to inform dose selection. The PK simulations described in section 6.3.1 Clinical Pharmacology Questions used the PPK model described in report rd241815.

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