NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	205422/S-007
Priority or Standard	Priority
Submit Date(s)	June 30, 2021
Received Date(s)	June 30, 2021
PDUFA Goal Date	December 30, 2021
Division/Office	Division of Psychiatry/Office of Neuroscience
Review Completion Date	December 27, 2021
Established/Proper Name	Brexpiprazole
(Proposed) Trade Name	Rexulti
Pharmacologic Class	Atypical antispychotic
Code name	OPC-34712, LU AF41156
Applicant	Otsuka Pharmaceutical Company, Ltd.
Dosage form	Tablets
Applicant proposed Dosing Regimen	The recommended starting dosage for REXULTI is 0.5 mg once daily on Days 1 to 4. Titrate to 1 mg once daily on Day 5 through Day 7, then to 2 mg on Day 8 based on the patient's clinical response and tolerability. Weekly dose increases can be made in 1 mg increments. The recommended target REXULTI dosage is 2 mg to 4 mg once daily. The maximum recommended daily dosage is 4 mg.
Applicant Proposed Indication(s)/Population(s)	Treatment of schizophrenia in adults and pediatric patients aged 13 years and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	CTID58214004 | Schizophrenia (disorder) | Pediatric ages 13-17 years old
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of schizophrenia in adults and pediatric patients ages 13 years and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	CTID58214004 | Schizophrenia (disorder) | Pediatric ages 13-17 years old
Recommended Dosing Regimen	The recommended starting dosage for REXULTI for the treatment of schizophrenia in pediatric patients 13 to 17 years of age is 0.5 mg once daily on Days 1 to 4, taken orally with or without food. Titrate to 1 mg once daily on Day 5 through Day 7, then to 2 mg on Day 8 based on the patient's clinical response and tolerability. Weekly dose increases can be made in 1 mg increments. The recommended target REXULTI dosage is 2 mg to 4 mg once daily. The maximum recommended daily dosage is 4 mg.

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See separately archived memos for discipline signatures and electronic signature page for Division Director.

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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AIMS	Abnormal Involuntary Movement Score
AR	adverse reaction
BARS	Barnes Akathisia Rating Scale
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRT	clinical review template
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	data monitoring committee
ECG	electrocardiogram
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
iPSP	initial pediatric study plan
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorder
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPSR	proposed pediatric study request
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 Rating Scale
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Brexpiprazole (OPC-34712, OPC-331, and Lu AF41156; proprietary name "Rexulti") is an atypical antipsychotic co-developed by Otsuka Pharmaceutical Co, Ltd (Otsuka) and H. Lundbeck A/S (Lundbeck). It was approved in 2015 for adjunctive treatment of major depressive disorder (MDD) and treatment of schizophrenia. It is a partial agonist at serotonergic 5-HT1A and at dopaminergic D2 receptors, and antagonist at serotonergic 5-HT2A receptors.

With this submission, the Applicant is seeking to expand the indication for treatment of schizophrenia to pediatric patients ages 13 to 17 years. The proposed dosing regimen is 0.5 mg once daily on Days 1 to 4, followed by titration to 1 mg once daily on Day 5 through Day 7, then to 2 mg on Day 8, followed by weekly dose increases in 1-mg increments based on response and tolerability, with a target dosage of 2 mg to 4 mg once daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Division of Psychiatry has 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. This determination was based on similarity of disease characteristics, similarity of symptomatic changes observed in acute schizophrenia clinical trials in pediatric patients and adults receiving placebo, and 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.

The evidence required to support an indication for the treatment of schizophrenia in pediatric patients that relies on extrapolation consists of:

- An approved indication in adults
- A pharmacokinetic (PK) analysis to determine a dosing regimen that provides similar drug exposures (at levels demonstrated to be effective in adults) in pediatric and adult patients. This analysis requires pharmacokinetic data from both adult and pediatric populations.
- A long-term open-label safety study(ies) in pediatric patients

Brexpiprazole was approved for the treatment of schizophrenia in adult patients in 2015. The current submission includes the required PK analysis demonstrating that similar doses provide similar drug exposures in adult and pediatric patients, as well as 12 months of long-term open-label safety data in patients ages 13 to 17 years. Taken together, these data allow for an approval based on extrapolation of efficacy with pediatric-specific safety information in product labeling.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Brexpiprazole is an atypical antipsychotic approved in 2015 for adjunctive treatment of major depressive disorder and treatment of schizophrenia in adults. In January 2020, the Division of Psychiatry issued a General Advice Letter describing conditions where the Division would extrapolate pediatric effectiveness from approved adult bipolar and schizophrenia indications. Based on this Letter, the Applicant has submitted Supplement 007 to expand their schizophrenia indication to pediatric patients 13 years of age and older. The current submission includes the required PK analysis demonstrating that similar doses provide similar drug exposures in adult and pediatric patients, as well as 12 months of long-term open-label safety data from an ongoing study in patients ages 13 to 17 years.

There were no unexpected, clinically-concerning risks in the pediatric population exposed to brexpiprazole based on the submitted 12-month open-label data. Using the same parameters for abnormal laboratory values as in adult patients, there were no clinically-meaningful differences in rates of adverse reactions. Submitted data suggests that elevated prolactin levels were common among adolescent patients; however, because the Applicant did not provide information on treatment-emergent hyperprolactinemia for rollover subjects, the incidence of increases from normal to high prolactin could not be calculated. Increased blood prolactin is already labeled for brexpiprazole. The Division will issue a postmarketing requirement to submit additional data to enable calculation of adolescent hyperprolactinemia incidence rates. This will inform whether additional pediatric-focused language should be added to labeling.

Taken together, these data allow for an approval based on extrapolation of efficacy with pediatric-specific safety information in product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Schizophrenia is a severe and chronic mental illness affecting approximately 1% of the population. The onset of illness is typically sometime between one's late teens and mid-thirties. This chronic, disabling disease is characterized by abnormal behavior and psychosis. Symptoms are categorized into to positive (e.g., hallucinations and delusions) and negative (e.g., social withdrawal and lack of emotion, energy, and motivation) domains, with most available medications having their predominant effects	Schizophrenia is a severe and debilitating illness. For many patients, existing treatment options are unable to adequately control their symptoms, or may cause intolerable adverse reactions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	on positive symptoms. Although there are a number of approved treatments for this condition, an individual patient may require several trials with different antipsychotic drugs before an effective and reasonably-tolerated treatment is identified.	
Current Treatment Options	Five atypical antipsychotics are approved for the treatment of schizophrenia in pediatric patients ages 13 to 17 years: aripiprazole, lurasidone, paliperidone, olanzapine, quetiapine, and risperidone. Olanzapine is considered second-line treatment given the increased risk of weight gain and dyslipidemia (in adolescents vs. adults). Some of the relevant class safety issues for atypical antipsychotics include extrapyramidal side effects, tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, weight gain, metabolic changes, and blood dyscrasias.	Although there are a number of approved atypical antipsychotics currently on the market, individual patient response to a given antipsychotic cannot be predicted. For an individual patient, several trials of different products are often required before an effective treatment can be identified. There are also some patients for whom an effective treatment has yet to be identified, despite multiple trials. Thus, having additional treatment options is always valuable.
Benefit	Effectiveness is pediatric patients ages 13 to 17 years is based on extrapolation from adult effectiveness.	Brexpiprazole was approved for the treatment of schizophrenia in adult patients in 2015. The current submission includes the required PK analysis demonstrating that similar doses provide similar drug exposures in adult and pediatric patients. Thus, the Applicant has provided the necessary data on which to base extrapolation of effectiveness from adults to pediatric patients ages 13 to 17 years.
Risk and Risk Management	There were no unexpected, clinically-concerning risks in the pediatric population exposed to brexpiprazole based on the submitted 12-month open-label data. Using the same cut-off values for abnormal laboratory values as in adult patients, there were some minor differences in rates of adverse reactions (such as shifts from normal baseline to elevated	Pediatric-specifc rates of adverse reactions were added to labeling. Weight gain was presented in labeling using z-scores to partially account for normal growth.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	glucose and total cholesterol). Generally, the difference in the percentage of patients shifting to abnormal values was similar between adult and pediatric patients. Based on the adverse event data, there may be greater rates of prolactin elevations in pediatric patients compared to adult patients with schizophrenia. However, data on whether prolactin elevations were treatment-emergent were not available for patients that had enrolled in the open-label study from an ongoing double-blind study. Without this data, incidence rates for treatment-emergent hyperprolactinemia in adolescents could not be calculated.	Blood prolactin increased is already labeled as a brexpiprazole adverse reaction. The Division will issue a postmarketing requirement to submit data from the ongoing double-blind study once it is completed. This will allow the Division to determine whether specific pediatric language regarding hyperprolactinemia should be included in labeling.

1.4. Patient Experience Data

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

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	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):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Schizophrenia is a chronic and debilitating illness that has an estimated lifetime adult prevalence of 0.5 to 1%. The onset of illness is typically sometime between one's late teens and mid-thirties. Symptoms are categorized into positive (e.g., hallucinations and delusions) and negative (e.g., social withdrawal and lack of emotion, energy, and motivation) domains, with most available medications having their predominant effects on positive symptoms. According to the DSM-5[1], the diagnostic criteria for schizophrenia are the same for the pediatric and adult populations, but the symptomatology and prevalence of schizophrenia in these two populations have been recognized to be somewhat different. 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 uncommon.[2] Although there are a number of approved treatments for this condition, an individual patient may require several trials with different antipsychotic drugs before an effective and reasonably-tolerated treatment is identified.

Based on the similarity of disease characteristics, similarity of symptomatic changes observed in acute schizophrenia clinical trials in pediatric patients and adults receiving placebo, and on FDA analyses of multiple antipsychotic drugs that demonstrated a similar exposure-response relationship in pediatric and adult patients with schizophrenia, FDA has 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.[3,4] An adolescent schizophrenia program would need to include pharmacokinetic information and safety information in adolescents (13 to 17 years-old) with schizophrenia.

2.2. Analysis of Current Treatment Options

A number of "typical" and "atypical" antipsychotics are currently available for the treatment of schizophrenia. However, only five atypical antipsychotics have been approved for the treatment of schizophrenia in pediatric patients ages 13 to 17 years: aripiprazole, lurasidone, paliperidone, olanzapine, quetiapine, and risperidone. Olanzapine is considered second-line treatment given the increased risk of weight gain and dyslipidemia (in adolescents vs. adults).

[1] American Psychiatric Association. 2013. Diagnostic and statistical manual of mental disorders (5th ed.)
[2] McMlellan et al, J Am Acad Child Adolesc Psychiatry, 2013;52(9):976–990
[3] Kalaria et al, Clin Pharmacol Ther. 2019 Nov;106(5):1046-1055
[4] Kalaria et al, J Clin Pharmacol. 2020 Jul;60(7):848-859

Some of the relevant class safety issues for atypical antipsychotics include extrapyramidal side effects, tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, weight gain, metabolic changes, and blood dyscrasias.

Although there are a number of approved atypical antipsychotics currently on the market, individual patient response to a given antipsychotic cannot be predicted. For an individual patient, several trials of different products are often required before an effective treatment can be identified. There are also some patients for whom an effective treatment has yet to be identified, despite multiple trials. Thus, having additional treatment options is always valuable.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Brexpiprazole was approved in July 2015 for adjunctive treatment of MDD and treatment of schizophrenia. In November 2016, FDA issued a Safety Labeling Change Notification requiring the addition of Falls under the Warnings and Precaution section of the brexpiprazole label; the associated labeling supplement was approved in February 2017. In June 2017, the Applicant submitted a Prior Approval Labeling Supplement to add a new subsection under Warnings and Precautions for Pathological Gambling and Other Compulsive Behaviors; this supplement was approved in February 2018.

3.2. Summary of Presubmission/Submission Regulatory Activity

When brexpiprazole was approved in 2015, the Agency issued several post-marketing requirements (PMRs) under the authority of the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). For schizophrenia, the Agency waived the pediatric study requirement for ages 0 to 12 years because onset of schizophrenia prior to 13 years of age is rare. The Agency granted a deferral for studies in pediatric patients ages 13 to 17 years because the product was ready for approval for use in adults and the pediatric studies had not yet been completed. The required studies for this population included:

2929-1 Deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients aged 13 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing brexpiprazole in the relevant pediatric population.

Final Protocol Submission: 03/2014 (Submitted)
Study/Trial Completion: 05/2016
Final Report Submission: 11/2016

2929-2 Deferred pediatric study under PREA for the treatment of schizophrenia in children aged 13 to 17 years. Conduct a Phase 3, Efficacy: multicenter, randomized, double-blind trial with two phases: Phase 1 - placebo- and active-controlled, short-term (6 weeks) study; Phase 2 – active-controlled long-term extension (26 weeks) study. Goal of both phases is to obtain data on the efficacy and safety of brexpiprazole in the relevant pediatric population.

Final Protocol Submission: 06/2016
Study/Trial Completion: 12/2020
Final Report Submission: 06/2021

2929-3 Deferred pediatric study under PREA for the treatment of schizophrenia in adolescents aged 13 to 17 years. Conduct a Phase 3, Safety: open-label, multicenter, long-term (2 years) study to obtain data on the safety of brexpiprazole in the relevant pediatric population.

Final Protocol Submission: 06/2016
Study/Trial Completion: 12/2022
Final Report Submission: 06/2023

On August 26, 2016, the Applicant requested a deferral extension for PMR 2929-1 because of delays involving study participants, sites, and/or management. The extension was granted on October 8, 2016, with new dates as follows:

Study/Trial Completion: 02/2017
Final Report Submission: 08/2017

On November 10, 2016, the Applicant submitted a Proposed Pediatric Study Request (PPSR). The Agency determined that the PPSR was inadequate because, given that the proposed PPSR did not include a plan (b) (4)

On August 1, 2017, the Applicant submitted the final study report for Study 331-10-233, a phase 1, multicenter, open-label, dose-escalation study to assess the safety, tolerability, and PK of oral brexpiprazole in adolescents. Upon review of the submission, the Agency determined that this submission fulfilled PMR 2929-1 and issued a PMR Fulfillment letter on September 12, 2018.

The Applicant addressed these concerns in a revised PPSR, submitted in December 2017, and the Agency issued a Pediatric Written Request (PWR) on April 19, 2018. The PWR included requests for:

- (b) (4)
-

Because the full study report for a multiple dose safety, tolerability, and PK study in pediatric patients (age 13 to 17 years) with a primary diagnosis of schizophrenia or bipolar disorder had already been submitted in August 2017, the PWR noted that this data would be necessary to inform any pediatric labeling for schizophrenia or bipolar disorder and acknowledged submission of this study report.

On January 13, 2020, the Agency issued a General Advice letter informing the Applicant (and other atypical antipsychotic NDA holders) that the Division of Psychiatry 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

described the information required to support an indication for the treatment of schizophrenia relying on extrapolation. The Applicant subsequently submitted a request to be released from PMR 2929-2, for a modification to PMR 2929-3, and to amend their PWR taking this new approach into account. The Agency released PMR 2929-2 and, in a separate communication, released PMR 2929-3 and issued new PMR 2929-5:

2929-5 Deferred pediatric study under PREA for the treatment of schizophrenia in adolescents aged 13 to17 years. Conduct a Phase 3, Safety: open-label, multicenter, long-term (1 year) study with at least 100 patients exposed for at least 6 months to obtain data on the safety of brexpiprazole in the relevant pediatric population.

Final Protocol Submission: 06/2016
Study Completion: 03/2021
Final Report Submission: 09/2021

The PMR release for 2929-2 and the release and reissue for 2929-3/2929-5 letters were sent on June 18, 2020; the revised PWR was issued on June 29, 2020.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Because the evaluation of efficacy under this supplement is based on extrapolation, there are no clinical efficacy studies. Therefore, no clinical study site inspections were requested. Two sites were selected for biopharmaceutical inspections; however, the Office of Study Integrity and Surveillance determined that inspections were not warranted at this time for both sites (see 15.3.2 and 15.3.3 for details).

4.2. Product Quality

No new product quality information was submitted with this supplement.

4.3. Clinical Microbiology

No new microbiology information was submitted with this supplement.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

For this NDA submission, the Applicant did not submit any new nonclinical studies. The Applicant submitted two Juvenile Animal Studies in rats and dogs (Report # 023805 and 024102) to INDs 101871 (SDN 82), 103958 (SDN 43), and 106158 (SDN 16), for the indications of schizophrenia, major depressive disorder, and attention deficit hyperactivity disorder, respectively, on December 8, 2009. Although appropriately conducted and reviewed (generally the results did not show safety concerns), these juvenile animal studies are not relevant to the current NDA submission, as the Division of Psychiatry does not routinely require juvenile animal studies to support clinical studies if the intended patient population is 13 years of age or older. Therefore, information from these studies was removed from section 8.4 of the label as they are not relevant for the new proposed patient population.

6 Clinical Pharmacology

6.1. Executive Summary

In this efficacy supplement, the Applicant is seeking approval for the use of brexpiprazole in the treatment of schizophrenia in pediatric patients aged 13 to 17 years. No clinical efficacy data in the pediatric population are included to support this supplemental application. Efficacy of brexpiprazole in the adolescent population is extrapolated from that in adult patients.

The extrapolation strategy is described in the Agency's General Advice Letter dated January 13, 2020, which states:

> The Division of Psychiatry has 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 or older...the following will be required to support an indication for the treatment of schizophrenia ... in pediatric patients that relies on extrapolation:
>
> - An approved indication in adults
> - A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposures (at levels demonstrated to be effective in adults) in pediatric and adult patients. This analysis will require pharmacokinetic data from both the adult and pediatric populations
> - A long-term open label safety study(ies) in pediatric patients

The Applicant submitted a full interim report from a single open-label safety study in adolescent patients 13 to 17 years old with schizophrenia (Study 331-10-236) and two phase 1 PK studies in pediatric patients (Study 331-10-233 in adolescents and Study 331-201-00103 in children 6 to 12 years old) to support extrapolation of a schizophrenia indication from adult to adolescent patients. In addition, PK simulations using an established population PK model in adults, children, and adolescents were conducted to determine a pediatric dosing regimen that provides similar drug exposure in adolescent and adult patients.

6.2. Summary of Clinical Pharmacology Assessment

A request to inspect the PK study in adolescents (Study 33110-233) was sent to the Office of Study Integrity and Surveillance (OSIS). Per OSIS memo (See Appendices in Section 18.4) inspection of the study is not warranted at this time.

The Office of Clinical Pharmacology (OCP)/Division of Neuropsychiatric Pharmacology (DNP) have reviewed the submission and determined that, from a clinical pharmacology perspective, the submitted data support approval of brexpiprazole for the treatment of schizophrenia in pediatric patients aged 13 to 17 years old.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Brexpiprazole is a partial agonist of serotonin 5-HT1A and dopamine D2 receptors, and an antagonist of serotonin 5-HT2A receptor. It is mainly metabolized with major involvement of CYP3A4 and CYP2D6. Steady state was reached after 10 to 12 days of once daily administration of brexpiprazole. The mean terminal half-lives were about 91 hours and 86 hours for brexpiprazole and DM-3411, respectively. At steady state, inactive metabolite DM-3411 represents 23-48% of brexpiprazole plasma exposure in adults.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended initial dosage for brexpiprazole in pediatric patients aged 13 to 17 years is 0.5 mg once daily on Days 1 to 4. The dosage can be titrated to 1 mg once daily on Day 5 through Day 7, then to 2 mg on Day 8 based on the patient's clinical response and tolerability. Weekly dose increases can be made in 1-mg increments. The recommended target brexpiprazole dosage is 2 mg to 4 mg once daily. The maximum recommended daily dosage is 4 mg.

Therapeutic Individualization

Same as in currently approved brexpiprazole label.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A multiple-dose PK study has been conducted in pediatric patients 13 to 17 years old. Population PK analysis indicated systemic exposure of brexpiprazole in pediatric patients (13 to 17 years of age) was comparable to that in adult patients after the same dose of brexpiprazole For other information on brexpiprazole PK, refer to currently approved brexpiprazole label.

6.3.2. Clinical Pharmacology Questions

How is the observed brexpiprazole exposure in pediatric patients aged 13 to 17 years old compared to adults following brexpiprazole administration?

Brexpiprazole exposures on Day 14 (steady state) after once daily dosing in adults and adolescents are compiled in **Table 1** for PK evaluable population (subjects who reached steady state per Applicant's criteria: deviation of C_{24hr} trough concentration on Day 14 of the fixed dose period within (b) (4)% of the predose concentration). As shown in **Table 1** and **Figure 1**, after

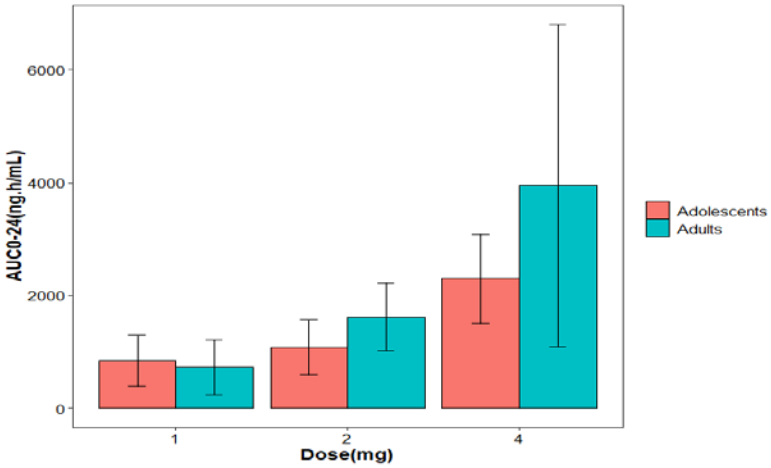
same dose administration, compared to adults, brexpiprazole mean exposure (AUC) in adolescent patients were ~16% higher at 1-mg dose level, while exposures at 2 mg and 4 mg were lower, ~33% and 42%, respectively. However, it is noted that though mean exposure of brexpiprazole AUC in adolescents were numerically different from the adult data, the ranges of exposure in adolescents were generally within those in adults after the same dose administration.

Table 1: Brexpiprazole PK Parameters (Mean [SD]) After 14 days Once Daily Dosing (PK Evaluable Population)

Adults			
Dose (mg)	Cmax,ss (ng/mL)	Cmin,ss (ng/mL)	AUCtau(hr*ng/L)
1 (n=12)	39.2 (26.0)	21.2 (10.9)	728 (493)
2 (n=6)	81.2 (28.3)	56.8(23.0)	1620 (594)
4 (n=5)	199 (134)	112(75.3)	3950 (2860)
Adolescents			
0.5 (n=2)	35.1	20.9	597
1 (n=5)	46.4 (21.4)	29.1 (17.3)	841 (455)
2 (n=4)	63.0 (26.0)	33.3 (17.4)	1080 (489)
4 (n=7)	129 (43.7)	80.1 (31.0)	2300 (793)

Source: adult data Study 331-08-205 (Table PK-1.1.1 in study 233 CSR); adolescent data Study 331-10-233 (Tables PKT-4.1 to PKT-4.5 in study 233 CSR)

Figure 1: AUC Comparison (PK evaluable population)



Source: Adult data Study 331-08-205; adolescent data Study 331-10-233

The inter-subject variability (**Table 2**) of brexpiprazole exposure (AUC_{24hr}) appears to be high in both adults (mean %CV ~59%) and adolescents (mean %CV ~45%). There are several factors that may contribute to the observed large variability:

1) The small sample size in each dose cohort (n=4-6, except adults 1 mg n=12).
2) Adult subjects were all inpatients during the study; for the adolescent study, only subjects in Cohorts 4 and 5 were dosed as inpatients and other subjects were dosed as

outpatients. There might be some medication compliance issues associated with these outpatients.

3) The large variability in CYP2D6 genotype status in adults (from ultrarapid CYP2D6 metabolizer identified in adults to CYP2D6 poor metabolizers in both age groups).
4) A broad body weight range: adolescents (43 to 116 kg) and adults (60 to 120 kg).

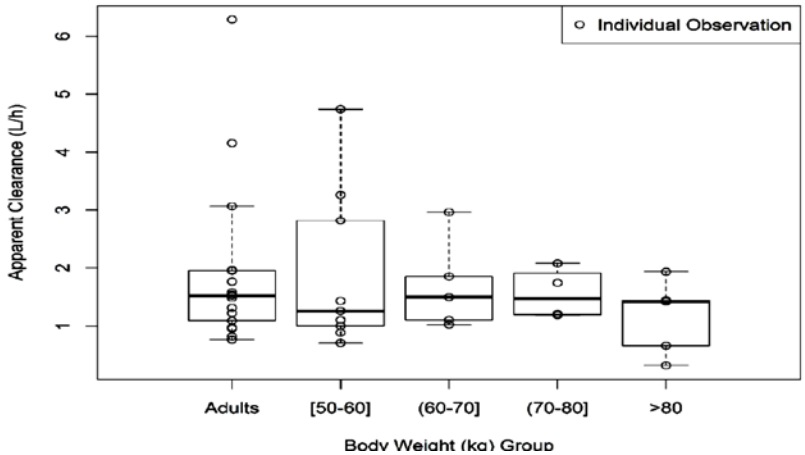
Table 2: Inter-Subject Variability (% CV) for AUC_{24hr} at Steady State (PK Evaluable Population)

	1 mg	2 mg	4 mg
Adults	67.7% (n=12)	36.7% (n=6)	72.4% (n=5)
Adolescents	54.1% (n=5)	45.2% (n=4)	34.4% (n=7)

Source: Study 331-08-205 and Study 331-10-233.

In addition, no significant difference was observed in the apparent clearance (CL/F) in the adult population versus adolescent population with different body weight groups (**Figure 2**).

Figure 2: Apparent Clearance in Adults *vs.* Adolescents by Body Weight Groups



Source: PKF-15 CSR 331-10-233; analysis dataset from Study 331-08-205 and Study 331-10-233

For the major inactive metabolite DM-3411, steady state circulation level was about 35%, 67%, and 43% of the parent at dose levels 1 mg, 2 mg, and 4 mg, respectively, in adolescent patients. In adults, DM-3411 represented 23% to 48% of brexpiprazole AUC at steady-state (brexpiprazole label). After same dose administration, at 1 mg, comparable circulation levels were observed between the two age groups, while at 2 mg and 4 mg dose levels, DM-3411 circulated at a higher and lower levels, respectively, compared to adults (**Table 3**).

Table 3: DM-3411 PK Parameters (Mean [SD]) After 14 Days Once Daily Dosing (PK evaluable population)

Adult			
Dose (mg)	Cmax,ss (ng/mL)	Cmin,ss (ng/mL)	AUCtau(hr*ng/L)
1 (n=12)	15.2 (8.76)	-	299 (170)
2 (n=6)	17.3(2.92)	-	374 (65.7)
4 (n=5)	64.3 (28.4)	-	1280 (508)
Adolescents			
1 (n=5)	14.7 (5.1)	10.5 (4.57)	295 (113)
2 (n=4)	36.9 (14.4)	22.7 (12.7)	720 (333)
4 (n=7)	53.4 (14.8)	34.6 (9.25)	998 (263)

- : not available
Source: Adult data Study 331-08-205 (Table PK-1.1.1 in study 233 CSR); adolescent data Study 331-10-233 (Tables PKT-4.1 to PKT-4.5 in study 233 CSR)

Overall, there appears to be no significant difference in exposure range between adults and adolescents after the same dose administration of brexpiprazole. Compared to adults, brexpiprazole mean exposure in adolescent patients was ~16% higher at 1-mg dose level, while exposures at 2 mg and 4 mg were lower, ~33% and 42%, respectively. Large intersubject variability due to factors like sample size, CYP2D6 genotype, body weight range, and medication compliance issues may contribute to the observed inconsistency in PK exposures between dose groups and between age groups following brexpiprazole administration.

Individual review of Study 331-10-233 including associated bioanalytical methods will be checked into DARRTS after the Multidisciplinary Review and Evaluation is archived.

Does the clinical pharmacology program provide supportive evidence of effectiveness? Is the proposed dosing regimen appropriate for adolescents for which the indication is being sought?

Yes. The clinical pharmacology program provides supportive evidence of effectiveness for brexpiprazole in the treatment of schizophrenia in adolescent patients, and the proposed dosing regimen appears appropriate.

Efficacy of brexpiprazole in the adolescent population aged 13 to 17 years is extrapolated from that in adult subjects according to the Agency's General Advice Letter dated January 13, 2020. The Applicant conducted two phase 1 PK studies in pediatric patients (Study 331-10-233 in adolescents and Study 331-201-00103 in children 6 to 12 years old) to support efficacy extrapolation. Although the sample size of the phase 1 studies is limited and the inter-subject variability is high, the observed data indicate that there is no significant difference in the exposure range of brexpiprazole between adults and adolescents after the same dose administration.

In addition, the Applicant has conducted a population PK model to compare the PK of brexpiprazole in adults and pediatric subjects aged 13 to 17 years. Briefly, the population PK model was developed from a dataset of 3674 evaluable plasma concentrations from 161 subjects enrolled in five clinical studies. The population PK model was able to describe PK of brexpiprazole in both adult and pediatric population, and the PK simulations indicated the exposure at steady state were comparable between adolescents and adults based on proposed dosing regimen.

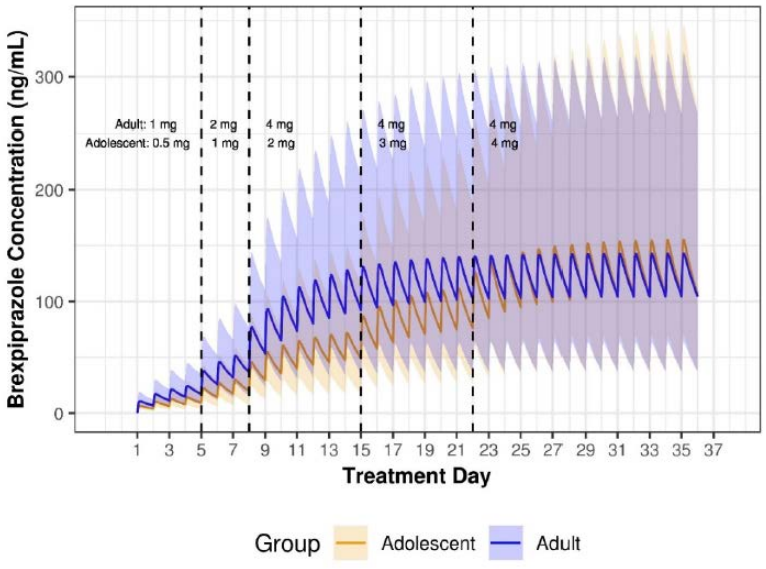
In the initiation of therapy, a lower starting dose and a slower titration schedule are proposed for adolescent patients to improve tolerability, compared to the approved dosing regimen in adults (**Table 4**). Following the respective titration schedules, PK profiles (median (90% prediction interval)) are simulated in adolescents and adults (**Figure 3**).

Table 4: Titration Schedule for Adults and Proposed Titration Schedule for Adolescents Aged 13-17 Years

Treatment Day	Adult	Adolescents
Day 1-4	1 mg / day	0.5 mg / day
Day 5-7	2 mg / day	1 mg / day
Day 8 (and onwards)	4 mg / day (based on patient response and tolerability, the recommended target dose is 2-4 mg / day, maximum dose is 4 mg / day)	2 mg / day (based on patient response and tolerability; weekly dose increases can be made in 1 mg increments. The maximum recommended daily dosage is 4 mg.)

Source: Applicant's Response to Clinical Pharmacology information request dated 10/22/2021, Page 8, Table 3

Figure 3: Median (5th-95th Percentile) Simulated PK Profile for Adults and Adolescents Aged 13-17 Years Following the Proposed Titration Schedule

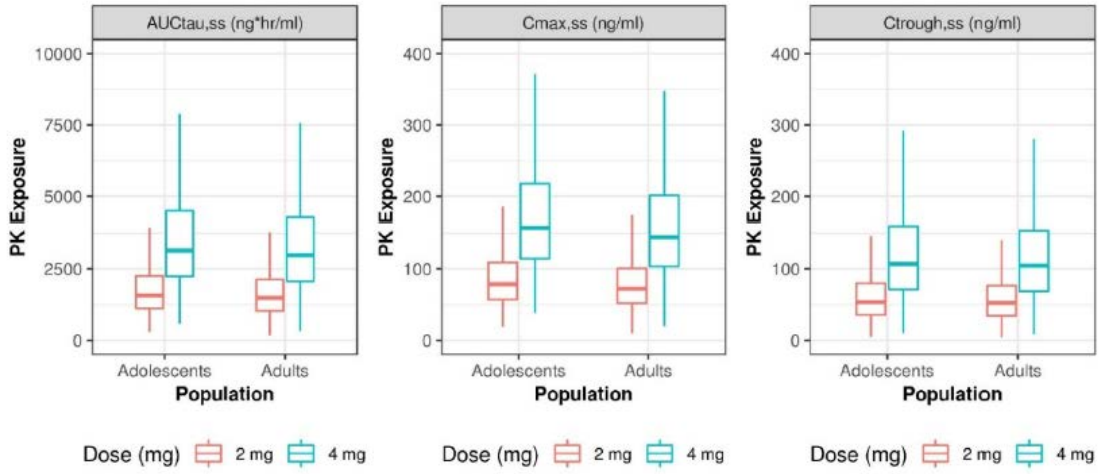


Source: Applicant's Response to Clinical Pharmacology information request dated 10/22/2021, Page 8, Figure 7

Because of a lower starting dose and a slower titration schedule, it takes longer for adolescents to reach the maximum 4-mg dose. The simulation results (**Figure 3**) indicate that during the titration phase, brexpiprazole concentrations would be lower in adolescents compared to adults. A decreased exposure may yield a better tolerability profile in adolescent patients. In addition, studies from adult patients suggest that the full antipsychotic effect of brexpiprazole may not be evident for a few weeks even after steady state exposures have been reached. Therefore, overall, the proposal titration scheme is adolescent patients seems appropriate.

At steady state, based on simulation results, PK exposure metrics ($AUC_{tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$) following daily doses of brexpiprazole (2 and 4 mg) seem comparable between adults and adolescents (**Figure 4**). Therefore, similar pharmacological effects are expected between these two patient populations.

Figure 4: PK Exposure at Steady State following Daily Dose of Brexpiprazole 2 and 4 mg for Adults and Adolescents Aged 13-17 Years



Source:Adapted from Applicant's Response to Clinical Pharmacology information request dated 10/22/2021, Page 9, Figure 8

Overall, the Applicant's proposed starting and maintenance doses in adolescent patients appear acceptable. Please refer to Pharmacometric Review for more details.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

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Table 5: Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow-Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety								
331-10-236 (Ongoing[a])	03238326	Open-label	Daily oral brexpiprazole: 1 mg 2 mg 3 mg 4 mg	Safety	24 months (only 12-month data submitted for review)	Rollover from ongoing efficacy and safety study[b]: 122 with 6-mo data 88 with 12-mo data De novo enrollees: 18 with 6-mo data 0 with 12-mo data	Ages 13 to 17 years, diagnosed with schizophrenia	7 centers including in the U.S., Serbia, Ukraine, Mexico, Romania, Poland, Spain
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
see Section 6: *Clinical Pharmacology*								

[a] Study 331-10-236 is being conducted for 24 months (b) (4).
[b] Study 331-10-234 is an ongoing 6-week efficacy and safety study of brexpiprazole, aripiprazole, and placebo being conducted (b) (4).
Source: Clinical Supervisor Created

7.2. Review Strategy

The Applicant submitted NDA 205422, S07 to expand their approval for the treatment of schizophrenia in adults to adolescents 13 years of age and older. The Applicant has satisfied the requirements for submitting a pediatric supplement based on extrapolation as per the Division's January 2020 General Advice Letter:

- A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposures (at levels demonstrated to be effective in adults) in pediatric and adult patients

- A long-term open label safety study(ies) in pediatric patients

The Office of Clinical Pharmacology has reviewed the Applicant's pharmacokinetic data and has determined that extrapolation of brexpiprazole's efficacy from adults to adolescents is appropriate (see Section 6: *Clinical Pharmacology*). The Applicant also submitted 12-month open-label safety data from ongoing Study 331-10-236 for pediatric patients 13 years of age and older with schizophrenia. This data was reviewed to identify safety differences between the adult and pediatric populations for a benefit-risk analysis and for labeling.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Agency's conclusion on effectiveness is based on extrapolation from adults. However, to support the proposed indication for treatment of schizophrenia in pediatric patients, the Applicant submitted long-term open-label safety data. That study is described below.

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8.2. Review of Safety

8.2.1. Safety Review Approach

Important safety concerns associated with brexpiprazole in adults include neuroleptic malignant syndrome, tardive dyskinesia, hyperglycemia, dyslipidemia, weight gain, orthostatic hypotension, and extrapyramidal symptoms. The available data from Study 331-10-236 were examined for these safety concerns as well as novel safety signals.

The safety review focused on the following data:

- Study 331-10-236 interim study report and 120-day safety update and submitted datasets for adverse events, laboratory measures, and vital signs
- Study 331-10-234 interim synopsis and narratives for all deaths, serious adverse events (SAEs), and treatment-emergent adverse events (TEAEs) leading to discontinuation

8.2.2. Study 331-10-236

Trial Design

Study 331-10-236 is a long-term (24-month), multicenter, single-arm, open-label trial designed to examine the long-term safety and tolerability of brexpiprazole in patients ages 13 to 17 years with schizophrenia. This study is ongoing, so the Applicant submitted an interim study report.

Subjects could enter Study 331-10-236 upon completion of the short-term double-blind Study 331-10-234, or as *de novo* participants. Study 331-10-234 is also ongoing and intended to fulfill a European commitment; it will not be reviewed here. For de novo subjects who did not participate in Trial 331-10-234, the initial diagnosis of schizophrenia for this trial was made and documented, and the diagnosis confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL), at screening. Approximately 350 patients are anticipated to be enrolled.

Rollover subjects from Trial 331-10-234 initiated the first dose of open-label brexpiprazole 1 day after the last dose of double-blind treatment, starting at 0.5 mg/day, increasing to 1 mg/day on Day 5, with an optional increase to 2 mg/day if tolerated on Day 8. If this dose was well tolerated, but the response was inadequate, weekly dose increases could be made in 1-mg increments up to a maximum dose of 4 mg/day, based on the clinical judgment of the investigator. The dose of brexpiprazole could also be decreased based on tolerability in 1-mg decrements.

De novo subjects entered either a conversion period or the open-label treatment period after screening, depending on their current antipsychotic treatment. The conversion period could involve either a washout of prohibited medications or cross-titration. Once monotherapy with brexpiprazole and the washout of prohibited medications was achieved, subjects began the open-label treatment period. De novo patients began brexpiprazole monotherapy dosing of

either 0.5 mg (no conversion) or 1, 2, or 3 mg (after conversion) in the open-label treatment period. De novo patients not requiring conversion followed the same titration schedule as rollover subjects. For all subjects, the maximum dose of brexpiprazole was 4 mg/day.

Study Assessments

The primary endpoints for this trial were the frequency and severity of adverse events (AEs), serious TEAEs (clinical and laboratory), and discontinuation from trial due to AEs.

The following assessments were included as secondary safety endpoints:

- Mean change from baseline and incidence of clinically significant abnormalities in clinical laboratory tests and urinalysis results (including fasting blood lipids, glucose and insulin, serum prolactin, glycosylated hemoglobin (HbA1c) and creatine phosphokinase (CPK)), vital signs (supine and standing positions), weight, height, body mass index (BMI), waist circumference, and ECG parameters
- Mean change from baseline on the Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), and Barnes Akathisia Rating Scale (BARS)
- Analysis of potential suicidal ideation and behavior events recorded on the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Comprehensive psychotropic side effects as assessed by Udvalg for Kliniske Undersogelser (UKU) side effect rating scale
- The frequency of symptom items for the clinician-administered New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT)
- Baseline and postbaseline Tanner Staging Scale data
- Time to discontinuation due to AE

The Applicant also included the following secondary efficacy endpoints:

- Change from baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score and the Positive and Negative Subscale Scores
- Change from baseline in the Children's Global Assessment Scale (CGAS) Score
- Clinical Global Impression Severity (CGI-S) scale
- Clinical Global Impression Improvement (CGI-I) scale

Protocol Amendments

A protocol modification was implemented on June 16, 2020, in response to the COVID-19 pandemic. This modification included a provision for telehealth visits and guidance for recording protocol deviations, AEs, and discontinuations due to COVID-19.

Compliance with Good Clinical Practices

The Applicant asserts that this trial was conducted in compliance with Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no

trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the Institutional Review Board or Independent Ethics Committee at each respective trial center.

Protocol Violations/Deviations

There were 155 protocol deviations as of the data cutoff, 110 (71.0%) of which were related to COVID-19, mainly due to remote assessments. Eighty-nine (52.7%) of the enrolled subjects had at least one major protocol deviation, 73 (43.2%) had at least one COVID-related protocol deviation, and 39 (23.1%) had at least one protocol deviation that were not related to COVID-19 (PDEV-2). A summary of protocol deviations is presented in Table 6, below.

Table 6. Summary of Major Protocol Deviations by Type of Deviation

Deviation Classification	**Rollover** (N=149) n (%)	**De Novo** (N = 20) n (%)
Any Deviation	88 (59)	1 (5)
Entry Criteria	3 (2)	0
Procedural Deviations	74 (50)	1 (5)
Dosing	15 (10)	0
Prohibited Medications	12 (8)	0

Source: Adapted from Table 10.2-1, Study 331-10-236 interim study report

Table of Demographic Characteristics

Table 7 presents the baseline and demographic characteristics of subjects enrolled in Study 331-10-236 as of the data cutoff for NDA submission. Subjects appear reasonably representative of the U.S. population generally and the population of adolescents with schizophrenia in particular in terms of sex and age. With regard to race, white patients are over-represented.

Table 7: Demographics and Baseline Characteristics, Study 311-10-236

Demographic Parameters	Rollover (N=149) n (%)	De Novo (N=20) n (%)	Total (N=169) n (%)
Sex			
Male	69 (46)	11 (55)	80 (47)
Female	80 (54)	9 (45)	89 (53)
Age			
Mean years (SD)	15.6 (1.5)	15.5 (1.0)	15.6 (1.4)
Median (years)	16.0	16.0	16.0
Min, max (years)	13, 18	13, 17	13, 18
Race			
White	117 (79)	18 (90)	135 (80)
Black or African American	10 (7)	1 (5)	11 (6.5)
Asian	1 (<1)	0	1 (<1)
American Indian or Alaska Native	1 (<1)	0	1 (<1)
Native Hawaiian or Other Pacific Islander	0	0	0
Other[1]	20 (13)	1 (5)	21 (12)
Ethnicity			
Hispanic or Latino	27 (18)	1 (5)	21 (12)
Not Hispanic or Latino	122 (82)	19 (95)	141 (83)

Source: Adapted from Table 11.2-1, Study 331-10-236 interim study report

8.2.3. Review of the Safety Database

Overall Exposure

Safety data were submitted for one open-label study in pediatric patients with schizophrenia: Study 331-10-236. See section 8.1.1. for a description of Study 331-10-236. There are 194 patients included in the safety population, which was defined as all subjects who had received at least one dose of study drug.

Table 8: Subject Disposition Study 331-10-236 Safety Population

Disposition	Rollover (N=174)	De Novo (N= 20)	Total (N=194)
Treated	174	20	194
Completed	39	0	39
Discontinued	38	2	40

Source: Reviewer-generated from ADSL dataset SN0402

The duration of exposure and mean average daily dose range are summarized below.

Table 9: Duration of Exposure and Mean Daily Dose Study 331-10-236

	≥ 4 weeks	≥ 3 months	≥ 6 months	≥ 12 months
	N (%) mean average daily dose	N (%) mean average daily dose	N (%) mean average daily dose	N (%) mean average daily dose
Rollover	N=165 (95) 2.2 mg/day	N=142 (82) 2.6 mg/day	N=122 (70) 2.8 mg/day	N=88 (51) 2.8 mg/day
De Novo	N=19 (95) 2.8 mg/day	N=19 (95) 2.9 mg/day	N=18 (90) 3.2 mg/day	--

Source: Table CT-4.1 120 Day Safety Update

Adequacy of the safety database:

A total of 140 pediatric patients were exposed to brexpiprazole for at least 6 months; 88 patients were exposed to brexpiprazole for at least 12 months. In the context of the known, well-characterized safety profile in adults, these exposures are adequate to evaluate the safety of this product in this pediatric population. The mean average daily dose range is within the currently recommended dose range of brexpiprazole for adults with schizophrenia.

8.2.4. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The application was submitted in eCTD format in both ADAM and SDTM data were provided. The submission is of acceptable quality.

Categorization of Adverse Events

As required by FDA Data Standards, the Applicant provided AEs that were coded in MedDRA. The Applicant reported using MedDRA version 23.1. For accuracy, the coding of verbatim terms to dictionary-derived terms was checked. In addition, categorization of adverse events was also reviewed with adjustments made as appropriate. TEAEs were defined as events newly occurred or worsening from the time of the drug's first dose.

Routine Clinical Tests

The Applicant has included adequate clinical assessments and tools for Study 331-10-236. These include documentation of AEs, extrapyramidal effects (EPS), physiological monitoring of weight and metabolism, additional medical monitoring via vital signs, ECG and laboratory tests. In addition, the Applicant administered the Simpson-Angus Rating Scale (SAS) for EPS, the Barnes Akathisia Rating Scale (BARS) for akathisia and the Abnormal Involuntary Movement Score (AIMS) for dyskinesia, the Udvalg for Kliniske Undersogelser (UKU) psychotropic side effect scale, the New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT), the Tanner Staging Scale, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

8.2.5. Safety Results

Deaths

There were no deaths.

Serious Adverse Events

SAEs were reported for seven subjects. There were ten events: one each of abnormal sensation in eye, pilonidal cyst, psychomotor hyperactivity, suicidal ideation, and two each of psychotic disorder, schizophrenia, and suicide attempt. All SAEs except the pilonidal cyst appear to be associated with the condition being treated and none appear to have been caused by the study drug.

Dropouts and/or Discontinuations Due to Adverse Effects

A total of six TEAEs that led to discontinuation were reported in three subjects: positive cannabis drug screen, hyperpituitarism, weight increased, agitation, schizophrenia, and suicide attempt. Of these, one subject had weight gain and hyperpituitarism (elevated prolactin and thyroid stimulating hormone) that could be related to the study drug and one subject had agitation that could be related to study drug but there was inadequate information provided by the Applicant to make a thorough causality assessment for these events.

Significant Adverse Events

Extrapyramidal Symptoms

Adverse events of particular interest to an antipsychotic drug were those associated with extrapyramidal symptoms (EPS). The Applicant reported that 15 subjects (8%) had EPS-related AEs based on the MedDRA preferred terms akathisia, psychomotor hyperactivity, dystonia, muscle rigidity, muscle spasms, bradykinesia, extrapyramidal disorder, and tremor. Using the EPS systemized MedDRA query (SMQ) to summarize the AEs in the analysis dataset, there were 21 subjects (11%) who had an EPS-associated AE.

Table 10: EPS-associated TEAEs during open-label treatment Study 331-10-236 (safety population)

Preferred Term	N=194 n
Akathisia	8
Bradykinesia	1
Drooling	1
Dystonia	1
Extrapyramidal disorder	1
Muscle rigidity	3
Muscle spasms	1
Musculoskeletal stiffness	1
Oculogyric crisis	4
Psychomotor hyperactivity	1
Restlessness	1
Tremor	1

Source: reviewer-generated from ADAE dataset SN0402

There were no TEAEs related to dysphagia, neuroleptic malignant syndrome, or orthostasis.

The current labeling describes the risk for EPS and notes that dystonia is more frequent in younger individuals and males. The subjects who had TEAEs in the dystonia SMQ were balanced between males and females and were balanced across the age range studied.

Treatment Emergent Adverse Events and Adverse Reactions

The majority of adverse events reported from these studies were mild intensity, with a lesser number of moderate events. Most events were typical of those generally observed following the administration of brexpiprazole. As shown in the table below, increased weight, headache, and somnolence occurred in 10% of subjects. Anxiety, insomnia, and irritability topped the relatively small list of psychiatric disorder AEs with incidences of 3 to 4%.

Table 11: TEAEs that occurred in at least 5% of subjects in Study 331-10-236

Study 331-10-236	(N= 194)
	N (%)
Subjects with any TEAE	112 (58)
Weight increased	20 (10)
Headache	20 (10)
Somnolence	20 (10)
Nasopharyngitis	12 (6)

Source: CT-5.2.2.1 SN0402

Laboratory Findings

The risk of metabolic syndrome is a known class safety issue with atypical antipsychotics. The lab values used in the criteria for metabolic syndrome in adolescents are high fasting glucose, low fasting HDL, and high fasting triglycerides. There were 37 subjects who had a shift from normal (<100 mg/dL) to high (100 mg/dL or greater) fasting glucose (22% of subjects with baseline and post-baseline data), 31 subjects who had a shift from normal to low HDL (40 or higher to <40 mg/dL for males and 50 or higher to <50 mg/dL for females) (17% of subjects with baseline and post-baseline data), and 38 subjects who had a shift from normal to high triglycerides (<150 mg/dL to ≥150 mg/dL) (21% of subjects with baseline and post-baseline data) during the study.

In the current prescribing information (PI), the criteria for describing shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) or borderline (≥100 and <126 mg/dL) to high are different than those used in the criteria for metabolic syndrome in adolescents[5] and the normal reference range for fasting glucose. The Applicant has proposed to include the incidence of increases from normal to high using the same definitions as those in the approved labeling in adults, which yields an incidence of 2.7%.

Similarly, the triglycerides in the PI are defined as high when they reach 200 mg/dL or higher rather than 150 or higher. When these cutoffs are used, the incidence of increases from normal to high triglycerides is 13%. The definition for low HDL used was <40 mg/dL for both males and females, which yields an incidence of decreases from normal to low of 13%.

There were two treatment-emergent abnormal lab values with potential clinical relevance related to liver function: one subject with elevated bilirubin that resolved on subsequent measurement and one elevated alanine aminotransferase (ALT) at early termination with no subsequent values measured. There were no Hy's Law cases identified from the laboratory data.

There were two adverse events associated with elevated prolactin in two subjects: hyperpituitarism, which led to treatment discontinuation in one subject and galactorrhea in one subject. Fifty-nine (32%) subjects had a high prolactin of potential clinical relevance during the study but the Applicant did not provide information on treatment-emergent hyperprolactinemia for rollover subjects, so an incidence rate of increases from normal to high prolactin cannot be calculated. Increased prolactin is noted in a list of adverse reactions, but incidence is not described in adults in current labeling. As an example, olanzapine, another second-generation antipsychotic, carries a warning for hyperprolactinemia in labeling. The labeling for olanzapine describes a placebo-subtracted incidence of shift to high prolactin in adults of 19% in studies of up to 12 weeks duration and in adolescents of 40% in studies of up to 6 weeks duration.

[5] The International Diabetes Federation Consensus Worldwide Definition of the Metabolic Syndrome

There were no clinically-significant findings in hematological measures, CPK, renal parameters, or urinalyses.

Vital Signs

There were clinically important weight findings, which are discussed in section 8.5.

Based on orthostatic blood pressure measurements done at study visits, 11% of subjects met the criteria for orthostatic hypotension. The Applicant did not document associated symptoms or adverse events with these blood pressure findings.

Although brexpiprazole carries a class warning for body temperature dysregulation, there were no vital sign findings indicative of body temperature dysregulation in these data.

Electrocardiograms (ECGs)

There were no clinically significant events linked with electrocardiogram findings. One subject had an AE of mild tachycardia that resolved without treatment and one subject had an AE of intraventricular conduction defect that was also mild and recovered with no treatment. The Applicant reported the following ECG abnormalities: bradycardia and sinus bradycardia (in two subjects), two subjects with supraventricular premature beat (one subject also had a ventricular premature beat), and one instance each of atrioventricular block, right bundle branch block, and symmetrical t-wave inversion. These findings raise no new safety concerns in this patient population.

QT

Brexpiprazole is not known to prolong QTc interval to any clinically relevant extent. There were no clinically significant events associated with changes in QT intervals on ECG.

Immunogenicity

There were no immunogenicity data submitted in this application.

8.2.6. Analysis of Submission-Specific Safety Issues

Metabolic Syndrome

The Applicant calculated incidence of treatment-emergent metabolic syndrome, defined as meeting three or more of the following at a visit: waist circumference at least 102 cm in males or 88 cm in females, triglycerides of at least 150 mg/dL, HDL of less than 40 mg/dL in males or 50 mg/dL in females, supine systolic blood pressure of at least 130 mmHg and diastolic blood pressure of at least 85 mmHg, fasting glucose of at least 100 mg/dL. Using this definition three of 167 subjects with data or 2% met criteria for treatment-emergent metabolic syndrome.

Weight Gain

The mean change in weight from baseline increased at each subsequent timepoint, with a mean change at Month 6 of 3.2 kg, at Month 12 of 4.4 kg and at Month 24 of 6.1 kg. The mean change from baseline in long-term safety data in adults with schizophrenia is 1.3 kg at Week 26 and 2 kg at Week 52.

In terms of age and gender-adjusted body weight z-scores in the adolescent subjects, the mean change at Month 6 is 0.13, and at Month 12 and 24 is 0.16; 20% of subjects had an increase in z-score of at least 0.5 from baseline at Month 12.

C-SSRS

There was emergence of suicidal ideation in 4.6%, emergence of serious suicidal ideation in 0.5% of subjects, and emergence of suicidal behavior in 1% up to the 120-day update data cutoff. These incidences do not appear unusual for the patient population and the class warning in the approved prescribing information is adequate to describe the risk.

Other clinical safety assessments specific to antipsychotic drugs

No clinically significant changes from baseline were observed in SAS, AIMS, and BARS scores. UKU symptoms reported were all mild to moderate. Overall, the mean change from baseline to last visit in NY-AACENT summary score was reduced and did not reveal evidence of a clinically important change from baseline that could be attributed to brexpiprazole treatment.

8.2.7. Specific Safety Studies/Clinical Trials

No specific safety studies were submitted.

8.2.8. 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. One subject became pregnant during the study and was receiving active medication. The subject voluntarily terminated the pregnancy.

Pediatrics and Assessment of Effects on Growth

There were no reports of disturbed growth or development and there were no signals identified in Tanner Staging Scale assessments.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no reports of overdose, drug abuse, withdrawal, or rebound.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There is extensive experience with brexpiprazole as an adjunctive treatment of major depressive disorder and as primary treatment for schizophrenia in adults in the postmarket setting. Since approval, a warning was added for pathological gambling and other compulsive behaviors. The current language appears adequate for this new patient population and there are no new findings in the current study that warrant changes to the approved labeling.

Expectations on Safety in the Postmarket Setting

Given that even healthy adolescents have difficulty with impulse control, pharmacovigilance in the postmarket setting should include careful monitoring for emergence of new cases or increased severity of compulsive behaviors in this new patient population.

8.2.10. Integrated Assessment of Safety

The exposure numbers in the pediatric population are adequate to assess the long-term safety of the product and the safety assessments are adequate to characterize the safety profile in this new patient population.

There were very few serious adverse events and discontinuations due to adverse events and the major safety findings are consistent with what is known about brexpiprazole.

Eleven percent of subjects who had ARs consistent with extrapyramidal symptoms and the most common adverse reactions were headache, somnolence, and weight increased.

The safety findings were notable for the incidence in treatment-emergent abnormal fasting glucose, dyslipidemia, and clinically significant weight gain. Two percent of subjects met criteria for treatment-emergent metabolic syndrome. These findings warrant adding additional information about these effects specific to the pediatric patient population in the PI.

There were 11% of subjects who met criteria for orthostatic hypotension, which is a known risk of brexpiprazole and is already described in the PI in the Warnings and Precautions section. There were also around 5% of subjects who had emergent suicidal ideation or behavior on the C-SSRS during the study. The current class warning is adequate to communicate the risk.

Based on the laboratory data, there may be greater rates of prolactin elevations in pediatric patients compared to adult patients with schizophrenia. However, data on whether prolactin elevations were treatment-emergent were not available for patients that had enrolled in the

open-label study from an ongoing double-blind study. Without this data, incidence rates for treatment-emergent hyperprolactinemia in adolescents could not be calculated. Blood prolactin increased is already labeled as a brexpiprazole adverse reaction. The Division will issue a postmarketing requirement to submit data from the ongoing double-blind study once it is completed. This will allow the Division to determine whether specific pediatric language regarding hyperprolactinemia should be included in labeling.

Given the postmarket identification of risk of pathological gambling and other compulsive behaviors, routine pharmacovigilance should include monitoring for emergence of new cases or increased severity in this patient population.

8.3. Statistical Issues

Not applicable to this application

8.4. Conclusions and Recommendations

The data submitted are adequate to fulfill the postmarket requirement for long-term safety data in pediatric patients aged 13 to 17 with schizophrenia. Information should be added to the appropriate sections of labeling to reflect the safety findings. Because of these findings in the long-term safety study, the Applicant should be required to submit controlled data from the ongoing study 331-10-234 in a new postmarket requirement to further characterize the risk of hyperprolactinemia in this patient population.

9 Advisory Committee Meeting and Other External Consultations

Because there are several previously approved agents in the atypical antipsychotic class of drugs, the evaluation of the safety data did not reveal particular safety issues that were unexpected for this class, and efficacy is based on extrapolation from adults, this product was not presented at an Advisory Committee.

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10 Pediatrics

Upon initial approval of brexpiprazole in July 2015, the Agency issued the following PMRs relevant to this supplemental application:

2929-1 Deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients aged 13 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing brexpiprazole in the relevant pediatric population.

2929-2 Deferred pediatric study under PREA for the treatment of schizophrenia in children aged 13 to 17 years. Conduct a Phase 3, Efficacy: multicenter, randomized, double-blind trial with two phases: Phase 1 - placebo- and active-controlled, short-term (6 weeks) study; Phase 2 – active-controlled long-term extension (26 weeks) study. Goal of both phases is to obtain data on the efficacy and safety of brexpiprazole in the relevant pediatric population.

2929-3 Deferred pediatric study under PREA for the treatment of schizophrenia in adolescents aged 13 to17 years. Conduct a Phase 3, Safety: open-label, multicenter, long-term (2 years) study to obtain data on the safety of brexpiprazole in the relevant pediatric population.

PMR 2929-1 was fulfilled by Study 331-10-233 (fulfillment letter issued in September 2018), and PMRs 2929-2 and 2929-3 were released in June 2020. PMR 2929-5 was issued in June 2020 in lieu of 2929-3.

2929-5 Deferred pediatric study under PREA for the treatment of schizophrenia in adolescents aged 13 to17 years. Conduct a Phase 3, Safety: open-label, multicenter, long-term (1 year) study with at least 100 patients exposed for at least 6 months to obtain data on the safety of brexpiprazole in the relevant pediatric population.

Final Protocol Submission: 06/2016
Study Completion: 03/2021
Final Report Submission: 09/2021

PMR 2929-5 is fulfilled with this supplement NDA by Study 331-10-236.

Although this supplement includes studies requested under the PWR, it does not fulfill the PWR. Studies in pediatric bipolar disorder and irritability associated with autistic disorder are also required before the PWR can be considered fulfilled.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

New pediatric information will be added to the prescribing information in the following sections:

1. Indication
   - The approved population will be specified for each indication—adults only for adjunctive treatment of MDD; adults and pediatric patients ages 13 years and older for schizophrenia

2. Dosage and Administration
   - Dosing recommendations for pediatric patients added

5. Warnings and Precautions
   - Updated 5.6 Metabolic Changes with data from Study 331-10-236.

6. Adverse Reactions
   - Updated 6.1 to include a brief summary of pediatric data.

8. Pediatric Use
   - Described the conclusion on safety and effectiveness in schizophrenia
   - Retained the statement noting that safety and effectiveness for pediatric patient with MDD has not been established
   - (b) (4) .

12. Clinical Pharmacology
   - A brief summary of the pediatric PK data will be included in Section 12.3.

12 Risk Evaluation and Mitigation Strategies (REMS)

This product is currently approved without a REMS. Because no new issues were identified, a REMS will not be necessary.

13 Postmarketing Requirements and Commitment

Although we will consider the pediatric PMRs under PREA fulfilled, we will issue a new safety PMR under the FDA Amendments Act (FDAAA). The long-term open-label, uncontrolled safety data from study 331-10-236 in pediatric patients with schizophrenia revealed that there was a high incidence of abnormal prolactin values. Controlled safety data from study 331-10-234 will address uncertainties about the incidence of these serious risks and better inform the benefit/risk profile of the drug in the pediatric patient population. The new PMR is as follows:

4205-1 Submit final study report and datasets for ongoing study 331-10-234, a randomized, double-blind, placebo and active-controlled study in pediatric patients (aged 13 to 17) with schizophrenia.

Final Protocol Submission: 06/2016
Study/Trial Completion: 10/2024
Final Report Submission: 04/2025

14 Division Director (Clinical) Comments

The above document reflects my review of this application together with the primary review team.

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15 Appendices

15.1. References

See footnotes throughout document.

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 331-201-00103

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 9 Principle investigators and 58 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 331-10-233

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 13 Principle investigators and 87 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 331-10-236

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 51 Principle investigators and 233 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: 3		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. PHARMACOMETRIC REVIEW

Executive Summary

This document is a review of the Applicant's population pharmacokinetic (PK) analysis report and their response to an information request dated October 22, 2021, which inform dose selection in pediatric subjects aged 13 to 17 years for the treatment of schizophrenia. Additionally, the reviewer conducted an independent analysis to evaluate the adequacy of the Applicant's proposed dosing recommendations in this pediatric population.

Applicant's Analysis

Population PK Analysis

The final PopPK model was developed from a dataset of 3674 evaluable plasma concentrations from 161 subjects enrolled in five clinical studies to quantitatively describe the PK of brexipiprazole and to identify sources of interindividual variability. A nonlinear mixed effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.2.0 (ICON, Maryland) was used for the PopPK analysis.

Table 12: Summary of studies included in the population PK analysis

Protocol	Title	Subject Population	No. of Subjects	Dose
331-07-201(Arm 1)	Phase 1, Randomized, Double-blind, Placebo-controlled Study	Healthy Adults (18-42 yr)	38 (Arm1)	0.2, 0.5, 1, 2, and 4 mg
331-08-205	Phase 1, Multi-center, Randomized, Double-blind, Comparator-controlled Study	Schizoaffective Adults (23-53 yr)	24	1,2, and 4 mg
331-08-206	Phase 1, Open-label, Multiple-dose, Parallel-group Study	Healthy Adults (19-42 yr)	42	0.5,1, 2, and 3mg
331-10-233	Phase 1, Multicenter, Open-label, Dose-escalation Study	Adolescents With Psychiatric Disorders (13-17 yr)	43	0.5-4 mg
331-201-00103	Phase 1, Single-dose, Sequential Cohort, Nonrandomized Crossover	Children and Adolescents with CNS Disorders (6-12 yr)	24	0.75,1.5, and 3 mg

Source: Adapted from applicant's PopPK report 331-18-218, Page 21, Table 3.1.1-1

Table 13: Continuous Covariates by age group and study in the Population PK Development Dataset

Covariate	Subject Group	Mean	Min	Median	Max
Age (years)	Adults	32	30	18	53
	Children and Adolescents	13	6	13	17
	Total	25	6	24	53
Body Weight (kg)	Adults	82.7	59.4	81.1	121
	Children and Adolescents	57.2	20.1	58.1	115
	Total	72.9	20.1	75.4	121
ALT (IU/L)	Adults	26	10	21	88
	Children and Adolescents	16	7	14	55
	Total	22	7	18	88
eGFR* (mL/min)	Adults	105	72.6	104	170
	Children and Adolescents	192	88.8	182	437
	Total	139	72.6	118	437

*eGFR was derived using the MDRD Formula using creatinine in mg/dL:
$eGFR=186 \times Serum\ Creatinine^{-1.154} \times Age^{-0.203} \times (1.210 \text{ if Black}) \times (0.742 \text{ if Female})$

Source: Applicant's PopPK report 331-18-218, Page 30, Table 4.1.2-1

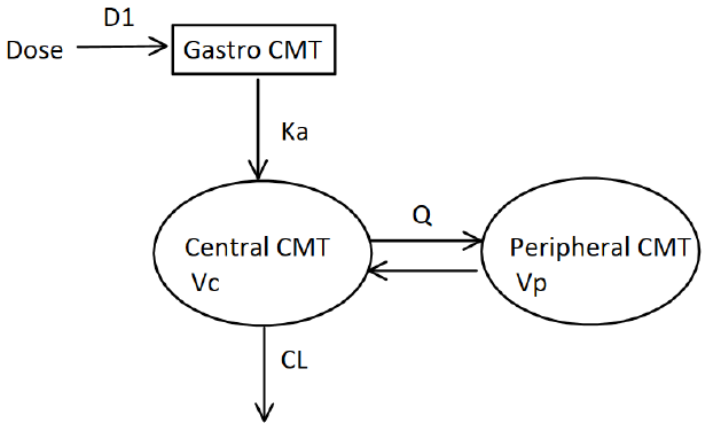
Table 14: Categorical Covariates by study in the Population PK Development Dataset

Covariate	Category	Adults (n=99)	Children and Adolescents (n=62)	Total (n=161)
Gender	Male	94 (95%)	38 (61%)	132 (82%)
	Female	5 (5%)	24 (39%)	29 (18%)
CYP2D6 Metabolic Status	Intermediate	10 (10%)	24 (39%)	34 (21%)
	Extensive	88 (89%)	29 (47%)	117 (73%)
	Unknown	1 (1%)	9 (15%)	10 (6%)
Race	Caucasian	66 (67%)	30 (48%)	96 (60%)
	Black	29 (29%)	32 (52%)	61 (38%)
	Asian	3 (3%)	0 (0%)	3 (2%)
	other	1 (1%)	0 (0%)	1 (<1%)

Source: Applicant's PopPK report 331-18-218, Page 30, Table 4.1.2-2

The PK of brexpiprazole was best described by a two-compartment model with sequential zero-first-order absorption and linear elimination, as illustrated in **Figure 5**. The final PK model had clearance and volume of distribution allometrically scaled by body weight (raised to the power of 0.75 for clearance, and 1 for volume of distribution). Impact of age, gender, race, CYP2D6 metabolic status (intermediate versus extensive), ALT, and eGFR on the PK of brexpiprazole were also investigated, but no other covariate was retained in the final PK model. Parameter estimates from the final population PK model are presented in **Table 8**.

Figure 5: Schematics of the final population PK model of brexpiprazole



Source: Applicant's PopPK report 331-18-218, Page 32, Figure 4.3.1-1

Reviewer's Comments: *The applicant's population PK model with standard allometric scaling appears to overpredict the PK profiles of brexpiprazole in pediatric population aged 6 to 17 years (Refer to Reviewer's Analysis for details). Therefore, an information request was sent to the Applicant to consider an alternative PK model, also described as refined PK model in this review, in which weight scaling factors for clearance and volume of distribution were estimated from the available data. The Applicant was asked to provide comparison of these two PK models (i.e., the final PK model and the refined PK model). Additionally, using the refined PK model, comparison of brexpiprazole's PK across age groups (adult and pediatric subjects aged 13 to 17 years) and weight groups (weights <=40kg or >40kg) at the proposed pediatric dose and the approved adult dose was also requested.*

In response to the information request dated October 22, 2021, the Applicant evaluated the refined PK model and provided various model diagnostics to compare the final PK model with the refined PK model including PK parameter estimates (**Table 8**) and pcVPCs (**Figure 6**). Their analysis shows similar parameter estimates for both PK models except for weight effects. The pcVPC plot comparison indicates that the refined PK model is better in describing the PK of brexpiprazole in pediatric subjects 6 to 17 years of age, especially subjects aged 6 to 12 years. Based on all the diagnostics, the Applicant concluded the population prediction of the refined model is slightly better compared with the current model; however, the overall goodness of fit and predictability in adolescents for the current model and the refined model are comparable.

Reviewer's Comments: *Both the final PK model and refined PK model appeared reasonable when describing the PK data of the target population (i.e., adolescent subjects aged 13 to 17 years. The dose recommendations for this age group based on either of these PK model should be similar. However, considering the inadequacy of the final PK model in describing the PK of pediatric subjects aged 6 to 12 years, the reviewer considered the refined PK model of brexpiprazole as a better PK model to predict PK exposures in pediatric subject aged 13 to 17 years.*

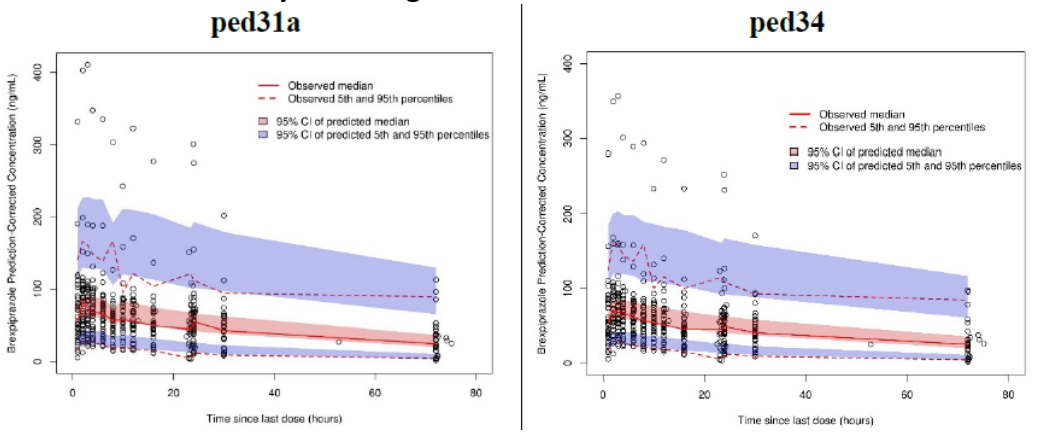
Table 15: Parameter Estimation for Current Final Model (ped31a) and Refined Model (ped34)

Parameter	Definition	Estimate (RSE %) of ped31a	Estimate (RSE %) of ped34
Fixed Effects			
D1 (mg/hr)	Rate of dose into oral absorption compartment	0.931 (5%)	0.925 (5%)
Ka (1/hr)	Oral first-order absorption rate constant	1.49 (7%)	1.47 (6%)
CL (L/hr)	Apparent clearance for subjects who are not poor or ultra- rapid CYP2D6 metabolizers	1.34 (5%)	1.33 (4%)
Vc (L)	Apparent central volume of distribution	78.0 (3%)	77.6 (3%)
Q (L/hr)	Inter-compartmental clearance	0.844 (18%)	0.831 (13%)
Vp (L)	Volume of distribution in Peripheral compartment	27.5 (11%)	28.4 (6%)
CL_weight	Effect of weight on CL and Q: power for (CL or Q/70)	0.75 (Fixed)	0.207 (56%)
V_weight	Effect of weight on Vc and Vp: power for (Vc or Vp/70)	1 (Fixed)	0.77 (10%)
Random Effect: Inter-Individual Variability CV % (RSE %)			
IIV_D1	IIV on D1	58.7% (17%)	58.4% (14%)
IIV_Ka	IIV on Ka	71.0% (16%)	70.0% (14%)
IIV_CL	IIV on CL	57.1% (15%)	53.1% (15%)
IIV_Vc	IIV on Vc	33.3% (16%)	31.6% (15%)
IIV_Vp	IIV on Vp	48.5% (30%)	48.4% (32%)
Residual Variability Estimate (RSE %)			
Error 1	Proportional residual error	0.034 (14%)	0.034 (12%)
Error 2	Additive residual error	0.003 (542%)	0.004 (275%)
Minimum value of objective function		12910 (reference)	12751 (-32)

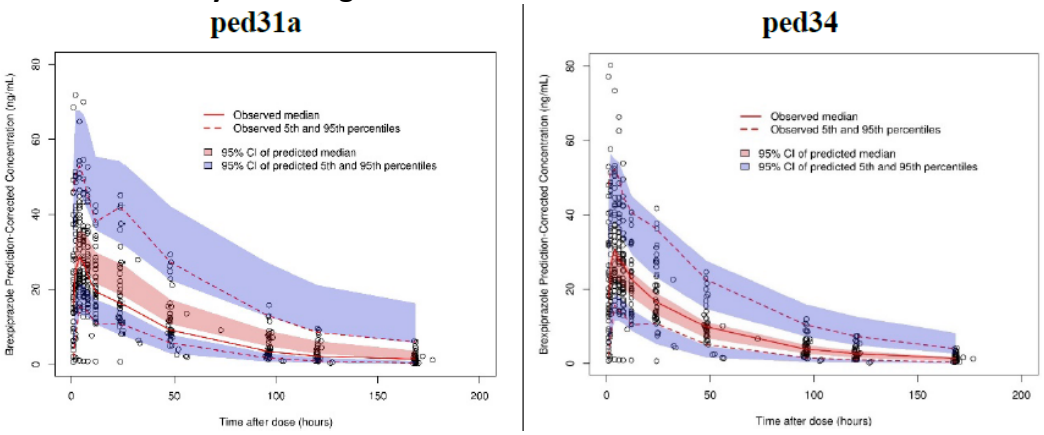
Source: Applicant's Response to Clinical Pharmacology information request dated 10/22/2021, Page 4, Table 1

Figure 6: Prediction corrected VPC for the final (left panel) and refined model (right panel) following multiple daily dosing of brexpiprazole in pediatric subjects 6-17 years of age.

A. Adolescents 13-17 years of age



B. Children 6-12 years of age



Source: Applicant's Response to Clinical Pharmacology information request dated 10/22/2021, Page 3, Figure 3 and 4

PK Simulation for Adolescent and Adult Exposure Matching

The Applicant's refined PopPK model was used to support efficacy extrapolation from adults to adolescents 13 to 17 years of age. The PK simulations were performed to compare adolescents aged 13 to 17 years with adults at the proposed pediatric dose and approved adult doses, respectively (**Table 4**). A virtual population of 2400 pediatric subjects 13 to 17 years of age were generated from the CDC growth chart (n=20/month/gender) using the lambda-mu-sigma (LMS) methods.

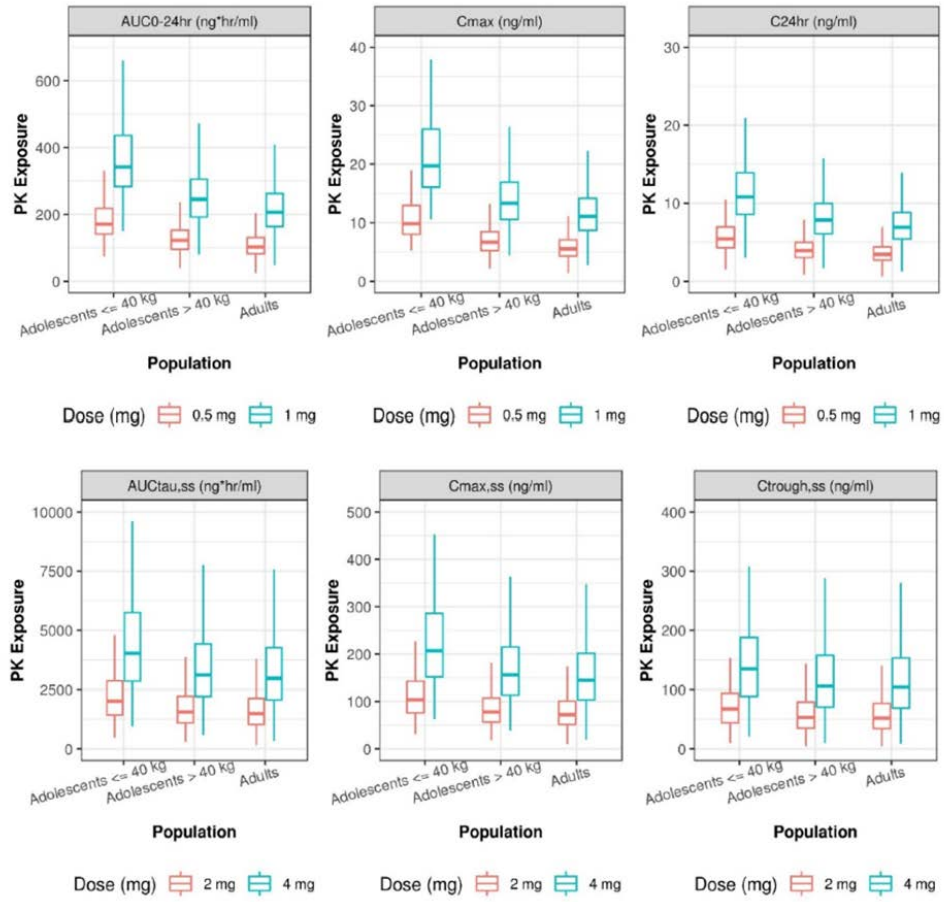
Comparison of the median (90% prediction interval) simulated PK profiles between adults and adolescents aged 13 to 17 years following the proposed titration schedule is shown in **Figure 3**. The results indicate that it takes longer for adolescents to reach the maximum dose at 4 mg due to a slower titration schedule. During the titration phase, brexpiprazole concentrations would be lower in adolescents due to lower doses compared to adults; at steady state, brexpiprazole concentrations in adolescents would be comparable to those in adults.

The PK exposure metrics ($AUC_{0\text{-}24hr}$, C_{max}, C_{24hr}) following single dose of brexpiprazole (0.5 and 1 mg) and steady state PK exposure metrics ($AUC_{tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$) following daily doses of brexpiprazole (2 and 4 mg) were also compared between adults and adolescents (**Figure 4**) Single dose PK exposures in adolescents at proposed starting dose (0.5 mg) are lower than the PK exposures attained in adults at the approved starting dose (1 mg), as expected. Steady state PK exposure in adolescents at 2 and 4 mg are comparable with PK exposure in adults at the same dose level.

The PK exposure following single doses of brexpiprazole 0.5 and 1 mg and steady state PK exposure following daily doses of brexpiprazole 2 and 4 mg for adolescents are further stratified based on weight (≤ 40kg and > 40kg) and compared with those for adults (**Figure 7**). At the same dose level, PK exposure (Cmax, AUC and Ctrough) in adolescents ≤ 40kg would be higher than those of adults. Of note, the patients ≤ 40 kg represent less than 5% of the target age population in the 13 to 17 years old age group. The PK exposure (C_{max}, AUC and C_{trough}) in adolescents >40 kg appears to be comparable to those of adults.

Reviewer's comment: *The Applicant's PK simulation results are consistent with the reviewer's independent analysis. The Applicant's rationale for dose in adolescents ≤ 40 kg is reasonable considering smaller representation of this weight group (~5%) in the 13 to 17 years of age category. Also, the proposed dosing language requires weekly increases at 1-mg increments after reaching a target dose of 2 mg, based on patient's clinical response and tolerability.*

Figure 7: PK Exposure following Single Dose of Brexpiprazole 0.5 and 1 mg (Upper Panel) and Steady State PK Exposure Following Daily Dose of Brexpiprazole 2 and 4 mg (Lower Panel) for Adults and Adolescents Aged 13-17 Years with Weight Cutoff at 40 kg



Source: Applicant's Response to Clinical Pharmacology information request dated 10/22/2021, Page 10, Figure 9

Reviewer's Analysis

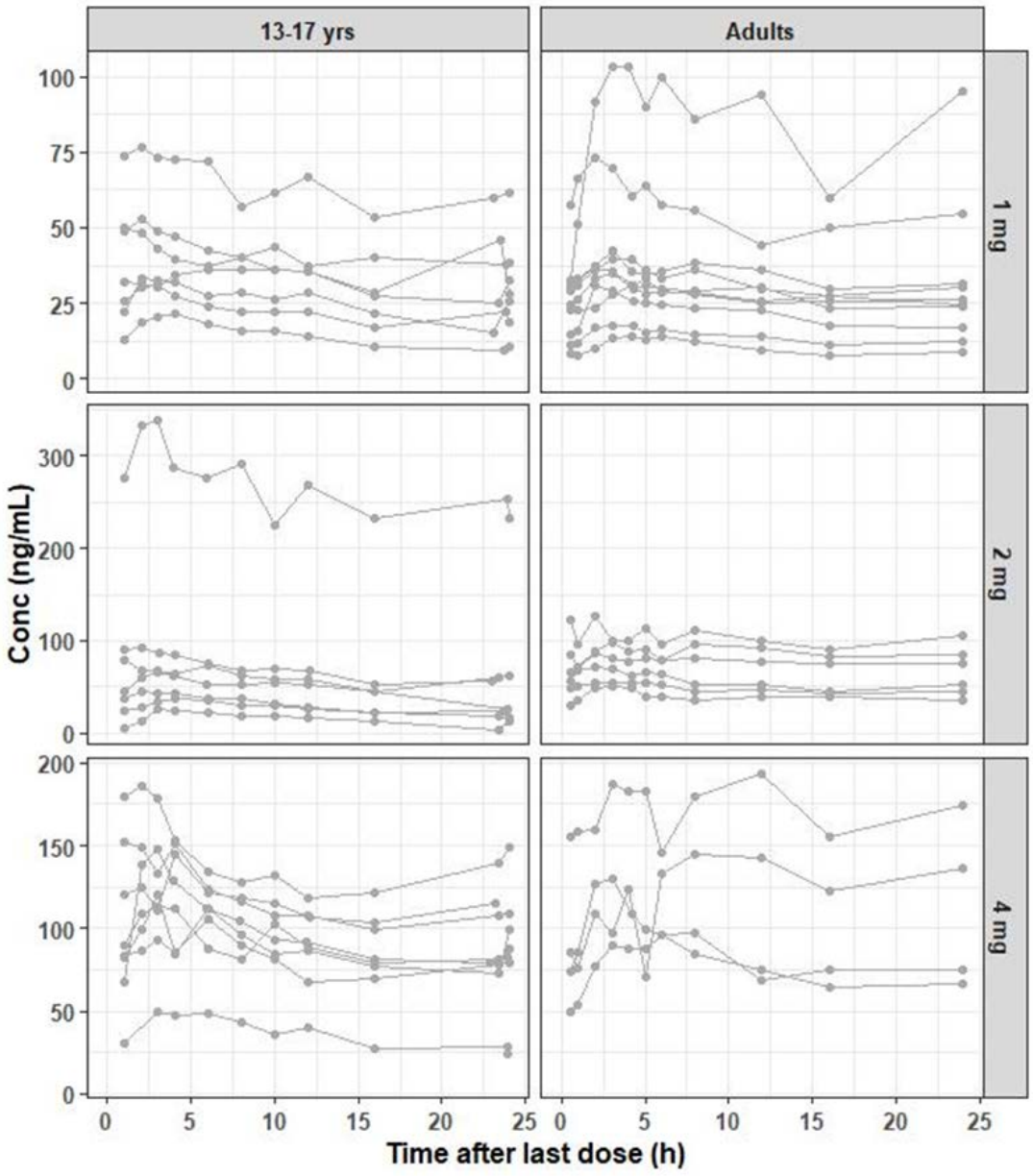
The reviewer conducted an independent analysis to evaluate the adequacy of the applicant's proposed dosing recommendations in pediatric subjects aged 13 to 17 years for the treatment of schizophrenia.

Overview of PK data comparing adult and pediatric subjects 13 to 17 years of age

The PK comparison of brexpiprazole for pediatric subjects aged 13 to 17 years (from Study 331-10-233) and adults (from Study 331-08-205) at 1-mg, 2-mg, and 4-mg dose levels are shown in **Figure 8** and **Table 9**. Overall, no clear trend in PK exposure between adults and adolescents after same dose administration of brexpiprazole was observed due to limited data (n<10 for most groups), high inter-subject variability (**Table 2** in Clin Pharm Review Section 6.3.2 and **Figure 8**), and between-study comparison (Study 331-08-205 and Study 331-10-233). However, the comparison of geometric mean ratios (90% CI) of dose-normalized C_{max}, dose-normalized AUC, and clearance between adolescent and adult subjects (PK evaluable population) showed

that the overall systemic exposure, as measured by C_{max} and AUC, appears to be slightly higher, and CL/F appears to be slightly lower in adolescent subjects as compared with adults (**Table 10**). In addition, within same study (Study 331-201-00103), higher PK profiles were observed in lower age groups (**Table 11**), which is consistent with the comparison results in PK evaluable population from Study 331-08-205 and 331-10-233.

Figure 8: Observed Brexpiprazole Concentration Versus Time Post Dose for 1 mg, 2 mg, and 4 mg Doses in Adult and Pediatric Patients Aged 13 to 17 Years in Study 331-10-233 (Left Panels) and Study 331-08-205 (Right Panels)



Source: Reviewer's Analysis

Table 16: Comparison of Median C_{max} and AUC of Brexpiprazole of Pediatric Patients Aged 13-17 Years in Study 331-10-233 versus Adult Patients in Study 331-08-205 at 1-mg, 2-mg, and 4-mg Dose Level

Dose	N		Median Cmax (ng/mL)			Median AUC (ng.h/mL)		
	Adults	Peds	Adults	Peds	%Change	Adults	Peds	%Change
1 mg	10	7	36	36	0%	653	792	21%
2 mg	6	7	79	66	-16%	1533	846	-45%
4 mg	4	8	138	133	-4%	2487	2211	-11%

Source: Reviewer's Analysis

Table 17: Geometric Mean Ratios and 90% Confidence Intervals for Brexpiprazole PK Parameters following Administration of 1 to 4 mg Brexpiprazole in Adolescent with Schizophrenia or Other Related Psychiatric Disorders vs. Adults with Schizophrenia or Schizoaffective Disorder

Population	PK Parameter	n in Trial 331-08-205	n in Trial 331-10-233	GMR	90% CI
PK Evaluable Population[a]	AUC_{τ}/Dose ([h*ng/mL]/mg)	17	21	1.09	0.797 - 1.50
	$C_{max,ss}$/Dose ([ng/mL]/mg)	18	22	1.29	0.952 - 1.73
	CL/F (mL/h)	17	21	0.914	0.666 - 1.25

GMR = geometric mean ratio.

[a]The PK evaluable population included subjects with at least 1 PK parameter and that reached steady state.

Source: Applicant Clinical Study Report CSR 331-10-233, Table 11.5.2.5-1

Table 18: Comparison of Mean Cmax and AUC of Brexpiprazole of Patients Aged 6-9 Years versus Patients Aged 10-13 in Study 331-201-00103 at 0.75-mg, 1.5-mg, and 3-mg Dose Level

Dose	N		Mean Cmax (ng/mL)			Mean AUC (ng.h/mL)		
	6-9	10-13	6-9	10-13	% Change	6-9	10-13	% Change
0.75mg	11	12	27.7	15.4*	79.9%	938	795*	18.0%
1.5 mg	11	12	41.8	30.8	35.7%	1720	1590	8.2%
3 mg	4	8	83.6*	69.8	19.8%	3440*	3620	-5.0%

Note: *Calculated using dose proportionality principle.

Source: Reviewer's Analysis

PK comparison between adult and adolescent aged 13-17 years using population modeling approach

The final dataset for PopPK analysis includes a total of 3674 evaluable brexpiprazole concentrations from 161 subjects from five clinical studies, among them, 39% subjects were from pediatric population aged 6 to 17 years (Studies 331-10-233 and 331-201-00103). The available pediatric data was adequate to characterize PK of brexpiprazole in pediatric subject aged 13 to 17 years using population PK modeling approach.

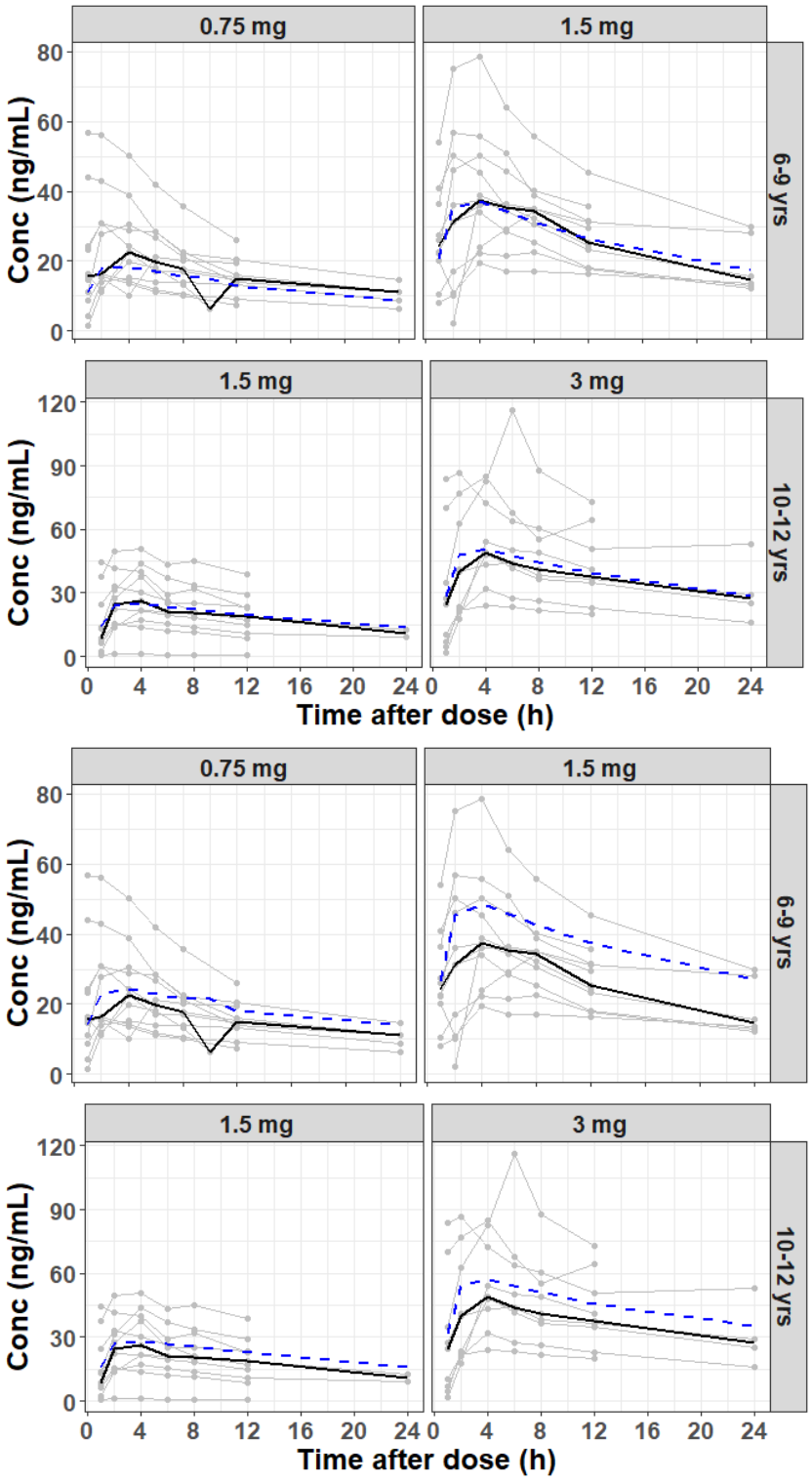
The reviewer was able to run the Applicant's final PK model, but the Applicant's final PK model overestimated brexipiprazole PK profiles in pediatric population, especially 6 to 12 years of age (**Figure 9**). Therefore, reviewer refined the Applicant's final PK model by using model estimated scaling factors instead of standard allometric scaling approach. The refined model performance was better than the Applicant's final PK model, while similar PK model parameters were estimated between the two models except for the weight scaling factor for clearance and volume of distribution. An information request was sent to the Applicant and the Applicant's response to the information request dated October 22, 2021, confirmed the reviewer's results. Please refer to Applicant's Analysis for more details.

The impact of weight on PK parameters was evaluated across age groups. Considerable overlap of weights was observed between adolescents and adults, which resulted in similar PK parameters between these two age groups (**Figure 10**).

The PK simulations were also performed based on the refined popPK model of brexpiprazole. The demographic information required for the PK simulation was taken from the available PK dataset of brexpiprazole using random sampling with replacement approach. The PK profiles were simulated for four dose groups (i.e., single dose of 0.5 mg and 1 mg, and the steady-state dose of 2 mg and 4 mg). The PK profiles of 50 subjects per dose group were then simulated (n=20) to create 1000 PK profiles for each age group (**Figure 11**).

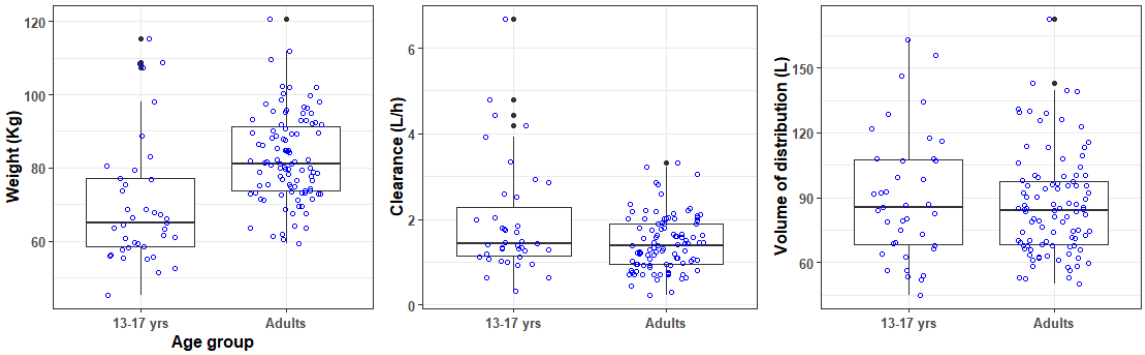
Various PK parameters including C_{max}, AUC and C_{trough} after single dose of 0.5 mg and 1 mg, and steady-state dose of 2 mg and 4 mg were derived from these PK profiles and evaluated across age groups (**Figure 12**). The concentration ranges simulated for pediatric subjects aged 13 to 17 years were similar to the adult exposures when compared at the same dose levels. The differences in median concentrations between different age groups are less than 20% across all doses (**Table 12**), which suggested that PK exposures in subject aged 13 to 17 years at the proposed doses were similar to the exposures achieved in adults after the approved dose of 2 to 4 mg daily.

Figure 9: Comparison of observed and model predicted brexipiprazole concentration (Upper Panel: Applicant's Final Model, Lower Panel: Reviewer's Refined Model) in pediatric patients (aged 6-12 years) at 0.75 mg, 1.5 mg, and 3 mg Dose Level (Study 331-201-00103)



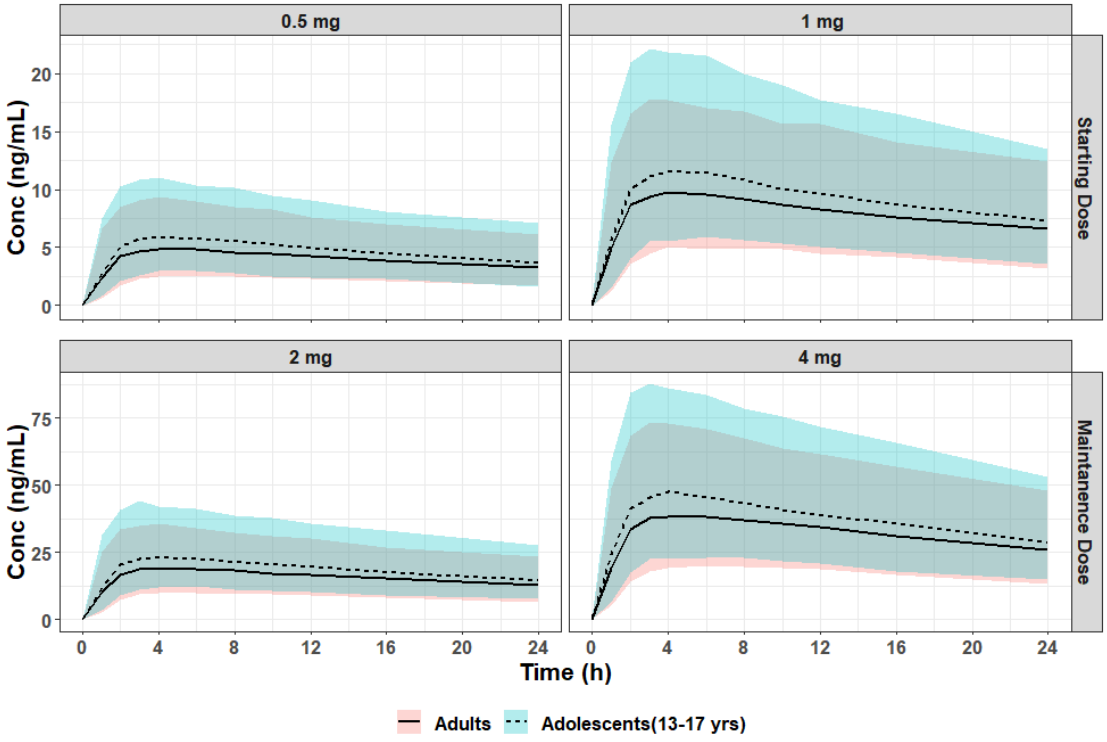
Source: Reviewer's Analysis

Figure 10: Comparison of Weight, Clearance and Volume of Distribution across Age Group



Source: Reviewer's Analysis

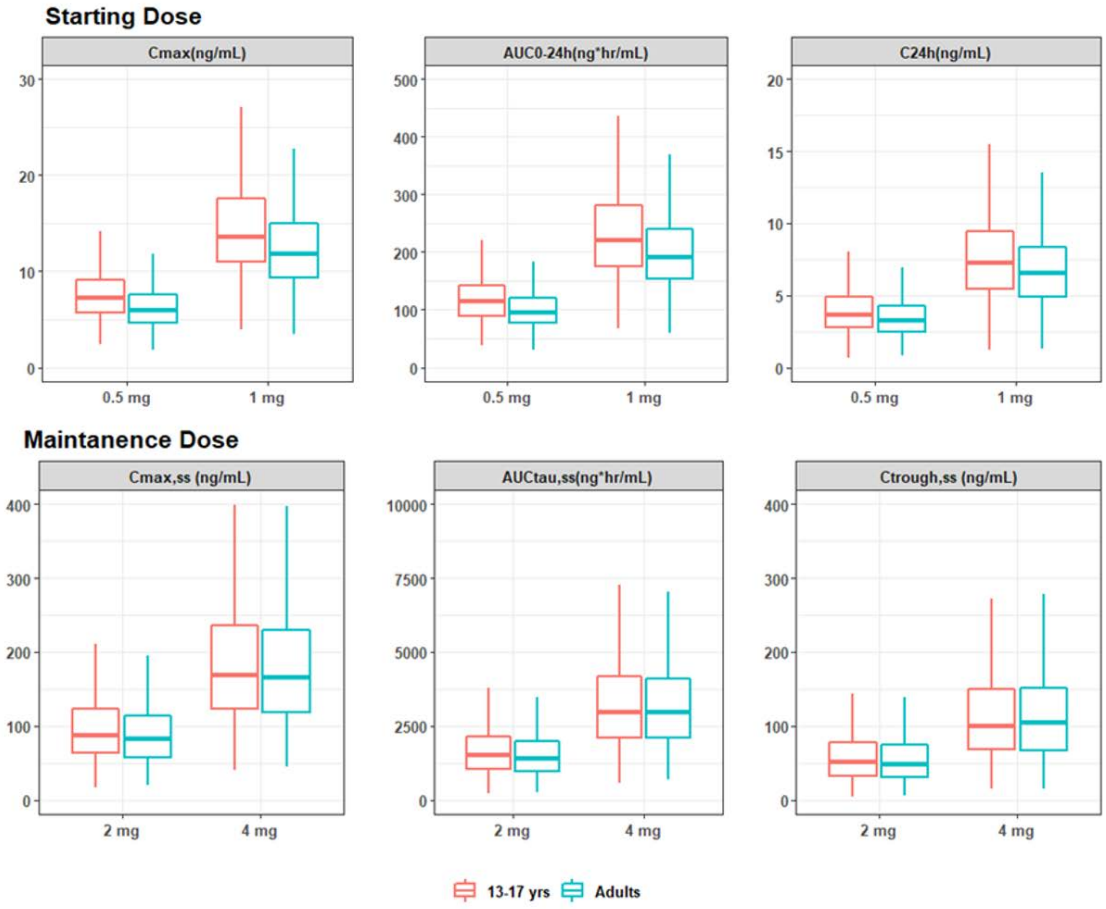
Figure 11: Simulated PK Profiles for Starting Dose (0.5mg and 1 mg, single dose) and Maintenance Dose (2 mg and 4 mg, steady state)



Note: For starting dose (0.5 mg and 1 mg), PK profiles were simulated following single dose, and for maintenance dose, steady state PK profiles were simulated. The lines represent the median of the simulated data while the shaded area represent simulated 90% confidence interval of the same.

Source: Reviewer's Analysis

Figure 12: PK Exposure following Single Dose of Brexpiprazole 0.5 and 1 mg (Left Panel) and Steady State PK Exposure Following Daily Dose of Brexpiprazole 2 and 4 mg (Right Panel) for Adults and Adolescents Aged 13-17 Years



Source: Reviewer's Analysis

Table 19: Summary of Brexpiprazole C_{max}, C_{trough}, and AUC_{0-24h} by Age and Dose Group

Starting Dose	**Age Group**	**C_{max}(ng/mL) Mean±SD**	**C_{24h}(ng/mL) Mean±SD**	**AUC_{0-24h} (ng*hr/mL) Mean±SD**
0.5 mg	Adults	6.3 [4.1,8.5]	3.5 [2.1,4.9]	102 [68,135]
	Adolsecents	7.6 [4.9,10.3]	3.9 [2.3,5.6]	119 [77,161]
1 mg	Adults	12.6 [8.1,17.1]	6.9 [4.1,9.8]	202 [132,272]
	Adolsecents	14.9 [9.3,20.5]	7.8 [4.5,11.1]	235 [152,318]
Maintenance Dose	**Age Group**	**$C_{max,ss}$ (ng/mL) Mean±SD**	**$C_{trough,ss}$(ng/mL) Mean±SD**	**$AUC_{tau,ss}$(ng*hr/mL) Mean±SD**
2 mg	Adults	92.1 [43.6,140.6]	56.8 [20.5,93]	1590 [721,2460]
	Adolsecents	100.4 [46.5,154.3]	60.6 [21.5,99.6]	1725 [757,2694]
4 mg	Adults	195.3 [87.5,303.1]	123.6 [41.8,205.4]	3401 [1438,5364]
	Adolsecents	197.9 [95.9,299.9]	119.1 [42.2,195.9]	3380 [1552,5208]

Source: Reviewer's Analysis

Conclusion

- For subjects aged 13 to 17 years, the PK exposures after the proposed doses were similar to adult PK exposures achieved after the approved dose of 2 to 4 mg daily.
- Applicant's proposed doses are acceptable for the treatment of schizophrenia in adolescents 13 to 17 years old.

Listing of Analyses Codes and Output Files

File Name	**Description**	**Location**
pk_analysis_brexipiprazole.R	PK and PopPK analysis file	M:\Review\NDA205422_Brexpiprazole\reviewer\Rscript

References

1. Applicant popPK report: Population Pharmacokinetic Analysis of Brexpiprazole (OPC-34712) in Adults, Children, and Adolescents (Report # 331-18-218)
2. Response to information request: Clinical Pharmacology & PK Profile Response (October 22, 2021)

15.3.2. OSIS MEMO 1

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 9/17/2021

TO: Division of Psychiatry (DP)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 205422/S-007

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) conducted an inspection at the site in Non-responsive The final classification for the inspection was No Action Indicated (NAI).

Based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address	Clinical Investigator
Clinical	Atlanta Center for Medical Research	501 Fairburn Road Southwest, Atlanta, GA	Dr. Robert A. Riesenberg, M.D.

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/s/

NICOLA M FENTY-STEWART
09/17/2021 05:51:35 PM

15.3.3. OSIS MEMO 2

205422MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 10/4/2021

TO: Division of Psychiatry (DP)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 205422/S-007

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

Woodland International Research, Little Rock: The Office of Regulatory Affairs (ORA) inspected the site in Non-responsive Non-responsive

The final classification for the inspection was No Action Indicated (NAI).

(b) (4)

After review of the inspectional findings and the written response from the site, OSIS recommended that all study data be accepted for Agency review. (OSIS Final EIR Review – (b) (4)).

Therefore, based on the rationale described above, inspections are not warranted at this time.

Facility Type	Facility Name	Facility Address
Clinical	Woodland International Research Group, Inc.	910 Autumn Road, Little Rock, AR
Analytical	(b) (4)	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAMES J LUMALCURI
10/04/2021 09:12:45 AM

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KOFI B ANSAH
12/27/2021 03:47:11 PM

BERNARD A FISCHER on behalf of PAMELA J HORN
12/27/2021 03:51:31 PM

BERNARD A FISCHER
12/27/2021 03:52:32 PM

TIFFANY R FARCHIONE
12/27/2021 04:55:39 PM