NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental NDA submission
Application Number(s)	NDA 205422/S-014
Priority or Standard	Standard
Submit Date(s)	07/10/2024
Received Date(s)	07/10/2024
PDUFA Goal Date	05/10/2025 (Action Date: 05/09/2025)
Division/Office	Division of Psychiatry (DP)/Office of Neuroscience (ON)
Review Completion Date	May 8, 2025
Established/Proper Name	Brexpiprazole
Trade Name	Rexulti
Pharmacologic Class	Atypical antipsychotic
Code name	OPC-34712
Applicant	Otsuka Pharmaceutical Company, Ltd.
Dosage form	Tablets
Applicant Proposed Dosing Regimen	The recommended starting REXULTI dosage for the treatment of schizophrenia in pediatric patients 13 to 17 years of age is 0.5 mg orally once daily on Days 1 to 4. On Days 5 through 7, titrate to 1 mg per day and on Day 8 titrate to 2 mg based on clinical response and tolerability. Weekly dose increases can be made in 1 mg increments. A recommended target dosage is 2 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 ages 13 years and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Not applicable.
Recommendation on Regulatory Action	Supplement approval; PMR 4205-1 fulfilled
Recommended Indication(s)/Population(s) (if applicable)	Not applicable.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Not applicable.
Recommended Dosing Regimen	Not applicable.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Sujin Wolff, PharmD
Nonclinical Reviewer	Julie Frank, PhD
Nonclinical Team Leader	Amy Avila, PhD
Office of Clinical Pharmacology Reviewer(s)	Peihao Fan, PhD
Office of Clinical Pharmacology Team Leader(s)	Venkateswaran ChithambaramPillai, PhD
Clinical Reviewer	Rachael Blackman, MD, PhD
Clinical Team Leader	Valentina Mantua, MD, PhD
Statistical Reviewer	Ales Kotalik, PhD
Statistical Team Leader	Peiling Yang, PhD
Cross-Disciplinary Team Leader	Valentina Mantua, MD, PhD
Division Director (DP)	Tiffany R. Farchione, MD

Additional Reviewers of Application

OPQ	CMC Reviewer: Joyce Crich, PhD Quality Application Lead: Joyce Crich, PhD Branch Chief: Gurpreet Gill-Sangha, PhD RPBM: Teshara Bouie
OPDP	Rachael Oyewole, PharmD Taylor Burnett Mmagu
DMPP	Laurie Buonaccorsi, PharmD
OSE/DMEPA	Loretta Holmes, BSN, PharmD Yevgeniya (Jen) Kogan, PharmD, BCSCP
DDLO	Eileen Craig, MD
DPMH	DPMH Reviewer: Sonaly McClymont, MD Team Lead: Shetarra Walker, MD, MSCR, FAAP RPM: Heather Buck, MS, MBA

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

Signatures

See archived signature memos for each discipline.

Glossary

5-HT	serotonin
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
AR	adverse reaction
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
CGAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CI	confidence interval
CK	creatinine kinase
COA	Clinical Outcome Assessment
C-SSRS	Colombia-Suicide Severity Rating Scale
D2	dopamine 2
DBP	diastolic blood pressure
DMC	data monitoring committee
ECG	electrocardiogram
EPS	extrapyramidal symptoms
FDCA	Federal Food, Drug, and Cosmetic Act of 1938
GABA	gamma-aminobutyric acid
IMP	investigational medicinal product
IND	Investigational New Drug
IUD	intrauterine device
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime
MAOI	monoamine oxidase inhibitor
MAR	missing at random
MDD	major depressive disorder
MMRM	mixed-effects model for repeated measures
MNAR	missing not at random
NDA	new drug application
NY AACENT	New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PANSS	Positive and Negative Syndrome Scale
PeRC	Pediatric Review Committee
PK	pharmacokinetic
PMR	postmarketing requirement
PPSR	Proposed Pediatric Study Request
P-Q-LES-Q	Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire
PREA	Pediatric Research Equity Act

PWR	Pediatric Written Request
SAE	serious adverse event
SAS	Simpson Angus Scale
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
TEAE	treatment emergent adverse event
TSH	thyroid stimulating hormone
UKU	Udvalg for Kliniske Undersogelser
ULN	upper limit of normal

1 Executive Summary

1.1. Product Introduction

Brexpiprazole is an atypical antipsychotic drug, co-developed by Otsuka Pharmaceuticals Co, Ltd and H. Lundbeck A/S (together referred to as the Applicant), that exerts its pharmacological effect through partial agonism of the serotonin subtype-1a (5-HT1a) and dopamine 2 (D2) receptors, and antagonism of the serotonin subtype-2a (5-HT2a) receptor.

Brexpiprazole was first approved on July 10, 2015, for the treatment of schizophrenia in adults and for the adjunctive treatment of major depressive disorder (MDD).

On December 27, 2021, brexpiprazole was approved for the treatment of schizophrenia in pediatric subjects aged 13 to 17 years based on extrapolation of effectiveness from adults plus pediatric-specific safety information (b) (4)

On May 10, 2023, brexpiprazole was also approved for the treatment of agitation associated with dementia due to Alzheimer's disease (NDA 205422/S-009).

With this supplemental new drug application (sNDA), the Applicant is submitting the results and data of Study 331-10-234, a randomized, double-blind, placebo- and active-controlled study in pediatric subjects (aged 13 to 17 years) with schizophrenia conducted to fulfill a 505(o) postmarketing requirement (PMR) as per Approval Letter dated December 27, 2021.

The Applicant proposes updates to the United States Prescribing Information (USPI) with the new clinical trial efficacy and safety data to support the indication for the treatment of schizophrenia in patients aged 13 and older that was approved in 2021.

The proposed dosing regimen for the pediatric population is unchanged and consists of a titration from 0.5 mg once daily on Days 1 to 4; to 1 mg per day on Days 5 through 7, and to 2 mg based on clinical response and tolerability on Day 8. A recommended target dosage is 2 to 4 mg once daily. The maximum recommended daily dosage is 4 mg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted one adequate and well-controlled trial, Study 331-10-234, in pediatric subjects ages 13 to 17 years with schizophrenia.

Initial approval of brexpiprazole for the treatment of pediatric subjects aged 13 to 17 years with schizophrenia in 2021 relied on extrapolation of effectiveness from adults and was supported by:

- The approved indication in adults
- A pharmacokinetic (PK) analysis demonstrating that similar doses provide similar drug

exposures in adult and pediatric subjects.

• 12 months of long-term open label safety data in subjects ages 13 to 17 years.

Data from Study 331-10-234 support effectiveness of brexpiprazole in pediatric schizophrenia and are consistent with data based on extrapolation from adults which supported substantial evidence of effectiveness for brexpiprazole for the treatment of schizophrenia in pediatric subjects aged 13 to 17 years.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Brexpiprazole is an atypical antipsychotic already approved for pediatric patients (age 13 to 17 years) with schizophrenia based on extrapolation of effectiveness from adults and safety data from a long-term open-label study in pediatric patients (Study 331-10-236). The Applicant conducted Study 331-10-234 to address a European regulatory requirement for a clinical study to evaluate safety and effectiveness in pediatric patients; Study 331-10-234 was ongoing at the time of FDA's extrapolation-based approval. Because the Agency identified a high incidence of elevated prolactin levels in Study 331-10-236, FDA issued a postmarketing requirement (PMR) to submit the data from Study 331-10-234 when completed (b) (4)

Study 331-10-234 was a 6-week randomized, double-blind, placebo- and active-controlled trial in which subjects were randomized 1:1:1 to brexpiprazole (flexible dosing of 2 to 4 mg), placebo, or aripiprazole (flexible dosing of 10 to 20 mg). The primary efficacy analysis demonstrated a statistically significantly larger reduction in Positive and Negative Syndrome Scale (PANSS) total score from baseline to Week 6 in subjects in the brexpiprazole arm compared to subjects in the placebo arm, with a point estimate (95% CI) of -5.33 (-9.55, -1.10) points, which is considered clinically meaningful and corresponding to a p-value of 0.0136. Study 331-10-234 was an adequate and well controlled investigation that supports effectiveness of brexpiprazole for the treatment of schizophrenia in pediatric subjects aged 13 and older.

The safety evaluation of brexpiprazole for schizophrenia in pediatric subjects (age 13 to 17 years) is consistent with the known safety profile of brexpiprazole. There was a mean prolactin elevation of 3.3 ng/mL observed in female subjects in the brexpiprazole group compared to a 2.8 ng/mL mean decrease in the placebo group. For male subjects, a 1.4 ng/mL mean decrease was observed in the brexpiprazole group compared to a 0.4 ng/mL mean decrease in the placebo group. Overall, more subjects in the brexpiprazole group compared to the placebo group had shifts from normal prolactin levels at baseline to abnormal (>20 ng/mL) during the course of treatment.

Efficacy results of Study 331-10-234 are consistent with the extrapolation findings used to initially approve the indication of treatment of schizophrenia in pediatric patents 13 years and older. Safety data confirm the observation of elevated prolactin levels and will be described in labeling. Study 331-10-234 fulfills PMR 4205-1.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Schizophrenia is a serious mental illness characterized by chronic or recurrent psychosis (e.g., delusions, hallucinations, and thought disorganization). • Schizophrenia is also frequently associated with negative symptoms (e.g., social withdrawal, avolition, blunted affect) and cognitive deficits (e.g., attention, executive function, working memory, and social cognition). • The onset of illness is typically sometime between one's late teens and mid-thirties. • Individuals with schizophrenia experience significant impairments in social and occupational functioning and, on average, have a life expectancy around 15 years less than individuals without schizophrenia. • Approximately 50% of individuals with schizophrenia experience a relapse/exacerbation in psychotic symptoms within one year after their last episode; most relapses occur in the context of medication nonadherence. • The worldwide prevalence of schizophrenia is approximately 0.5 to 1%, and schizophrenia is one of the leading causes of years lost due to disability worldwide.	Schizophrenia is a serious condition, associated with significant disability and a shortened life expectancy. For many patients, existing treatment options are unable to adequately control their symptoms, or may cause intolerable adverse reactions.
Current Treatment Options	• Antipsychotic medications are the first-line medication therapy for schizophrenia; current practice guidelines recommend that antipsychotic medication should be initiated as soon as possible in an acute schizophrenia exacerbation and continued indefinitely to reduce the risk of relapse. • Antipsychotic medications have been shown to be effective for reducing positive symptoms of schizophrenia (e.g., delusions, hallucinations, disorganized thinking and behavior). Negative symptoms and cognitive deficits of schizophrenia generally show	Antipsychotic medications reduce the severity of positive symptoms of schizophrenia and the risk of psychosis exacerbations. Although there are a number of approved atypical antipsychotic medications currently on the market, individual patient response to a given antipsychotic medication cannot be predicted at this time. For an individual

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	little to no improvement from antipsychotic treatment. • Antipsychotic medications are broadly categorized as first-generation/ typical antipsychotic medications (e.g., chlorpromazine, fluphenazine, haloperidol, etc.) and second-generation/atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, quetiapine, and aripiprazole). In general, first-generation antipsychotic medications have a higher risk for causing extrapyramidal side effects than second-generation antipsychotic medications. • In addition to brexpiprazaole, six atypical antipsychotic medications 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 versus adults). • Some of the relevant class safety issues for atypical antipsychotic medications include extrapyramidal side effects, tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, weight gain, metabolic changes, and blood dyscrasias. • In addition to antipsychotic medications, patients with schizophrenia are frequently treated with adjunctive medications to target depression, anxiety, obsessions and compulsions, and side effects of antipsychotics (e.g., dystonia, parkinsonism, tardive dyskinesia, and akathisia). • When integrated with pharmacotherapy, psychosocial interventions have been shown to improve the course of schizophrenia. These interventions include cognitive behavioral therapy, assertive community treatment, supported employment, and social skills therapy.	patient, several trials of different products are often required.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant conducted a single 6-week multi-center, randomized, double-blind, placebo- and active-controlled outpatient trial (331-10-234) in 316 pediatric subjects 13 to 17 years of age with schizophrenia. • Brexpiprazole was titrated from the starting dose of 0.5 mg to the minimum dose of 2 mg from Day 1 to 8 and then flexibly dosed from 2 to 4 mg as per current product labeling. • Subjects were randomized 1:1:1 to brexpiprazole or placebo or active aripiprazole. An active aripiprazole arm was added to fulfill a European regulatory requirement and was dosed flexibly from 10 to 20 mg daily. • The primary efficacy endpoint was the change from baseline to Week 6 in PANSS total score, which is considered an acceptable endpoint for a pediatric schizophrenia study. • Of the 316 randomized subjects, all 314 (99.4%) were analyzed for efficacy (110 in the brexpiprazole arm and 103 in the placebo arm). Postbaseline assessments for PANSS total score were missing for the two subjects (one in the aripiprazole group and one in the placebo group). Demographic and baseline characteristics were imbalanced between the treatment groups. • Subjects in the brexpiprazole arm achieved a statistically significantly larger reduction in PANSS total score (-22.75 ± 1.49 PANSS points) change from baseline to Week 6 compared to subjects in the placebo arm (-17.42 ± 1.58), with a point estimate (95% CI) of -5.33 (-9.55, -1.10) points, which is considered clinically meaningful and corresponding to a p-value of 0.0136. • Both brexpiprazole and aripiprazole arms show a clear separation from placebo by Week 3 and a continuous improvement in PANSS total score over the duration of the study.	The Applicant conducted a single 6-week adequate and well-controlled phase 3 study (331-10-234) to evaluate efficacy of brexpiprazole in pediatric subjects 13 to 17 years of age with schizophrenia compared to placebo. Subjects in the brexpiprazole arm showed a clinically meaningful reduction in PANSS total score, and the primary efficacy analysis demonstrated a statistically significant superiority to placebo. The proposed dosing regimen is acceptable for this product, which can be titrated based on clinical assessments and is supported by the efficacy data. Results of Study 331-10-234 are consistent with previous findings of effectiveness of brexpiprazole in the treatment of schizophrenia in pediatric subjects 13 years and older based on extrapolation of efficacy from adults using a PK analysis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• In Study 331-10-234, adverse events (AEs) that occurred in at least 2% of subjects and at a rate greater than placebo (in order of incidence relative to the brexpiprazole group) are EPS, headache, nausea, and akathisia. • Overall AEs that occurred in Study 331-10-234 were consistent with the known safety profile of brexpiprazole (regardless of age). • Analysis of changes in laboratory measures did not indicate any clinically relevant differences between brexpiprazole and placebo in the pediatric study population except for prolactin • For females in Study 331-10-234, a 3.3 ng/mL mean increase (from baseline to last visit) was observed in the brexpiprazole group (versus a 2.8 ng/mL mean decrease in the placebo group). For males in Study 331-10-234, a 1.4 ng/mL mean decrease (from baseline to last visit) was observed in the brexpiprazole group (versus 0.4 ng/mL mean decrease in the placebo group). Overall, more subjects in the brexpiprazole group compared to the placebo group had shifts from normal prolactin levels at baseline to abnormal (>20 ng/mL) during the course of treatment. There was one event of galactorrhea not associated with elevated prolactin levels.	The clinical safety of brexpiprazole in the pediatric population is informed by short- and long-term studies in schizophrenia. Overall, data from Study 331-10-234 were consistent with the known safety profile of brexpiprazole (regardless of age). Study 331-10-234 data will be used to update product labeling. Safety findings will be included in sections 6 (EPS) (b) (4) of the product label.

1.4. Patient Experience Data

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

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8.1 (Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire)
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 8.1 (Children's Global Assessment Scale, Clinical Global Impression - Severity)
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1.Analysis of Condition

Schizophrenia 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. Although there are a number of approved treatments for schizophrenia, an individual patient may require several trials with different antipsychotic medications before an effective and reasonably-tolerated treatment is identified.

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 are recognized to be somewhat different. Within the pediatric age group, a diagnosis of schizophrenia is most commonly made in pediatric patients aged 13 to 17 years of age, and the symptoms in this age group are generally similar to those in adults. Schizophrenia has also been described in pediatric patients younger than 13 years of age, but it is uncommon.[2]

2.2. Analysis of Current Treatment Options

A number of "typical" and "atypical" antipsychotic medications are currently available for the treatment of schizophrenia. Some of the relevant class safety issues for atypical antipsychotic medications include extrapyramidal side effects, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, weight gain, metabolic changes, and blood dyscrasias.

Although there are a number of approved atypical antipsychotic medications currently on the market, individual patient response to a given antipsychotic medication 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.

A number of atypical antipsychotic medications have been approved for the treatment of schizophrenia in pediatric patients ages 13 to 17 years: aripiprazole, lurasidone, paliperidone, olanzapine, quetiapine, and risperidone as well as the Applicant's product brexpiprazole (based on extrapolation data). Olanzapine is considered second-line treatment given the increased risk of weight gain and dyslipidemia (in adolescents versus 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 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Brexpiprazole was initially approved as Rexulti on July 10, 2015, for the treatment of schizophrenia in adults and for the adjunctive treatment of major depressive disorder in adults (NDA 205422). On September 23, 2016, it was approved for the maintenance treatment of schizophrenia in adults (NDA 205422/S-001); on December 27, 2021, for the treatment of schizophrenia in pediatric patients ages 13 years and older (NDA 205422/S-007); and on May 10, 2023, for the treatment of agitation associated with dementia due to Alzheimer's disease (NDA 205422/S-009).

3.2. Summary of Presubmission/Submission Regulatory Activity

Following the initial approval of Rexulti 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 subjects 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
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

(b) (4) the Applicant submitted a Proposed (b) (4)
The Agency determined that (b) (4) was inadequate (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 submitted a revised PPSR in December 2017, and the Agency issued a Pediatric Written Request (PWR) on April 19, 2018. The PWR included requests for:

- An adequate and well-controlled pediatric efficacy and safety study in patients 13 to 17 years of age with schizophrenia

- Pediatric long-term safety study in patients with schizophrenia, bipolar I disorder, and irritability associated with ASD

Because the full study report for a multiple dose safety, tolerability, and PK study in pediatric subjects (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 the study report.

On January 13, 2020, the Agency issued a General Advice letter informing the Applicant (and

(b) (4) that the Division of Psychiatry determined that it was 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 to 17 years. Conduct a 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.

On June 30, 2021, the Applicant submitted supplemental NDA 205422-S-007 seeking the addition of the indication for treatment of schizophrenia in pediatric patients ages 13 to 17 years based on extrapolation of effectiveness from adults and safety data in pediatric subjects. On December 27, 2021, S-007 was approved. The Agency also determined S-007 fulfilled PMR 2929-5 and issued a PMR Fulfillment with the approval letter.

During the review of S-007, the Agency noted that the interim data from Study 331-10-236, an ongoing long-term, open-label safety study in pediatric subjects, revealed a high incidence of abnormal prolactin values; therefore, the Agency issued a new PMR 4205-1 under Section 505(o)(3) of the Food, Drug, and Cosmetic Act:

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 13-17) with schizophrenia.

Final Protocol Submission: June 2016
Study Completion: October 2024
Final Report Submission: April 2025

On November 8, 2023, the Applicant submitted supplement S-011 which included data from negative studies conducted to explore the potential indication of treatment of irritability associated with autism spectrum disorder (ASD). (b) (4)

The current supplemental application includes data from Study 331-10-234. Although the submitted data does not affect the indication statement, it does provide for double-blind safety data and fulfills PMR 4205-1.

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

4.1. Office of Scientific Investigations (OSI)

Sites #166 and #242 were inspected in support of NDA 205422-S14. The inspections covered Protocol 331-10-234.

At Site #166, the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL) was conducted by an unqualified clinician to determine eligibility for five subjects. At Site #242, documentation of concomitant medications was not clear for seven subjects including two subjects where it was unclear about whether lorazepam use (which may impact the primary endpoint) met protocol-specific timing requirements. Therefore, OSI recommended sensitivity analyses excluding the 5 subjects from Site #166 and seven subjects from Site #262 in question.

Overall, the sensitivity analyses performed by the statistical team excluding the subjects OSI recommended to exclude from the primary efficacy analysis resulted in negligible changes.

OSI inspection concluded inspected clinical data at the respective sites appeared reliable for the prolactin levels.

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.

4.4. Devices and Companion Diagnostic Issues

Not Applicable.

5 Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted with this supplement. Previously, the Applicant conducted two juvenile animal studies in rats and dogs and results from these studies were included in Section 8.4 of the label under supplement S-011.

6 Clinical Pharmacology

6.1.Executive Summary

In this supplement (NDA 205422/S-014), no new clinical pharmacology information has been submitted. There were no new labeling changes proposed in the sections related to clinical pharmacology. Please refer to the previous clinical pharmacology review (NDA 205422, S-007 archived in DARRTS on 12/27/2021) for additional information.

7 Sources of Clinical Data and Review Strategy

7.1.Table of Clinical Studies

Table 1: 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 subjects enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
331-10-234	NCT03198078	Randomized, double-blind, placebo- and active-controlled trial	Daily oral - brexpiprazole: 2-4 mg, - aripiprazole: 10-20 mg, or - placebo	Primary: Change from baseline to Week 6 in PANSS Total Score	6 weeks treatment duration 21-day follow-up for subjects that did not enter the open-label rollover trial after completion of treatment	316 were randomized (376 were screened) Brexpiprazole: 110 Aripiprazole: 102 Placebo: 104	pediatric subjects (13 to 17 years old) with schizophrenia	62 sites with subjects in 10 countries (United States, Mexico, France, Italy, Poland, Romania, Serbia, Spain, Ukraine, and Russia)

Source: Clinical reviewer created

7.2.Review Strategy

The efficacy review is based on Study 331-10-234, a randomized, double-blind, active controlled study, conducted in pediatric subjects aged 13 to 17 years with schizophrenia.

The safety review is also based on double-blind data from Study 331-10-234. (b) (4)

8 Statistical and Clinical Evaluation

8.1.Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 331-10-234

Trial Design

Study 331-10-234 was a multi-center, randomized, double-blind, placebo- and active-controlled outpatient trial designed to evaluate the efficacy and safety of brexpiprazole compared to placebo in pediatric subjects (ages 13 to 17 years) with schizophrenia (see trial schematic below, Figure 1). In the trial, the screening period was up to 28 days and the double-blind treatment duration was 6 weeks. For subjects that did not roll over into the open-label safety Study 331-10-236, a 21-day follow-up phone call was conducted.

There was a minimum 3-day washout period. At the baseline visit (Day 1), if subjects continued to meet all the inclusion criteria (including Positive and Negative Syndrome Scale [PANSS] Total Score ≥ 80) and none of the exclusion criteria, they were randomized 1:1:1 to one of three double-blind treatment arms:

- Brexpiprazole 2 to 4 mg daily:
  Day 1 to 4: 0.5 mg tablet daily
  Day 5 to 7: 1 mg brexpiprazole daily
  Day 8 to 14: 2 mg brexpiprazole daily (minimum dose)
  Day 15 to Day 21: The dosage was either changed from 2 mg to 3 mg, or it was kept at 2 mg.
  After Day 21: The investigators either kept the subject at a maintenance dosage, increased the dosage by 1 mg to a maximum of 4 mg/day, or decreased the dosage by 1 mg.

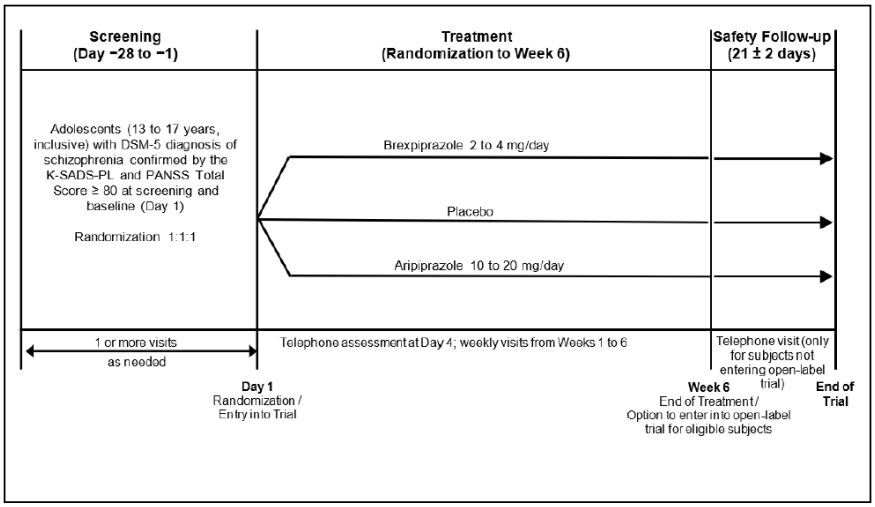
- Aripiprazole 10 to 20 mg daily:
  Day 1 to 4: 2 mg tablet daily
  Day 5 to Day 7: 5 mg aripiprazole daily from
  Day 8 to Day 14: 10 mg aripiprazole
  Day 15 to 21: The dosage was either changed from 10 mg to 15 mg, or it was kept at 10 mg.
  After Day 21: The investigators either kept the subject at a maintenance dosage, increased the dosage by 5 mg to a maximum of 20 mg, or decreased the dosage by 5 mg.

- Placebo tablet daily.

Evaluations occurred on Days 1 (baseline) and 4, and at Weeks 1, 2, 3, 4, 5, and 6 during the

double-blind treatment period. All visits (except for screening, Day 1, and Week 6 which were in-clinic visits) were allowed to be completed as virtual visits during the COVID-19 pandemic. If completely unavoidable, the Week 6 visit could be a virtual visit only. Telecommunications technology was used to conduct the virtual visits with the caregiver and subject remaining at their home to complete trial assessments and questionnaires with online technology. Using online communication tools with incorporated telemedicine, the caregiver and subject were able to interact with the trial personnel. Virtual interactions (and at any other time) allowed trial personnel to assess the subject and need for a physical evaluation in-clinic visit (required at the discretion of the investigator).

Figure 1: Trial Design Schematic (Study 331-10-234)



Source: Applicant's Study 331-10-234 Report, Figure 9.1-1

Clinical Reviewer's Comments: *The trial was designed and powered for the primary statistical comparison of interest of brexpiprazole 2 to 4 mg versus placebo; however, it also included an aripiprazole arm to fulfill a European regulatory requirement. Accommodations were made during the COVID-19 pandemic such that some visits were converted to virtual. Accommodations were reasonable given the nature of the pandemic and enabled to study subjects to continue. The trial design is acceptable for addressing the study's objectives.*

Study Eligibility Criteria

Pediatric subjects with schizophrenia aged 13 to 17 years were the target population for this trial. The trial's key inclusion/exclusion criteria are listed below (criteria as phrased in the protocol).

Key Inclusion Criteria:

- Male and female subjects 13 to 17 years of age, inclusive, at the time of informed consent/assent and at baseline (Day 1).

- Subjects with a current primary diagnosis of schizophrenia, as defined by DSM-5 criteria and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL), and a history of the illness (diagnosis or symptoms) for at least 6 months prior to screening (as per subject, family, or healthcare provider, or by previous medical records). The initial diagnosis of schizophrenia must be made and documented initially by an adequately trained clinician (psychiatrist or local medical equivalent who is experienced in treating adolescents with schizophrenia), and the diagnosis should be confirmed afterwards by utilizing the K-SADS-PL performed by an adequately trained rater. (Subjects with a diagnosis of attention deficit hyperactivity disorder [ADHD] and treated with stimulants or other ADHD medications within 28 days are prohibited.)

- Subjects with a PANSS Total Score ≥ 80 at screening and at baseline (Day 1).

Key Exclusion Criteria:

- Sexually active males or females who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of the investigational medical product (IMP). If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control patch, birth control depot injection, condom with spermicide, or sponge with spermicide.

- Females who are breast-feeding or who have a positive pregnancy test result prior to receiving IMP.

- Subjects with a DSM-5 diagnosis other than schizophrenia that has been the primary focus of treatment within 3 months of screening.

- Subjects with a clinical presentation or history that is consistent with delirium, dementia, amnesia, or other cognitive disorders; subjects with psychotic symptoms that are better accounted for by another general medical condition(s) or direct effect of a substance (e.g., medication, illicit drug use).

- Subjects who have been hospitalized > 21 days for a current exacerbation of schizophrenia at the time of the baseline visit.

- Subjects with known intellectual disability defined as an intelligence quotient less than 70; or, either clinical evidence or known social or school history indicative of intellectual disability.

- The subject is considered treatment resistant to antipsychotic medication, including aripiprazole or brexpiprazole, at an adequate dose and duration as confirmed by medical history, investigator judgment, or subject report. Subjects with a history of relapse due to lack of medication compliance or drug abuse can be considered based on investigator judgment.

- Subjects who have a significant risk of committing violent acts, serious self-harm, or suicide based on history (e.g., suicide attempt in the past 1 year) or routine psychiatric status examination, or those who are homicidal or are considered to be a high risk to others, or who have an answer of "yes" on Questions 4 or 5 (current or over the past 1 month) on the suicidal ideation section of the baseline screening version of the C-SSRS.

- Subjects with current hypothyroidism or hyperthyroidism (unless the condition has been stabilized with medications for at least the past 90 days). Eligibility of subjects that have an abnormal free T4 result that is considered not clinically significant can be discussed with the Medical Advisor prior to randomization.

- Subjects with IDDM are excluded. Subjects with non-IDDM may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria:

  - HbA1c < 7.0%,

  - Screening fasting glucose must be ≤ 125 mg/dL or non-fasting glucose < 200 mg/dL. If the non-fasting glucose is ≥ 200 mg/dL, subjects must be retested in the fasting state. At retest, fasting glucose must be ≤ 125 mg/dL

  - Subject has been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening,

  - Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, AND

  - Subject's diabetes is not newly diagnosed during screening for the trial.

- Subjects with uncontrolled hypertension (diastolic blood pressure [DBP] > 95 mmHg) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in systolic blood pressure (SBP) or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure, OR development of symptoms.

- Subjects who have epilepsy, a history of seizures (except for a single childhood febrile seizure or post-traumatic seizure), or a history of severe head trauma or stroke, or have a history or current evidence of other unstable medical conditions that would expose them to undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the trial, including but not limited to hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the investigator (e.g., history of myocardial infarction or ischemic heart disease, arrhythmia, congestive heart failure, or cancer); subjects with a comorbid serious systemic illness that requires pharmacotherapy; subjects with a history of electroconvulsive therapy.

- Subjects who test positive for drugs of abuse at screening are excluded. A positive test for amphetamines, barbiturates, opiates, benzodiazepines may not result in exclusion of the subjects if the investigator determines that the positive test is a result of prescription medicine(s). When a subject tests positive for cannabinoids (tetrahydrocannabinol) at screening, the Investigator is required to evaluate the subject's ability to abstain from using this substance during the trial and to discuss his/her evaluation with the Medical Advisor prior to randomization.

- The following laboratory test and ECG results are exclusionary:

  1) Platelets ≤ 75000/mm3
  2) Hemoglobin ≤ 11 g/dL
  3) Neutrophils, absolute ≤ 1000/mm3
  4) WBC count ≤ 2800/mm3
  5) AST > 3 × upper limit of normal
  6) ALT > 3 × upper limit of normal
  7) Creatinine ≥ 2 mg/dL
  8) HbA1c ≥ 7.0%
  9) CPK > 3 × upper limit of normal
  10) Abnormal free T4, unless discussed with and approved by the Medical Advisor. (Note: Free T4 is measured only if result for thyroid stimulating hormone [TSH] is abnormal.)
  11) QTcF or QTcN ≥ 450 msec for males and ≥ 470 msec for females

- Subjects who would be likely to require prohibited concomitant therapy during the trial, including subjects receiving CYP2D6 or CYP3A4 inhibitors or CYP3A4 inducers at screening or who are anticipated to require use of such agents during the trial.

- Subjects with a history of neuroleptic malignant syndrome.

Clinical Reviewer's Comments: *The Applicant's comprehensive inclusion and exclusion criteria consisted of appropriate diagnostic and tolerability criteria, appropriate prohibited concomitant medications, and acceptance thresholds for clinically significant abnormal laboratory values and medical history. Overall, the subject enrollment criteria are adequate.*

Procedures and Schedule of Events

Refer to Table 2 for the Applicant's schedule of procedures and study assessments.

Table 2: Schedule of Assessments (Study 331-10-234)

Assessment	Screening	6-week Double-Blind Treatment Period								Follow-up Visit
		Day 1	Day 4	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6/ET	21 days after last IMP
Informed consent, demography, medical history, psychiatry history	X									
Entrance criteria	X	X								
Prior medications	X	X								
K-SADS-PL	X									
PANSS	X	X		X	X	X	X	X	X	
CGAS	X	X		X	X	X	X	X	X	
CGI-S		X		X	X	X	X	X	X	
CGI-I				X	X	X	X	X	X	
P-Q-LES-Q		X							X	
C-SSRS		X		X	X	X	X	X	X	
SAS, AIMS, BARS	X	X		X	X	X	X	X	X	
UKU	X	X		X	X	X	X	X	X	
NY-ACCENT	X	X		X	X	X	X	X	X	
Tanner Staging	X								X	
Physical Examination	X								X	
Body weight and waist circumference	X	X		X	X	X	X	X	X	
Height	X								X	
Dispense Investigational Product		X		X	X	X	X	X		
Clinical laboratory tests	X	X					X		X	
HbA1c and TSH	X	X							X	
Vital signs	X	X		X	X	X	X	X	X	

ECG	X	X							X	
Serum pregnancy test	X	X					X		X	
Urine pregnancy test	X	X							X	
Urine drug screen	X						X		X	
Pharmacokinetic samples		X					X		X	
Pharmacogenomic sample		X								
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X

AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, CGAS = Children's Global Assessment Scale, CGI-I = Clinical Global Impression - Improvement scale, CGI-S = Clinical Global Impression - Severity of Illness scale, C-SSRS = Columbia-Suicide Severity Rating Scale, ET = early termination, IMP = Investigational Medicinal Product, K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version, NY-ACCENT = New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment, PANSS = Positive and Negative Syndrome Scale, P-Q-LES-Q = Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire, SAS = Simpson Angus Scale, UKU = Udvalg for Kliniske Undersogelser
Source: Clinical reviewer created from Applicant Schedule of Activities from Study 331-10-234 Protocol Amendment 03, Table 3.7-1

Subject Completion, Discontinuation, or Withdrawal

The Applicant defined the treatment period as the time during which subjects are evaluated for primary or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of IMP. Trial completers were defined as subjects who were evaluated at the last scheduled visit during the treatment period (i.e., subjects who completed the Week 6 visit). Protocol specified post-treatment follow-up contacts were not considered as the "last scheduled visit." Non-completers were defined as those who "discontinued the trial."

Study Product Information and Compliance

The Applicant provided weekly blister cards, each containing enough tablets for 7 (+3) days. IMP (i.e., brexpiprazole, aripiprazole, and placebo) was dispensed to subjects by responsible trial personnel. Documentation of accountability and compliance verification was contained in the subject's trial records.

Clinical Reviewer's Comments: *The blind and randomization procedures were robust.*

Dose Selection

The Applicant selected the dose range of 2 to 4 mg for brexipirazole based on results of pivotal safety and efficacy in adult subjects with schizophrenia, as this dosage range was shown to be efficacious. No dose adjustment was deemed necessary in pediatric subjects by the Applicant based on the safety and PK data from Study 331-10-233. Thus, the same dosage range of 2 to 4 mg was proposed for Study 331-10-234. The dose initiation scheme used in adults (1 mg for 3

days followed by 2 mg for 3 days) was evaluated in the final cohort of Study 331-10-233 with no safety or tolerability concerns. Therefore, the same dose initiation was used in pediatric subjects 13 to 17 years of age in Study 331-10-234.

Prior and Concomitant Therapy

Refer to Table 3 and Table 4, respectively, below for a list of medications that required washout before the trial and a list of medications prohibited during the trial that had to be discontinued at least 24 hours before the first dose of IMP. The use of all supplements, vitamins, and over-the-counter medications (with the exception of episodic use of ibuprofen, acetaminophen, naproxen, or equivalent) had to be approved by the Medical Advisor. During the trial, benzodiazepines were not permitted, and routine use needed to be discontinued for at least 2 weeks prior to the baseline visit; intramuscular benzodiazepines were prohibited. Exceptions to allow benzodiazepine use during the trial are outlined in Table 5. Subjects were restricted to no more than one benzodiazepine beyond screening and short-term use of specific oral benzodiazepines was allowed for the control of agitation or insomnia. For treatment of insomnia, non-benzodiazepine sleep aids were permitted; however, they were not permitted on the same day as administration of a benzodiazepine regardless of the indication. For treatment of EPS, anticholinergics (e.g., benztropine up to 4 mg/day or its equivalent) were permitted. For akathisia or tremor, propranolol (up to 60 mg/day) was permitted. Within 12 hours of a scheduled efficacy and safety assessment (including EPS scales), benzodiazepines, non-benzodiazepine sleep aids, anticholinergics, and propranolol were not permitted to be administered.

During the trial, with the exception of inpatient group therapy, new-onset psychotherapy was not permitted. If subjects had been engaged in regular (i.e., weekly) psychotherapy for at least 6 weeks prior to the screening, they could continue their psychotherapy as long as they committed to maintain their participation during the course of the trial.

Table 3: Washout of Prohibited Medications Required Before the Trial (Study 331-10-234)

Medication	Required Washout Prior to Dosing
Antipsychotics	
Oral aripiprazole	14 days
Oral antipsychotics (other than cariprazine and clozapine)	7 days
Depot or long-acting injectable antipsychotics	5 × half-life of the medication prior to screening
Cariprazine (Vraylar) and clozapine	6 months
Antidepressants	
Fluoxetine or Symbyax, MAOIs	28 days
Citalopram and escitalopram	14 days
Venlafaxine and desvenlafaxine	8 days
All other antidepressants	3 days 14 days
Atomoxetine	28 days with the diagnosis of ADHD; minimum 5× half-life for subjects without diagnosis of ADHD
Stimulants	

Mood stabilizers (i.e., lithium or anticonvulsants)	7 days
Varenicline	5 days
Oral benzodiazepines used as rescue therapy during washout Lorazepam, oxazepam, diazepam, or clonazepam Other benzodiazepines	 12 hours before scales 14 days
CYP2D6 inhibitors and CYP3A4 inhibitors and inducers	14 days

MAOIs = monoamine oxidase inhibitors.
Source: Clinical reviewer adapted using Protocol 331-10-234, Table 4.1-1

Table 4: List of Prohibited Medications During the Trial

	Prohibited Medications
1.	All psychotropic agents including, but not limited to, the following: a) Antipsychotics, including IR IM and depot or long-acting injectable formulations b) Antidepressants (including MAOIs) c) Symbyax d) Mood stabilizers (i.e., lithium or anticonvulsants) e) Benzodiazepines, except specific benzodiazepines when used as rescue therapy f) Stimulants with the diagnosis of ADHD and treatment with stimulants within 28 days, otherwise washout of > 5× half- life for subjects without diagnosis of ADHD g) Other psychotropics (i.e., atomoxetine)
2.	Ramelteon and other non-benzodiazepine sleep aids, except for limited use of specific medications for the treatment of insomnia
3.	Antihistamines (except for loratadine and cetirizine)
4.	Varenicline
5.	Other nutritional supplements and nonprescription herbal preparations with central nervous system effects (e.g., St. John's Wort, omega-3 fatty acids, kava extracts, GABA supplements) unless approved in advance by the medical monitor
6.	CYP2D6 inhibitors and CYP3A4 inhibitors and inducers
7.	Investigational agents

GABA = gamma-aminobutyric acid; IR = immediate-release.
Source: Clinical reviewer adapted using Protocol 331-10-234, Table 4.1-2

Table 5: Oral Benzodiazepine Rescue Therapy During the Trial (Study 331-10-234)

Oral Benzodiazepine	**Maximum Allowable Dose (mg/day)**		
	Screening	**Baseline to Week 2 Visit**	**After Week 2 Visit to Week 6 Visit**
Lorazepam	3	3	3
Oxazepam	45	45	45
Diazepam	15	15	15
Clonazepam	1.5	1.5	1.5

Source: Clinical reviewer adapted using Protocol 331-10-234, Table 4.1-3

Clinical Reviewer's Comments: *Study 331-10-234 had an adequate treatment duration of 6 weeks, justified dose-selection, and appropriate eligibility criteria. The study design is acceptable to evaluate the effects of brexpiprazole for the treatment of schizophrenia in*

pediatric subjects.

Study Endpoints

Efficacy Outcome Instruments

PANSS: This is a clinician-rated scale measuring the subject's symptoms of schizophrenia under the subscales of positive symptoms, negative symptoms, and general psychopathology. Each symptom (there are 30 symptom constructs total) is rated on a 7-point scale: 1=absent and 7=extreme.

CGAS: This is a clinician-rated scale measuring the subject's global functioning and impairment. It is rated on a 100-point scale; higher scores represent better functioning.

CGI-S: This is a clinician-rated scale measuring the subject's global functioning. CGI-S is rated on a 7-point scale: 1=normal, not at all ill and 7=among the most extremely ill.

CGI-I: This is a clinician-rated scale measuring the subject's improvement and whether or not it is due entirely to the drug treatment. Baseline (prior to treatment with IMP) is used as the comparison to subject's condition at time of the rating. CGI-I is rated on a 7-point scale: 1=very much improved, 7=very much worse.

Clinical Reviewer's Comments: *PANSS was the accepted primary efficacy outcome measure for other pediatric schizophrenia studies that have supported a pediatric schizophrenia indication for other atypical antipsychotic medications (such as risperidone) and is also a fit-for-purpose primary efficacy outcome measure for Study 331-10-234.*

Endpoints
As outlined in the trial protocol, the study endpoints were the following:

Primary endpoint
Change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) Total Score.

Secondary endpoints
Efficacy
- Change in the PANSS Positive and Negative Subscale Scores.
- Percentage of subjects achieving response. Response was defined as at least 30% improvement from baseline in PANSS Total Score or Clinical Global Impression Improvement (CGI-I) score of 1 or 2.
- Percentage of subjects achieving remission. Remission was defined as a score of ≤ 3 on each of the following specific PANSS items: delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), passive/apathetic social withdrawal (N4), and lack of spontaneity and conversation flow (N6).
- Change in the Children's Global Assessment Scale (CGAS) score.

- Change in the Clinical Global Impression Severity (CGI-S) scale.
- Clinical Global Impression Improvement scale.

Safety

- The frequency and severity of adverse events (AEs), serious AEs (SAEs) (clinical and laboratory), and discontinuation from the trial due to AEs.
- Weight, height, body mass index, and waist circumference.
- Analysis of potential suicide events recorded on the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Clinical laboratory tests and urinalysis results (including serum prolactin), vital signs, physical examinations, and electrocardiogram (ECG) parameters.
- Changes on the Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS).
- Comprehensive psychotropic side effects as assessed by the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale.
- Cognitive adverse effects as assessed by the New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY AACENT).

<u>Exploratory endpoints</u>

- The number of hospitalizations for each subject.
- Change from screening to Week 6 in the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-Q-LES-Q; in translated languages, when applicable).

Statistical Analysis Plan

A sample size of 105 subjects per arm was planned to provide at least 80% power at a nominal 2-sided alpha level of 0.05 to detect a 7.4-point reduction in PANSS Total Score change from baseline to Week 6 for brexpiprazole versus placebo assuming a standard deviation (SD) of 19 with a 1:1:1 allocation ratio. Therefore, the overall sample size of this trial was planned to be 315 subjects.

The following analysis populations were defined for this study:

- **Randomized Sample**: All subjects who are randomized into the trial.
- **Safety Sample**: All subjects who are randomized into the trial and who receive at least one dose of IMP.
- **Efficacy Sample**: All subjects who are randomized into the trial who take at least one dose of IMP and who have a baseline and at least one postbaseline efficacy evaluation for the PANSS Total Score.

All efficacy analyses were based on the efficacy sample.

Primary efficacy analysis for PANSS Total Score:

The primary estimand was defined by the Applicant as:

- Population: Adolescents (13 to 17 years old) with a primary diagnosis of schizophrenia who would benefit from pharmacological treatment.
- Endpoint: Change from Baseline to Week 6 in the PANSS Total Score
- Intercurrent Events: Refers to premature treatment discontinuation (i.e., early dropout) prior to Week 6 attributable to adverse events, lack of efficacy, withdrawal of consent/assent, or any other causes. The intercurrent event was handled through the hypothetical strategy.
- Treatment condition: one of the randomized treatment groups of the following per protocol: brexpiprazole, aripiprazole or placebo
- Population-level summary: Difference in endpoint means between the brexpiprazole arm and the placebo arm.

The Applicant selected the hypothetical strategy to evaluate the pharmacological effect had no withdrawals occurred. Subjects who withdraw from IMP treatment either could have lost their treatment effect had the subjects not taken any other treatment after withdrawal or could have had their treatment effect masked had the subjects taken other treatment after withdrawal. This would mean that any observations made after subjects stop IMP would most likely not contribute relevant information about the treatment effect of the drug. Due to this strategy, the last efficacy assessment after premature trial discontinuation was assessed only once at the Early Termination Visit.

A restricted maximum likelihood-based mixed-effects model for repeated measures (MMRM) was used to analyze the primary efficacy endpoint in the Efficacy Sample. The MMRM model included fixed-effect factors of treatment, (pooled) trial site, visit, treatment by visit interaction, and fixed effect covariates of baseline and baseline by visit interaction applied to longitudinal change from baseline from Week 1 to Week 6 in PANSS Total Score based on all available data. The Kenward-Roger approximation was used to estimate denominator degrees of freedom with an unstructured covariance matrix. Least squares mean change with standard error (SE) and the associated 95% confidence interval (CI) were presented by treatment group. Estimated treatment difference along with the 95% CI and the corresponding p-value for the treatment effects at Week 6 were reported.

Based on the hypothetical strategy, the Applicant considered the event of withdrawing study medication as missing at random (MAR). All missing data were handled by the MMRM methodology based on all data from protocol-specified visits in the efficacy sample under the assumption of MAR. As sensitivity analyses, multiple imputation was used to explore data missing mechanisms of missing not at random (MNAR). The Applicant also provided a tipping point analysis.

Statistical reviewer comment: *The Applicant selected a hypothetical strategy as the primary analysis to keep consistency with the analyses for the corresponding adult trials, despite concerns raised by the Agency. The Applicant also provided sensitivity analyses using alternative MNAR assumptions. The results of the sensitivity analyses are consistent with the primary analysis, mainly due to low rate of occurrence of the intercurrent event of study medication*

withdrawal. Refer to Section 11.4.1.1.3 of the clinical study report.

There was no multiple testing procedure to control the overall Type I error, and as such, only the primary analysis for the primary efficacy endpoint can be considered multiplicity protected. Other efficacy results are considered exploratory.

Of note, the pooling of study sites in the analysis model was pre-specified and necessary due to small numbers of subjects at some sites.

Protocol Amendments

There were three global amendments to the protocol. Pertinent changes to the study protocol are highlighted below. In addition, on July 24, 2020, an addendum to the protocol was added to accommodate the COVID-19 pandemic. To ensure subject safety and maintain protocol requirements, in-person visits were replaced with virtual visits as deemed necessary.

- Amendment 1 (August 28, 2018)
  - Removed inclusion criterion for previous response to antipsychotic treatment.
  - Removed inclusion criterion for history of relapse or exacerbation of symptoms when not receiving antipsychotic treatment.
  - Increased possible sample size to 160 per arm.
  - Added exclusion criterion of known poor metabolizers CYP2D6 or CYP3A4.
  - Modified exclusion criterion for subjects considered treatment resistant to antipsychotic medication.
  - Added exclusion criterion for subjects known to have medication compliance issues that lead to IM depot medication use.
  - Removed exclusion of subjects exposed to brexpiprazole.
- Amendment 2 (June 16, 2020)
  - This amendment served to introduce a COVID-19 Addendum for any protocol-specified activities that were not able to be performed or could not be performed due to COVD-19 considerations.
- Amendment 3 (July 5, 2022)
  - Replaced the previous sample size of 387 subjects in Section 7.1 with the reduced sample size to 315 subjects (105 subjects per arm).
  - Inserted the new power calculated for the study based on the reduced sample size (80%) in Section 7.1.
  - Changed the definition of Efficacy Sample in Section 7.2 to at least 1 postbaseline efficacy evaluation for the PANSS Total Score.
  - Added a statement regarding the primary endpoint analysis that the comparison between brexpiprazole and placebo would be tested at a 0.05 (2-sided) significance level.
  - Added a definition for remission to the secondary efficacy endpoint in Section 7.4.3 and Section 3.5.2.1 (based on the aripiprazole Trial 31 03-239 and Trial 331-10-232).
  - Deleted the use of the log rank test for testing differences in time from randomization to remission in Section 7.4.2 for consistency with other brexpiprazole

studies.
- Changed the analysis sample in Section 7.5 to the Randomization Sample.

There were three country specific protocols used in their respective countries with the relevant alterations to the general protocol outlined below.

- Poland (July 24, 2019): Created at the request of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland. Indicated in the eligibility criteria the conditions under which the postponement of treatment in the children would not pose a threat to them according to the investigator.
- Bulgaria (August 26, 2019): Created at the request of the Bulgarian Drug Agency. Required inpatient hospitalization for all subjects.
- Hungary (March 21, 2019; Amendment 1: May 29, 2019]: Created at the request of the Hungarian Competent Authority. Limited trial population age range to age 15 to 17 years only, required inpatient hospitalization, and clarified the enrollment criteria related to liver function tests.

Clinical Reviewer's Comments: *There are no major concerns that these protocol amendments negatively impacted the interpretation of study results.*

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the trial was conducted in compliance with Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consent or assent had to be obtained from subjects and/or their legally acceptable representative prior to trial procedures being performed. The Institutional Review Board or Independent Ethics Committee at each respective center approved the informed consent form, protocol, and amendments.

Financial Disclosure

Statements of financial interests were requested by Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) from 102 principal investigators and 477 sub-investigators (none of which were an employee of OPDC). As of August 20, 2024, OPDC received 579 financial disclosers back and no financial disclosure information was obtained from two sub-investigators. Of the three principal investigators that had financial interest information to disclose, all were from sites that did not enroll any subjects in the trial.

Real or potential competing interests of Data Monitoring Committee (DMC) members were required to be disclosed to OPDC and the DMC Medical Committee Manager by completing a Data Monitoring Committee Conflict of Interest Declaration Form and the Otsuka/Lundbeck Financial Disclosure Form. DMC members with actual conflicts of interest as determined by OPDC, were requests to resign.

Subject Disposition

Table 6 presents the subject disposition for the Randomized Sample. The number of subjects screened was 376, and 316 subjects were randomized to IMP (brexpiprazole n=110, aripiprazole n=102, and placebo n=104). All randomized subjects (n=316 [100%]) received at least one dose of double-blind IMP. Of the randomized subjects, all 316 were analyzed for safety and 314 (99.4%) were analyzed for efficacy. Postbaseline assessments for PANSS Total Score were missing for the two subjects (one in the aripiprazole group and one in the placebo group) that were excluded from the Efficacy Sample. During the trial, 6.3% of the subjects (n=20; brexpiprazole n=3 [2.7%], aripiprazole n=5 [4.9%], placebo n=12 [11.5%]) discontinued the trial. Discontinuations were primarily due to withdrawal by caregiver (n=9 [2.8%]), withdrawal by subject (n=3 [0.9%]), lack of efficacy (n=3 [0.9%]), and AEs (n=3 [0.9%]).

Table 6: Subject Disposition (Randomized Sample, Study 331-10-234)

	Brexpiprazole 2-4 mg (N=110)	Aripiprazole 10-20 mg (N=102)	Placebo (N=104)	Total (N=316)
COMPLETED	107 (97.3)	97 (95.1)	92 (88.5)	296 (93.7)
DISCONTINUED	3 (2.7)	5 (4.9)	12 (11.5)	20 (6.3)
ADVERSE EVENT	0	1 (1.0)	2 (1.9)	3 (0.9)
LACK OF EFFICACY	0	0	3 (2.9)	3 (0.9)
LOST TO FOLLOW-UP	1 (0.9)	0	0	1 (0.3)
PREGNANCY	0	1 (1.0)	0	1 (0.3)
WITHDRAWAL BY PARENT REPRESENTATIVE	1 (0.9)	3 (2.9)	5 (4.8)	9 (2.8)
WITHDRAWAL BY SUBJECT	1 (0.9)	0	2 (1.9)	3 (0.9)

Source: Clinical reviewer created using Applicant's adsl.xpt dataset

Clinical Reviewer's Comments: *There was a higher rate of discontinuation of subjects in the placebo group (11.5%) versus the brexpiprazole group (2.7%). Discontinuations in the placebo group due to lack of efficacy are expected. Most subjects discontinued the study due to withdrawal (either by the subject or the parent). It is unclear how many of these withdrawals are actually related to lack of efficacy versus other reasons.*

Protocol Violations/Deviations

The Applicant reviewed all collected protocol deviations for clinical relevance. The Applicant claims that none of the deviations were considered to have an impact on the outcome of the trial. A summary of trial protocol deviations is presented in Table 7. During the trial, major protocol deviations occurred for 102 subjects (32.3%) (brexpiprazole n=40 [36.4%], aripiprazole n=30 [29.4%], and placebo n=32 [30.8%]).

Table 7: Protocol Deviations (Safety Sample, Study 331-10-234)

	Brexpiprazole 2-4 mg (N=110)	Aripiprazole 10-20 mg (N=102)	Placebo (N=104)	Total (N=316)
Protocol Deviation Type				
COVID-19	1 (0.9)	0	0	1 (0.3)
DOSING	19 (17.3)	14 (13.7)	12 (11.5)	45 (14.2)
INCLUSION/EXCLUSION CRITERIA	12 (10.9)	8 (7.8)	10 (9.6)	30 (9.5)
PROCEDURAL DEVIATIONS	6 (5.5)	8 (7.8)	6 (5.8)	20 (6.3)
PROHIBITED CONCOMITANT MEDICATIONS	10 (9.1)	7 (6.9)	9 (8.7)	26 (8.2)

Source: Clinical reviewer created using Applicant's adsl.xpt and addv.xpt datasets

Clinical Reviewer's Comments: *Most of the procedural deviations were related to the COVID-19 pandemic leading to virtual visits. In addition, there were a number of the protocol deviations related to procedural deviations in the context of war in the region of some of the study sites, so laboratory tests were unable to be processed. Therefore, less laboratory safety data were able to be obtained as a result. However, the laboratory results are not expected to be skewed by the missing data. Aside from dosing deviations, rates of deviations by category tended to be similar between the brexpiprazole group and placebo group and, therefore, unlikely to bias the results toward demonstrating a positive treatment effect. Numerically higher dosing deviations were present in the brexpiprazole group (17.3% of subjects) versus the placebo groups (11.5%). However, the dosing deviations tended to be brief and related to not following the titration schedule. Therefore, the dosing deviations are unlikely to substantially affect the efficacy results of the study.*

Demographic Characteristics

A summary of demographic characteristics of the Efficacy Sample is presented below in Table 8. Of the 314 subjects in the Efficacy Sample, 150 (47.8%) were male and 164 (52.2%) were female. The mean (SD) age for subjects was 15.3 (1.45) years at baseline (n=99 [31.5%] younger than 15-years-old and n=215 [68.5%] in the ≥ 15-year-old age group). Most randomized subjects were White (n=203 [64.6%]) and were not Hispanic or Latino (n=212 [67.5%]). Race was documented as Other in 80 subjects (25.5%); most of whom were of multiple races. Most subjects were recruited in Europe (n=177 [56.4%]), with a lower proportion of subjects in the U.S. (n=43 [13.7%]) and Mexico (n=94 [29.9%]).

Other notable baseline characteristics include the subjects' mean (SD) weight at baseline which was 64.7 (16.6) kg. Subjects in the placebo group had a higher mean weight (68.0 kg). The subjects' mean (SD) height was 166.3 (10.2) cm, mean (SD) BMI was 23.8 (5.0) kg/m^2, and mean (SD) waist circumference was 78.6 (13.8) cm.

In general, for most demographic and baseline characteristic parameters, the three treatment groups were similar.

Table 8: Demographic Characteristics in the Efficacy Sample (Study 331-10-234)

	Brexpiprazole 2-4 mg N=110	Aripiprazole 10-20 mg N=101	Placebo N=103	Total N=314
Sex, n (%)				
Female	58 (52.7)	56 (55.4)	50 (48.5)	164 (52.2)
Male	52 (47.3)	45 (44.6)	53 (51.5)	150 (47.8)
Age, years				
Mean (SD)	15.3 (1.50)	15.3 (1.41)	15.3 (1.44)	15.3 (1.45)
Median	16.0	16.0	15.0	16.0
IQR	14.0, 17.0	14.0, 17.0	14.0, 17.0	14.0, 17.0
Min, Max	13.0, 17.0	13.0, 17.0	13.0, 18.0	13.0, 18.0
Age categories, n (%)				
≥ 15 Years	74 (67.3)	72 (71.3)	69 (67.0)	215 (68.5)
13-14 Years	36 (32.7)	29 (28.7)	34 (33.0)	99 (31.5)
Race, n (%)				
American Indian or Alaska Native	2 (1.8)	1 (1.0)	4 (3.9)	7 (2.2)
Asian	1 (<1)	1 (1.0)	0	2 (<1)
Black or African American	8 (7.3)	7 (6.9)	6 (5.8)	21 (6.7)
White	70 (63.6)	66 (65.3)	67 (65.0)	203 (64.6)
Other	29 (26.4)	26 (25.7)	25 (24.3)	80 (25.5)
Missing	0	0	1 (1.0)	1 (<1)
Ethnicity, n (%)				
Hispanic or Latino	34 (30.9)	31 (30.7)	34 (33.0)	99 (31.5)
Not Hispanic or Latino	75 (68.2)	70 (69.3)	67 (65.0)	212 (67.5)
Unknown	0	0	1 (1.0)	1 (<1)
Other	1 (<1)	0	1 (1.0)	2 (<1)
Region, n (%)				
Europe	63 (57.3)	57 (56.4)	57 (55.3)	177 (56.4)
Mexico	32 (29.1)	30 (29.7)	32 (31.1)	94 (29.9)
USA	15 (13.6)	14 (13.9)	14 (13.6)	43 (13.7)

Abbreviations: IQR = interquartile range, SD = standard deviation
Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt;

Other Baseline Characteristics

Refer to Table 9, below, for a summary of baseline disease characteristics and scale scores. The baseline mean (SD) for PANSS Total Score was 101.4 (14.8), Negative Subscale score was 25.6 (5.6), and Positive Subscale score was 24.3 (4.8). The baseline mean (SD) for CGAS was 47.9 (11.8) and for CGI-S scores was 4.8 (0.7). Across the three treatment groups, the baseline disease characteristics parameters were similar.

Table 9: Baseline Disease Characteristics in the Efficacy Sample (Study 331-10-234)

	Brexpiprazole 2-4 mg N=110	Aripiprazole 10-20 mg N=101	Placebo N=103	Total N=314
PANSS Negative Sub-Score				
Mean (SD)	25.8 (5.6)	25.1 (5.2)	25.7 (6.0)	25.6 (5.6)
Min, Max	12, 45	11, 38	14, 45	11, 45
PANSS Positive Sub-Score				
Mean (SD)	24.2 (5.1)	24.9 (4.0)	24.0 (5.2)	24.3 (4.8)
Min, Max	12, 40	16, 38	11, 37	11, 40
PANSS Total Score				
Mean (SD)	101.1 (14.9)	101.0 (13.1)	102.2 (16.3)	101.4 (14.8)
Min, Max	80, 150	81, 138	81, 152	80, 152
CGI-S Severity Score				
Mean (SD)	4.8 (0.7)	4.8 (0.7)	4.7 (0.7)	4.8 (0.7)
Min, Max	3, 6	4, 6	3, 6	3, 6
CGAS Assessment Score				
Mean (SD)	48.1 (11.4)	47.9 (12.1)	47.6 (12.0)	47.9 (11.8)
Min, Max	22, 74	25, 80	30, 73	22, 80
P-Q-LES-Q Total Score				
Mean (SD)	40.8 (9.0)	41.5 (8.5)	41.2 (9.6)	41.2 (9.0)
Min, Max	19, 70	21, 60	25, 70	19, 70

Abbreviations: SD = standard deviation
Source: Statistical reviewer analysis using Applicant submitted datasets adpanss.xpt, adcgis.xpt, adcgas.xpt, adpqlesq.xpt;

Prior to receiving the IMP, the following primary antipsychotic medications were taken by subjects in the Safety Sample (brexpiprazole, aripiprazole, and placebo groups, respectively):

- Risperidone: 58.2% of subjects took (59.1%, 52.0%, and 63.5%)
- Olanzapine: 19.9% of subjects took (25.5%, 15.7%, and 18.3%)
- Haloperidol: 14.6% of subjects took (10.9%, 15.7%, and 17.3%)
- Aripiprazole: 13.9% of subjects took (10.9%, 13.7%, and 17.3%)
- Quetiapine: 10.4% subjects took (12.7%, 11.8%, and 6.7%)

A history of psychotropic medication prior to the double-blind period is summarized in Table 10. Across groups, 92.7% of subjects were on psychotic medications (95.5% in the brexpiprazole group, 89.2% in the aripiprazole group, and 93.3% in the placebo group) prior to the double-blind period. The vast majority (92.4%) of subjects were on antipsychotic medications prior to the double-blind treatment period (95.5% in the brexpiprazole group, 89.2% in the aripiprazole group, and 93.3% in the placebo group).

Table 10: Prior Psychotropic Medication Use (Study 331-10-234; Safety Sample)

	Brexpiprazole 2-4 mg (N=110)	Aripiprazole 10-20 mg (N=102)	Placebo (N=104)	Total (N=316)
Total	105 (95.5)	91 (89.2)	97 (93.3)	293 (92.7)
ADHD Medications – Stimulants	2 (1.8)	1 (1.0)	2 (1.9)	5 (1.6)
ADHD Medications – Non-stimulants	1 (0.9)	1 (1.0)	1 (1.0)	3 (0.9)
Antidepressants	17 (15.5)	7 (6.9)	11 (10.6)	35 (11.1)
Anxiolytics – Benzodiazepines	15 (13.6)	12 (11.8)	14 (13.5)	41 (13.0)
Anxiolytics – Non-benzodiazepines	0 (0)	3 (2.9)	1 (1.0)	4 (1.3)
Antipsychotic Medications	104 (94.5)	91 (89.2)	97 (93.3)	292 (92.4)
Mood Stabilizers	6 (5.5)	5 (4.9)	6 (5.8)	17 (5.4)
Sedative and Hypnotics	0 (0)	1 (1.0)	1 (1.0)	2 (0.6)

Source: Clinical reviewer created using Applicant's adsl.xpt and adcm.xpt datasets
ADHD Medications – Stimulants: dexamfetamine, dexmethyphenidate, lisdexamfetamine, methyphenidate
ADHD Medications – Non-stimulants: atomoxetine, clonidine
Antidepressants: amitriptyline, bupropion, citalopram, doxepin, escitalopram, fluoxetine, fluvoxamine, imipramine, mianserin, paroxetine, sertraline, venlafaxine
Anxiolytics – Benzodiazepines: alprazolam, bromazepam, clonazepam, diazepam, gidazepam, lorazepam
Anxiolytics – Non-benzodiazepines: hydroxyzine, propranolol, temgicoluril
Antipsychotic Medications: amisulpride, aripiprazole, cariprazine, chlorpromazine, chlorprothixene, clozapine, flupentixol, fluphenazine, haloperidol, levomepromazine, loxapine, lurasidone, olanzapine, paliperidone, periciazine, perphenazine, prochlorperazine, promazine, quetiapine, risperidone, sulpiride, thioridazine, tiapride, trifluoperazine, ziprasidone, zuclopenthixol
Mood Stabilizers: carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid/valproate
Sedative and Hypnotics: diphenhydramine, zolpidem

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant calculated treatment compliance by taking the number of tablets taken by the subject during the trial and dividing by the total number of planned tablets to be taken by the subject during the trial. Across the three treatment groups, similar compliance (as reported by the Applicant) was observed (brexpiprazole n=107 [97.3%], aripiprazole n=100 [98.0%], and placebo n=103 [99.0%] were ≥ 90% compliant with IMP).

During the treatment period, 22.8% of the Safety Sample reported using one or more concomitant medications. Medications that produce a calming effect on a person (termed by the Applicant as "psycholeptics," i.e., anticonvulsants, antidepressants, antipsychotic medications, benzodiazepines, and sleep aids) were the most frequently reported group of concomitant medications (9.1% of brexpiprazole subjects, 10.8% aripiprazole subjects, and 7.7% placebo subjects). Lorazepam was the most common of these used (5.5% brexpiprazole subjects, 5.9% aripiprazole subjects, and 4.8% placebo subjects). Use of oral benzodiazepines during screening was limited for treatment of agitation or insomnia.

Clinical Reviewer's Comment: *Overall assessment of demographic and baseline characteristics did not reveal any significant imbalances between the treatment groups. Clinically relevant results related to weight are based on change from baseline and, therefore, would not be affected by differences between groups at baseline. One subject was coded as 18 years old in the dataset, as month and day of birth defaulted to January 1 because this information was not collected for study sites in the subject's country. However, as verified with the Applicant, the*

subject was 17 at the timing of enrollment. The dataset was not corrected as the deviation in age would not result in meaningful change in demographic characteristics. Rates of prior use of antipsychotic medications indicate the population as a whole was not antipsychotic treatment-naïve. Use of the most common concomitant medication used during the treatment period, lorazepam, was similar in the brexpiprazole (5.5% of subjects) and placebo (4.8%) groups.

Efficacy Results – Primary Endpoint

The primary analysis results are presented in Table 11. Subjects in the brexpiprazole arm achieved a statistically significantly larger reduction in PANSS total score change from baseline to week 6 compared to subjects in the placebo arm, with a point estimate (95% CI) of -5.33 (-9.55, -1.10) points, corresponding to a p-value of 0.0136. Subjects in the active comparator arm (aripiprazole) also showed a nominally statistically significant treatment effect compared to placebo.

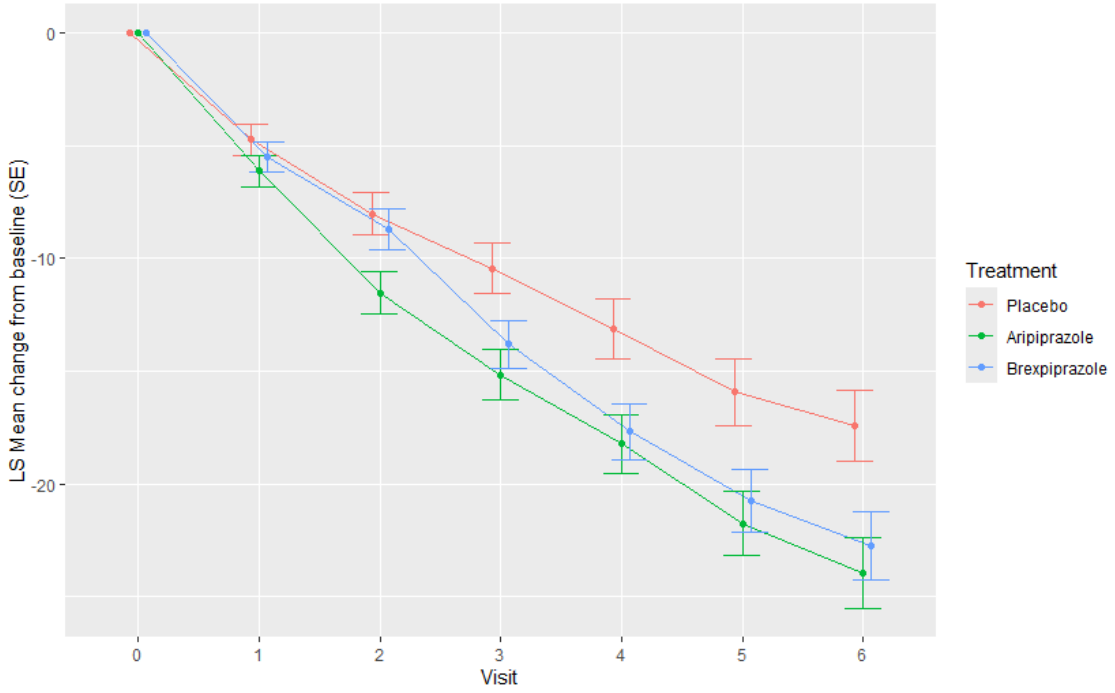
Table 11: Primary Analysis: PANSS Total Score Change from Baseline at Week 6 in the Efficacy Sample (Study 331-10-234)

	Brexpiprazole 2-4 mg N=110	Aripiprazole 10-20 mg N=101	Placebo N=103
Baseline, mean (SD)	101.06 (14.87)	101.03 (13.08)	102.17 (16.30)
Value at Week 6, mean (SD)	78.70 (17.53)	77.86 (17.70)	84.36 (21.02)
Missing, n (%)	4 (4%)	5 (5%)	11 (11%)
Change from baseline, adj.[1] mean (SE)	-22.75 (1.49)	-23.95 (1.57)	-17.42 (1.58)
Difference from Control, adj.[1] mean (adj.[1] CI)	-5.33 (-9.55, -1.10)	-6.53 (-10.8, -2.21)	-
p-value (adjusted[1])	0.0136	0.0032	-

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error
[1] Adjusted mean differences are from a mixed-effect model repeated measures method (MMRM) adjusting for treatment group, pooled site, and baseline score, estimating within-arm means at mean values of the covariates.
Source: Clinical Study Report Table 11.4.1-1 (Page 59); findings reproduced by the statistical reviewer using adpanss.xpt

The adjusted mean change from baseline in PANSS total score (+/- 1 SE) over the entire study period is presented in Figure 2. All study arms appear to show a continuous improvement in PANSS total score over the duration of the study. Both brexpiprazole and aripiprazole arms show a clear separation from placebo by Visit 3 (Week 3). The estimated adjusted means and SE at Visit 6 are as presented in Table 11 above.

Figure 2: Primary Analysis: PANSS Total Score Change from Baseline by Visit in the Efficacy Sample (Study 331-10-234)



Source: Reviewer's results, consistent with Figure 11.4.1.1.2-1 of the clinical study report.

The adjusted mean change from baseline in PANSS total score by study summary statistics over the entire study period (corresponding to Figure 2) are presented in Table 12.

Table 12: Primary Analysis: PANSS Total Score Change from Baseline by Visit in the Efficacy Sample (Study 331-10-234)

Visit	Treatment Arm	Adjusted Mean Change from Baseline	Std. Error	Treatment Comparison vs Placebo (95% CI)
Week 1	Brexpiprazole 2-4 mg	-5.49	0.67	-0.76 (-2.52, 0.99)
	Aripiprazole 10-20 mg	-6.11	0.70	-1.39 (-3.18, 0.41)
	Placebo	-4.73	0.69	NA
Week 2	Brexpiprazole 2-4 mg	-8.72	0.89	-0.70 (-3.12, 1.72)
	Aripiprazole 10-20 mg	-11.53	0.93	-3.50 (-5.97, -1.04)
	Placebo	-8.02	0.92	NA
Week 3	Brexpiprazole 2-4 mg	-13.82	1.07	-3.38 (-6.35, -0.40)
	Aripiprazole 10-20 mg	-15.17	1.12	-4.73 (-7.77, -1.69)
	Placebo	-10.44	1.12	NA
Week 4	Brexpiprazole 2-4 mg	-17.69	1.25	-4.56 (-8.07, -1.05)
	Aripiprazole 10-20 mg	-18.23	1.31	-5.10 (-8.69, -1.52)
	Placebo	-13.13	1.32	NA
Week 5	Brexpiprazole 2-4 mg	-20.74	1.39	-4.81 (-8.71, -0.91)
	Aripiprazole 10-20 mg	-21.74	1.45	-5.81 (-9.80, -1.82)
	Placebo	-15.94	1.46	NA
Week 6	Brexpiprazole 2-4 mg	-22.75	1.49	-5.33 (-9.55, -1.10)
	Aripiprazole 10-20 mg	-23.95	1.57	-6.53 (-10.8, -2.21)
	Placebo	-17.42	1.58	NA

Source: Clinical Study Report Table CT-5.2.1 (Page 261); findings reproduced by the statistical reviewer using adpanss.xpt

Sensitivity analyses of the primary efficacy endpoint under the MNAR assumption were conducted by the Applicant. Delta adjustment multiple imputation was applied to investigate the departure from MAR assumption. The delta was varied 0% to 100% by 10% of the observed treatment difference between brexpiprazole and placebo from the primary analysis of MMRM for each visit. By progressively increasing delta, the sensitivity analysis explored the tipping point at which conclusion from the primary analysis was overturned. The Applicant used four scenarios:

1) Dropout reasons due to AE as MNAR
2) Dropout reasons due to AE or lack of efficacy as MNAR
3) Dropout reasons due to either AE or subject withdrew consent as MNAR
4) All dropouts as MNAR

The results for all scenarios showed the primary results are very robust to missing data assumptions where, for all presented deltas, the comparison to placebo remains statistically significant. Refer to Table CT-5.2.7.2 of the Applicant's clinical study report. Additional sensitivity analyses by the Applicant included reference-based imputation and LOCF. The results of these analyses also supported the robustness of primary analysis results.

Statistical reviewer comment: *The results are very robust to missing data or modeling choices due to large magnitude of effect and low amount of missing data. As seen in the disposition section, there are only 20 discontinued subjects, 12 of which were in the placebo arm. As such, any reasonable sensitivity analysis of missing data does not have a notable effect on the results, as seen in the sensitivity analyses provided by the Applicant. The model was also not sensitive to the choice of covariance matrix.*

Primary Endpoint by Subgroups

Exploratory subgroup analyses of the primary endpoint are presented below (Table 13). The purpose of the subgroup analyses was to explore whether there was an inconsistent trend in efficacy across subgroups. Because the study only enrolled adolescents, subgroup analyses by age are omitted. Consistent with the Applicant's statistical analysis plan, the subgroup analyses were yielded by subsetting the primary dataset to the subgroup of interest and applying MMRM model with fixed effect of treatment, visit, treatment by visit interaction, baseline value, and baseline by visit interaction as covariate, and with an unstructured variance-covariance matrix structure, unless small size of the subgroup required the use of AR(1) structure. Results for groups of Asian race and Unknown race are omitted due to very low numbers (n=2 and 1, respectively)

The results from any subgroup analyses are considered exploratory and should be interpreted with caution, because the study was not designed or powered to compare treatment effects across subgroups. The results were generally consistent across subgroups and no obvious outlier subgroup was identified. The majority (65%) of the subjects were white and, as such, the

results for other races generally yielded very wide confidence intervals; hence, rendering uninformative results. The majority (56%) of subjects were from Europe, with only 14% in US. However, the results in the US supported efficacy and were generally consistent with the results in Europe.

Table 13: Exploratory Subgroup Analysis: PANSS Total Score Within Subgroups of Interest in the Efficacy Sample (Study 331-10-234)

	Brexpiprazole 2-4 mg N=110	Aripiprazole 10-20 mg N=101	Placebo N=103
Sex: Male			
N	52	45	53
Baseline, mean (SD)	102.96 (16.47)	101.02 (10.77)	103.75 (15.15)
Value at Week 6, mean (SD)	80.61 (19.99)	82.00 (14.33)	86.72 (22.03)
Missing, n (%)	3 (6%)	1 (2%)	7 (13%)
Change from baseline, adj.[1] mean (SE)	-21.6 (2.2)	-18.7 (2.4)	-16.3 (2.2)
Difference from Control, adj.[1] mean (adj.[1] CI)	-5.26 (-11.50, -0.94)	-2.40 (-8.85, 4.06)	-
Sex: Female			
N	58	56	50
Baseline, mean (SD)	99.36 (13.18)	101.04 (14.77)	100.48 (17.43)
Value at Week 6, mean (SD)	77.05 (15.09)	74.37 (19.57)	82.00 (19.92)
Missing, n (%)	1 (2%)	4 (7%)	4 (8%)
Change from baseline, adj.[1] mean (SE)	-22.9 (2.0)	-27.0 (2.0)	-17.6 (2.2)
Difference from Control, adj.[1] mean (adj.[1] CI)	-5.24 (-11.10, 0.58)	-9.36 (-15.20, -3.47)	-
Race: White			
N	70	66	67
Baseline, mean (SD)	102.07 (15.10)	101.32 (12.56)	101.87 (16.82)
Value at Week 6, mean (SD)	79.75 (17.58)	79.25 (18.17)	84.98 (20.92)
Missing, n (%)	2 (3%)	2 (3%)	7 (10%)
Change from baseline, adj.[1] mean (SE)	-21.6 (1.8)	-22.6 (1.9)	-15.9 (1.9)
Difference from Control, adj.[1] mean (adj.[1] CI)	-5.71 (-10.90, -0.54)	-6.64 (-11.90, -1.40)	-
Race: Black or African American			
N	8	7	6
Baseline, mean (SD)	95.38 (10.74)	97.29 (7.48)	99.17 (6.85)
Value at Week 6, mean (SD)	69.14 (13.93)	70.17 (22.11)	86.75 (22.35)
Missing, n (%)	1 (13%)	1 (14%)	2 (33%)
Change from baseline, adj.[1] mean (SE)	-26.9 (7.5)	-26.1 (7.6)	-4.0 (9.9)
Difference from Control, adj.[1] mean (adj.[1] CI)	-22.90 (-50.00, 4.24)	-22.10 (-49.30, 5.06)	-
Race: American Indian or Alaska Native			
N	2	1	4
Baseline, mean (SD)	99.50 (2.12)	95.00 (NA)	97.75 (20.66)
Value at Week 6, mean (SD)	71.00 (1.41)	64.00 (NA)	71.00 (15.81)
Missing, n (%)	0 (0%)	0 (0%)	0 (0%)
Change from baseline, adj.[1] mean (SE)	-28.1 (1.5)	-31.7 (0.1)	-26.8 (1.1)
Difference from Control, adj.[1] mean (adj.[1] CI)	-1.31 (-5.19, 2.56)	-4.94 (-7.39, -2.48)	-
Race: Other			
N	29	26	25
Baseline, mean (SD)	100.55 (16.01)	101.19 (15.87)	103.80 (16.44)
Value at Week 6, mean (SD)	80.32 (17.52)	75.79 (15.15)	83.91 (22.48)
Missing, n (%)	1 (3%)	2 (8%)	2 (8%)
Change from baseline, adj.[1] mean (SE)	-21.2 (3.0)	-25.2 (3.2)	-19.7 (3.3)
Difference from Control, adj.[1] mean (adj.[1] CI)	-1.47 (-10.30, 7.40)	-5.47 (-14.60, 3.70)	-
Region: Europe			
N	63	57	57
Baseline, mean (SD)	101.08 (14.13)	101.02 (12.47)	102.28 (16.67)
Value at Week 6, mean (SD)	78.46 (18.00)	79.30 (18.28)	86.66 (20.54)
Missing, n (%)	2 (3%)	1 (2%)	7 (12%)
Change from baseline, adj.[1] mean (SE)	-21.9 (1.8)	-21.8 (1.9)	-14.6 (2.0)
Difference from Control, adj.[1] mean (adj.[1] CI)	-7.33 (-12.60, -2.02)	-7.23 (-12.70, -1.80)	-

	Brexpiprazole 2-4 mg N=110	Aripiprazole 10-20 mg N=101	Placebo N=103
Region: Mexico			
N	32	30	32
Baseline, mean (SD)	102.78 (18.21)	101.80 (15.41)	104.41 (17.72)
Value at Week 6, mean (SD)	82.97 (15.47)	76.68 (14.73)	82.83 (20.93)
Missing, n (%)	1 (3%)	2 (7%)	2 (6%)
Change from baseline, adj.[1] mean (SE)	-20.4 (2.6)	-25.4 (2.7)	-21.4 (2.6)
Difference from Control, adj.[1] mean (adj.[1] CI)	1.07 (-6.27, 8.42)	-3.94 (-11.50, 3.60)	-
Region: USA			
N	15	14	14
Baseline, mean (SD)	97.33 (9.01)	99.43 (10.56)	96.57 (9.68)
Value at Week 6, mean (SD)	70.29 (17.71)	73.92 (21.69)	78.58 (23.56)
Missing, n (%)	1 (7%)	2 (14%)	2 (14%)
Change from baseline, adj.[1] mean (SE)	-27.5 (5.3)	-25.7 (5.5)	-15.6 (5.7)
Difference from Control, adj.[1] mean (adj.[1] CI)	-11.90 (-27.60, 3.82)	-10.10 (-26.20, 5.96)	-

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error

[1] Adjusted mean differences are from a mixed-effect model repeated measures method (MMRM) adjusting for treatment group and baseline score.

Source: Clinical Study Report Tables CT-5.2.9.1 to CT-5.2.9.9 pages 289 to 307; confirmed by the statistical reviewer

Data Quality and Integrity

The integrity of the study conduct and results did not appear to be significantly impacted by COVID-19. Approximately 37% of the subjects completed or discontinued the trial prior to the start of the pandemic on March 13, 2020. The primary analysis results were generally similar between these subjects and those who had some data collected after March 13, 2020. The main mitigation implemented by the Applicant was the addition of virtual visits in the COVID-19 addendum to the protocol.

No other data quality and integrity concerns were identified during the review.

Efficacy Results – Secondary and other relevant endpoints

Due to the lack of multiple testing procedure, only the primary endpoint is multiplicity protected. As such, any other analyses are considered purely exploratory. Table 14 contains the results for selected secondary endpoints presented by the Applicant. The brexpiprazole arm achieved a reduction in PANSS Positive and Negative subscore change from baseline to Week 6, with a point estimate (95% CI) of -1.44 (-2.65, -0.22) points and -0.88 (-2.04, 0.28) points respectively. Therefore, it appears the effect of brexpiprazole was generally similar on both Positive and Negative subscores of PANSS, and the overall effect on the primary endpoint was not primarily driven by either subscore.

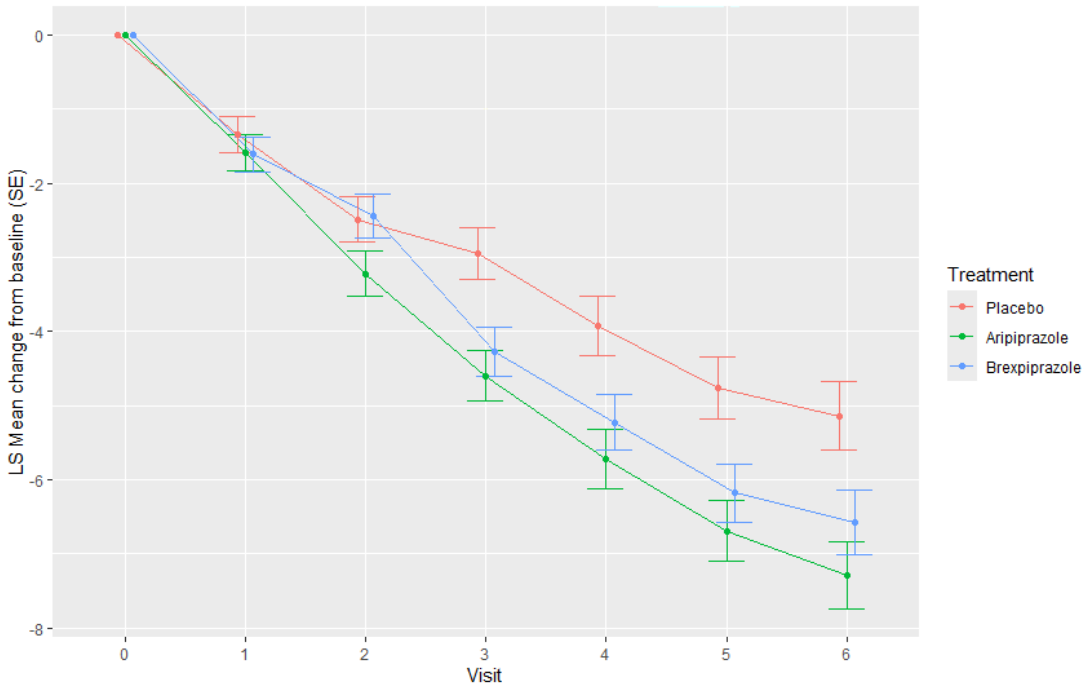
Table 14: Secondary Analysis: PANSS Positive and Negative Subscore Change from Baseline at Week 6 in the Efficacy Sample (Study 331-10-234)

	Brexpiprazole 2-4 mg N=110	Aripiprazole 10-20 mg N=101	Placebo N=103
PANSS Positive Subscore			
Baseline, mean (SD)	24.20 (5.12)	24.87 (4.01)	23.96 (5.19)
Value at Week 6, mean (SD)	17.63 (4.96)	17.47 (4.63)	18.88 (6.01)
Missing, n (%)	4 (4%)	5 (5%)	11 (11%)
Change from baseline, adj.[1] mean (SE)	-6.58 (0.43)	-7.29 (0.45)	-5.14 (0.46)
Difference from Control, adj.[1] mean (adj.[1] CI)	-1.44 (-2.65, -0.22)	-2.15 (-3.40, -0.91)	-
PANSS Negative Subscore			
Baseline, mean (SD)	25.77 (5.62)	25.11 (5.24)	25.75 (5.97)
Value at Week 6, mean (SD)	21.07 (5.40)	20.73 (5.84)	21.90 (5.89)
Missing, n (%)	4 (4%)	5 (5%)	11 (11%)
Change from baseline, adj.[1] mean (SE)	-4.70 (0.41)	-4.77 (0.43)	-3.82 (0.44)
Difference from Control, adj.[1] mean (adj.[1] CI)	-0.88 (-2.04, 0.28)	-0.95 (-2.14, 0.24)	-

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error
[1] Adjusted mean differences are from a mixed-effect model repeated measures method (MMRM) adjusting for treatment group, pooled site, and baseline score, estimating within-arm means at mean values of the covariates.
Source: Clinical Study Report Table 11.4.1.2.1-1 (Page 65); findings reproduced by the statistical reviewer using adpanss.xpt

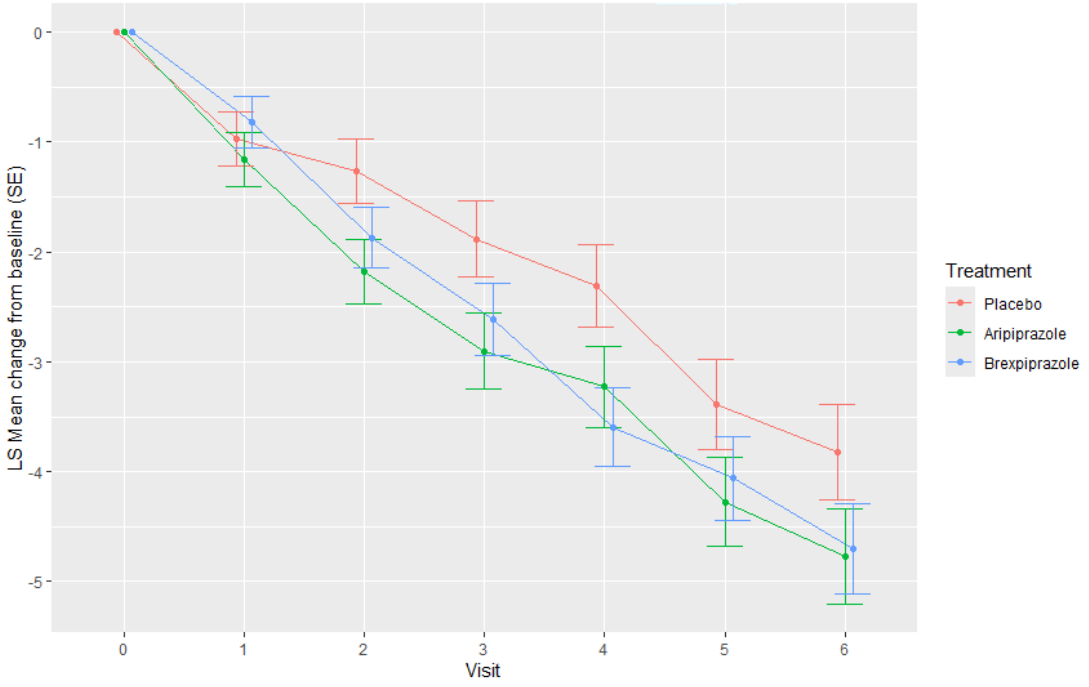
The adjusted mean changes from baseline in PANSS Positive and Negative subscore (+/- 1 SE) over the entire study period are presented in Figure 3 and Figure 4, respectively. Similar to the primary endpoint of PANSS total score, all study arms appear to show a continuous improvement over the duration of the study. Both brexpiprazole and aripiprazole arms show a continuous separation from placebo by or before Visit 3 (Week 3). The estimated adjusted means and SE at Visit 6 are as presented in Table 12 above.

Figure 3: Secondary Analysis: PANSS Positive Subscore Change from Baseline by Visit in the Efficacy Sample (Study 331-10-234)



Source: Reviewer's results, consistent with Figure 11.4.1.2.1-1 of the clinical study report.

Figure 4: Secondary Analysis: PANSS Negative Subscore Change from Baseline by Visit in the Efficacy Sample (Study 331-10-234)



Source: Reviewer's results, consistent with Figure 11.4.1.2.1-2 of the clinical study report.

Additional secondary efficacy results presented by the Applicant included CGAS score, CGI-S score, and response and remission rates. The additional secondary efficacy results were also generally supportive of the primary endpoint results.

Dose/Dose Response

Given that Study 331-10-234 implemented a flexible-dose treatment paradigm and did not include fixed-dose treatment arms, the underlying dose-response relationship is confounded by carry-over pharmacodynamic effects from prior dosages.

Durability of Response

Study 331-10-234 was a 6-week trial. Therefore, durability of effect beyond the 6-week primary endpoint is not discernible.

Persistence of Effect

Given that the Applicant did not collect efficacy measures during the follow-up period or include an off-treatment period, the persistence of effect is not discernible.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Additional Analyses Conducted on the Individual Trial

Not applicable.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

Study 331-10-234 was the only trial submitted by the Applicant. Therefore, this section is not applicable.

8.1.4. Integrated Assessment of Effectiveness

On January 13, 2020, the Agency issued a General Advice letter informing the Applicant 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 given similarity of disease in adults and pediatric patients. Brexpiprazole was approved in 2021 for the treatment of pediatric patients aged 13 to 17 years with schizophrenia based on extrapolation of effectiveness from adults supported by a PK analysis demonstrating that similar exposure-response in adult and pediatric subjects. Data from Study 331-10-234 are consistent with the findings of the review that supported approval of brexpiprazole for pediatric patients with schizophrenia in 2021.

8.2.Review of Safety

8.2.1. Safety Review Approach

The safety evaluation for this supplemental application is primarily based on analyses of Study 331-10-234. Details regarding the study design and subject population are provided in Section 8.1.1 of this review. The safety data generated from Study 331-10-234 provided double-blind, placebo-controlled data in pediatric subjects (age 13 to 17 years) to inform brexpiprazole use in patients 13 to 17 years of age with schizophrenia.

The safety of brexpiprazole for use in the pediatric population is also based on clinical safety information generated with the clinical development for other indications and included in the product information. The current product information describes safety data in pediatric subjects (age 13 to 17 years) with schizophrenia and pediatric subjects (age 5 to 17 years) with autism spectrum disorder (based on short-term, placebo-controlled and a long-term, open label study). The long-term, open-label Study 331-10-236 is still ongoing.

Given that the Applicant only conducted one placebo-controlled study, the presented analysis did not include any pooling of studies. The Safety Sample was based on subjects who were randomized and received at least one dose of brexpiprazole. Review of the safety data included the following descriptive analyses:

- Adverse events (e.g., extrapyramidal symptoms [EPS], metabolic changes, prolactin changes)
- Physical examination and vital sign measurements
- ECG parameters
- Laboratory measurements
- C-SSRS assessments for suicidal ideation and behavior
- EPS-related scales (i.e., Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], and Simpson-Angus Scale [SAS]).

8.2.2. Review of the Safety Database

Overall Exposure

Overall, a total of 433 pediatric subjects (schizophrenia and autism spectrum disorder) have been exposed to brexpiprazole in the clinical development program of brexpiprazole to date. For short-term studies, 119 pediatric subjects have been exposed and for long-term studies, 314 subjects have been exposed to brexpiprazole.

In response to an information request, the Applicant provided safety information from the open-label extension Study 331-10-236. As of September 13, 2025, 294 subjects were exposed to brexpiprazole (prior brexpiprazole group n=98, prior aripiprazole group n=89, prior placebo group n=87, and de novo group n=20) in Study 331-10-236 with 73.8% being exposed for at

least one year. Study 331-10-236 is ongoing and database lock is planned for June 2025.

A total of 316 subjects (Safety Sample) were exposed to at least one dose of brexpiprazole in Study 331-10-234. The average duration of exposure to study drug for the brexpiprazole group was 41.1 days (4.1 SD), for the aripiprazole group was 41.7 days (6.1 SD), and for the placebo groups 41.4 days (6.2 SD). Approximately 90.9% of subjects in the brexpiprazole group, 88.2% of the aripiprazole group, and 80.8% of the placebo group duration of exposure to study drug was least 6 weeks as depicted in Table 15.

Table 15: Number of Subjects by Duration of Exposure (Study 331-10-234; Safety Sample)

	Brexpiprazole 2-4 mg (N=110)	Aripiprazole 10-20 mg (N=102)	Placebo (N=104)	Total (N=316)
≥1 dose	110 (100%)	102 (100%)	104 (100%)	306 (100%)
≥4 weeks	108 (98.2%)	98 (96.1%)	96 (92.3%)	302 (95.6%)
≥6 weeks	100 (90.9%)	90 (88.2%)	84 (80.8%)	274 (86.7%)

Source: Clinical reviewer created using Applicant's adsl.xpt dataset

Adequacy of the safety database:

The ability to review the safety of brexpiprazole in the pediatric population age 13 to 17 years old with schizophrenia is limited by the relatively small size of the safety population (with 110 subjects in the brexpiprazole) and flexible-dosing regimen (as opposed to a more informative fixed-dosing regimen). Although the safety sample is limited, safety data from the 6-week Study 331-10-234 are sufficient to assess the short-term safety of brexpiprazole in the pediatric population (age 13 to 17 years old) and comparisons of the available data relative to adults are able to inform product labeling.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The application was submitted in eCTD format in which both ADAM and SDTM data were provided. The submission is of acceptable quality. No major concerns about data integrity were noted. OSI inspection concluded inspected clinical data at the respective sites appeared reliable for the primary efficacy endpoint and prolactin levels (see Section 4.1).

Categorization of Adverse Events

The Applicant assessed for AEs at each study visit throughout the treatment period and at follow-up (21 days after last dose of the investigational medicinal product [IMP]). AEs were categorized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA; version 25.1). The Applicant defined treatment-emergent adverse events (TEAEs) as an AE that started after start of IMP treatment; or if the event was continuous from baseline and was serious, IMP related, or resulted in death, discontinuation,

interruption or reduction of IMP.

Clinical Reviewer's Comment: *The Applicant's AE monitoring, severity determinations, and mapping of verbatim-to-preferred terms are overall acceptable. However, the mapping for eye movement disorders were better characterized as extrapyramidal disorder (EPS) based on verbatim descriptions.*

This reviewer grouped the following preferred terms together:

- *Extrapyramidal Disorder: blepharospasm, dystonia, extrapyramidal disorder, eye movement disorder, hypokinesia, muscle rigidity, musculoskeletal stiffness, psychomotor hyperactivity, tremor*
- *Somnolence: hypersomnia, sedation, somnolence*

Routine Clinical Tests

The Applicant included adequate clinical assessments and tools for Study 331-10-234. These included an array of serum chemistry and hematology, urinalysis, vital sign, and ECG assessments (see Table 2: Schedule of Assessments). Extrapyramidal symptoms were assessed by means of the Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS). The Columbia-Suicide Severity Rating Scale (C-SSRS) was used to monitor for suicidal ideation and behavior.

8.2.4. Safety Results

Deaths

No deaths occurred in Study 331-10-234.

Serious Adverse Events

In Study 331-10-234, there were 5 serious adverse events (SAEs) reported for 5 subjects (1.6%); one subject in the brexpiprazole group, one subject in the aripiprazole group, and three subjects in the placebo group (Table 16). All were related to worsening schizophrenia/ psychosis. SAEs do not constitute a new safety signal.

Table 16: Serious adverse events in Study 331-10-234 (Safety Sample)

	Treatment Group	Serious Adverse Event	Description	Timing	Severity	Relation to Study Drug (Applicant)	Action Taken	Outcome
1	Placebo	Worsening Schizophrenia	13-year-old withdrew on Day 17 due to lack of efficacy, symptoms worsened and on Day 20 subject was hospitalized for worsening schizophrenia	Day 20-38	Moderate	Not related	Not applicable	Recovered/ Resolved

2	Aripiprazole	Worsening of psychotic symptoms / Psychotic disorder	13-year-old hospitalized for worsening psychotic symptoms, concurrently experienced pruritis of hands; continued in study	Day 26-29	Mild	Not related	Dose reduced (per Applicant due to pruritis)	Recovered/ Resolved
3	Placebo	Worsening of psychotic symptoms / Psychotic disorder	17-year-old withdrew from study as a result of increased psychotic symptoms and was hospitalized	Day 8-37	Moderate	Not related	Study drug withdrawn (Day 12)	Recovered/ Resolved
4	Brexpiprazole	Worsening of symptoms of schizophrenia / Schizophrenia	17-year-old developed worsening symptoms of schizophrenia and was hospitalized; continued in the study	Day 14-38	Severe	Not Related	Dose not changed	Recovered/ Resolved
5	Placebo	Worsening of schizophrenia / Schizophrenia	17-year-old developed worsening symptoms of schizophrenia and was hospitalized; parent withdrew the subject from the study on Day 9	Day 6-19	Mild	Not related	Study drug withdrawn Day 9 (when subject withdrew)	Recovered/ Resolved

Source: Clinical reviewer created using Applicant's Clinical Study Report (Study 331-10-234)

Only one SAE occurred in a subject exposed to brexpiprazole (subject 4 in Table 16); this was a 17-year-old male who was randomized to the brexpiprazole group. On Day 13, the subject was reported to be agitated and restless. Additionally, the subject was reported to have decreased sleep. On Day 14, the subject was brought to the hospital and hospitalized for schizophrenia. Study medication was continued, and diazepam was added as a concomitant medication Day 14 to Day 18. The subject stopped taking brexipiprazole on Day 32. PANSS total score was 94 on Day -14, 98 on Day 1, 91 on Day 8, 106 on Day 16, 99 on Day 32, and 99 on Day 42. The event was considered resolved on Day 38.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant reports three subjects (0.9%) in Study 331-10-234 (Table 17) to have had AEs leading to discontinuation. One subject in the aripiprazole group experienced akathisia and two subjects in the placebo group experienced worsening schizophrenia/psychosis leading to discontinuation. No subjects in the brexpiprazole group experienced AEs that led to discontinuation.

Table 17: Discontinuation Due to Adverse Events in Study 331-10-234 (Safety Sample)

	Treatment Group	Adverse Event Leading to Discontinuation	Description	Timing	Severity	Serious Adverse Event	Relation to Study Drug (Applicant)	Outcome
1	Placebo	Worsening of psychotic symptoms /Psychotic disorder	17-year-old withdrew from study as a result of increased psychotic symptoms and was hospitalized	Day 8-37	Moderate	Yes	Not Related	Recovered/ Resolved
2	Aripiprazole	Akathisia	14-year-old developed akathisia; on Day 19 the study drug was withdrawn and subject discontinued from the study	Day 18-19	Moderate	No	Related	Recovered/ Resolved
3	Placebo	Exacerbation of schizophrenia symptoms / Schizophrenia	16-year-old experienced worsening of schizophrenia symptoms; study drug was stopped on Day 29 and the subject was discontinued from the study	Day 23- 50	Moderate	No	Not Related	Recovered/ Resolved

Source: Clinical reviewer created using Applicant's Clinical Study Report (Study 331-10-234)

Clinical Reviewer's Comment: *Worsening instances of symptoms of schizophrenia are expected in subjects receiving placebo as they are not receiving active medication. Akathisia is a known side effect of antipsychotic medications. This reviewer agrees with the Applicant's assessment that akathisia was related to study drug. The Applicant did not code the 17-year-old subject with SAE of worsening symptoms of schizophrenia in the placebo group whose parent withdrew the subject on Day 9 (Table 16, subject 5) as an AE leading to discontinuation. It is possible there was another motivation for the parent's withdrawal of the subject. However, this is unlikely based on the limited information provided. Therefore, four subjects are considered to have discontinued from the study due to AE; none in the brexpiprazole group.*

Significant Adverse Events

There were no prespecified AEs of special interest for Study 331-10-234.

Three AEs were considered severe in Study 331-10-234. In the brexpiprazole group, one subject in the brexpiprazole group had an increased creatinine kinase (CK) level and one had worsening schizophrenia; these do not constitute new safety signals. In the placebo group, one subject experienced psychomotor hyperactivity.

Treatment Emergent Adverse Events and Adverse Reactions

A summary of the incidence of AEs occurring at a higher incidence in the brexpiprazole group than the placebo group and in at least 2% of subjects that received brexpiprazole is presented in Table 18. The AEs associated with brexpiprazole occurring in at least 2% of subjects and greater than placebo (in order of incidence relative to the brexpiprazole group) are EPS, headache, nausea, akathisia, and hypersomnia. AEs related to EPS were regrouped as EPS as outlined in Section 8.2.3. (b) (4) Regrouping terms related to somnolence as outlined in Section 8.2.3 showed no effect between groups (7.3% in the brexpiprazole group versus 6.7% in the placebo group).

Table 18: Incidence of Adverse Events Reported by ≥2% of Subjects Receiving Brexpiprazole and Greater than Placebo in Study 331-10-234 (Safety Sample)

	Brexpiprazole *(N = 110)*		***Aripiprazole*** *(N = 102)*		***Placebo*** *(N = 104)*		***Total*** *(N=316)*	
Preferred Term	*Events*	*n (% of subjects)*	*Events*	*n (% of subjects)*	*Events*	*n (% of subjects)*	*Events*	*n (% of subjects)*
Gastrointestinal Disorders								
Nausea	7	7 (6.4%)	4	4 (3.9%)	5	4 (3.8%)	16	15 (4.7%)
Nervous System Disorders								
Akathisia	4	4 (3.6%)	9	7 (6.9%)	3	3 (2.9%)	16	14 (4.4%)
Extrapyramidal Disorder*	8	7 (6.4%)	14	7 (6.9%)	3	3 (2.9%)	25	17 (5.4%)
Headache	7	7 (6.4%)	6	5 (4.9%)	5	5 (4.8%)	18	17 (5.4%)

*Extrapyramidal Disorder: blepharospasm, dystonia, extrapyramidal disorder, eye movement disorder, hypokinesia, muscle rigidity, musculoskeletal stiffness, psychomotor hyperactivity, tremor;
Abbreviations: BREX: brexpiprazole; ARIP: aripiprazole
Source: Clinical reviewer created using Applicant's adsl.xpt and adae.xpt datasets

Clinical Reviewer's Comment: *Overall, the AEs that occurred in Study 331-10-234 are consistent with the known safety profile of brexpiprazole.*

Laboratory Findings

In Study 331-10-234, laboratory testing (hematology, serum chemistry [including blinded prolactin], and urinalysis) was conducted at Screening, Day 1, Week 4, and Week 6 (end-of-treatment) visits. HbA1c and thyrotropin (TSH) were collected at Screening, Day 1, and Week 6 visits. Table 19 describes the mean changes from baseline to last visit in laboratory parameters for each treatment group. Overall, analysis of changes in laboratory measures did not indicate any clinically relevant differences between brexpiprazole and placebo in the pediatric study population except for prolactin as detailed below in Section 8.2.5.

Table 19: Baseline and Mean Changes from Baseline to Last Visit in Laboratory Assessments in Study 331-10-234 (Safety Sample)

		Brexpiprazole 2-4 mg (N=110)	Aripiprazole 10-20 mg (N=102)	Placebo (N=104)	Total (N=316)
ALANINE AMINOTRANSFERASE (U/L)					
Baseline	n	110	102	104	316
	Mean (SD)	-1.0 (16.27)	0.6 (15.28)	-1.9 (11.86)	-0.8 (14.62)
Change from Baseline	n	105	98	98	301
	Mean (SD)	-1.0 (16.27)	0.6 (15.28)	-1.9 (11.86)	-0.8 (14.62)
ALKALINE PHOSPHATASE (U/L)					
Baseline	n	110	102	104	316
	Mean (SD)	-0.9 (47.45)	-5.9 (27.53)	-2.3 (18.14)	-3.0 (33.71)
Change from Baseline	n	105	98	98	301
	Mean (SD)	-0.9 (47.45)	-5.9 (27.53)	-2.3 (18.14)	-3.0 (33.71)
ASPARTATE AMINOTRANSFERASE (U/L)					
Baseline	n	110	102	104	316
	Mean (SD)	-0.7 (8.21)	-2.6 (30.40)	-0.7 (8.16)	-1.3 (18.56)
Change from Baseline	n	105	98	98	301
	Mean (SD)	-0.7 (8.21)	-2.6 (30.40)	-0.7 (8.16)	-1.3 (18.56)
BILIRUBIN (mg/dL)					
Baseline	n	105	97	101	303
	Mean (SD)	-0.1 (0.28)	0.0 (0.21)	0.0 (0.30)	0.0 (0.27)
Change from Baseline	n	105	96	91	292
	Mean (SD)	-0.1 (0.28)	0.0 (0.21)	0.0 (0.30)	0.0 (0.27)
CALCIUM (mg/dL)					
Baseline	n	110	102	104	316
	Mean (SD)	-0.1 (0.45)	0.0 (0.36)	-0.1 (0.42)	-0.1 (0.41)
Change from Baseline	n	105	98	98	301
	Mean (SD)	-0.1 (0.45)	0.0 (0.36)	-0.1 (0.42)	-0.1 (0.41)
CHLORIDE (mEq/L)					
Baseline	n	110	102	104	316
	Mean (SD)	0.6 (2.13)	0.7 (2.54)	0.5 (2.66)	0.6 (2.44)
Change from Baseline	n	105	98	98	301
	Mean (SD)	0.6 (2.13)	0.7 (2.54)	0.5 (2.66)	0.6 (2.44)
CHOLESTEROL, FASTING (mg/dL)					
Baseline	n	109	102	104	315
	Mean (SD)	-0.2 (28.88)	-5.4 (23.99)	-5.2 (29.64)	-3.5 (27.63)
Change from Baseline	n	102	98	96	296
	Mean (SD)	-0.2 (28.88)	-5.4 (23.99)	-5.2 (29.64)	-3.5 (27.63)

		Brexpiprazole 2-4 mg (N=110)	Aripiprazole 10-20 mg (N=102)	Placebo (N=104)	Total (N=316)
CREATINE KINASE (U/L)					
Baseline	n	110	102	104	316
	Mean (SD)	-1.5 (221.88)	-70.6 (897.52)	-0.3 (185.54)	-23.6 (538.26)
Change from Baseline	n	105	98	98	301
	Mean (SD)	-1.5 (221.88)	-70.6 (897.52)	-0.3 (185.54)	-23.6 (538.26)
CREATININE (mg/dL)					
Baseline	n	110	102	104	316
	Mean (SD)	0.0 (0.12)	0.0 (0.09)	0.0 (0.10)	0.0 (0.11)
Change from Baseline	n	105	98	98	301
	Mean (SD)	0.0 (0.12)	0.0 (0.09)	0.0 (0.10)	0.0 (0.11)
GLUCOSE, FASTING (mg/dL)					
Baseline	n	109	102	104	315
	Mean (SD)	1.1 (12.15)	0.8 (11.41)	0.7 (14.70)	0.9 (12.77)
Change from Baseline	n	102	98	96	296
	Mean (SD)	1.1 (12.15)	0.8 (11.41)	0.7 (14.70)	0.9 (12.77)
HDL CHOLESTEROL, FASTING (mg/dL)					
Baseline	n	107	100	101	308
	Mean (SD)	-0.1 (9.51)	-0.6 (9.16)	-2.1 (11.61)	-0.9 (10.12)
Change from Baseline	n	100	96	94	290
	Mean (SD)	-0.1 (9.51)	-0.6 (9.16)	-2.1 (11.61)	-0.9 (10.12)
HEMATOCRIT (%)					
Baseline	n	110	102	104	316
	Mean (SD)	-0.7 (3.10)	0.0 (2.57)	-0.1 (3.16)	-0.3 (2.96)
Change from Baseline	n	104	97	98	299
	Mean (SD)	-0.7 (3.10)	0.0 (2.57)	-0.1 (3.16)	-0.3 (2.96)
HEMOGLOBIN (g/dL)					
Baseline	n	110	102	104	316
	Mean (SD)	-0.3 (0.95)	0.0 (0.76)	0.0 (1.01)	-0.1 (0.92)
Change from Baseline	n	104	98	99	301
	Mean (SD)	-0.3 (0.95)	0.0 (0.76)	0.0 (1.01)	-0.1 (0.92)
HEMOGLOBIN A1C (%)					
Baseline	n	110	102	104	316
	Mean (SD)	0.0 (0.27)	0.0 (0.24)	0.0 (0.27)	0.0 (0.26)
Change from Baseline	n	102	96	95	293
	Mean (SD)	0.0 (0.27)	0.0 (0.24)	0.0 (0.27)	0.0 (0.26)
LACTATE DEHYDROGENASE (U/L)					
Baseline	n	110	102	103	315
	Mean (SD)	-6.5 (28.60)	-10.1 (36.87)	-0.1 (20.07)	-5.6 (29.52)
Change from Baseline	n	101	96	96	293
	Mean (SD)	-6.5 (28.60)	-10.1 (36.87)	-0.1 (20.07)	-5.6 (29.52)

		Brexpiprazole 2-4 mg (N=110)	Aripiprazole 10-20 mg (N=102)	Placebo (N=104)	Total (N=316)
LDL CHOLESTEROL, FASTING (mg/dL)					
Baseline	n	107	100	101	308
	Mean (SD)	0.2 (23.74)	-5.0 (20.41)	-3.4 (25.69)	-2.7 (23.38)
Change from Baseline	n	100	96	94	290
	Mean (SD)	0.2 (23.74)	-5.0 (20.41)	-3.4 (25.69)	-2.7 (23.38)
NEUTROPHILS (10^9/L)					
Baseline	n	110	102	104	316
	Mean (SD)	0.1 (1.45)	0.0 (1.55)	0.2 (1.82)	0.1 (1.61)
Change from Baseline	n	104	98	99	301
	Mean (SD)	0.1 (1.45)	0.0 (1.55)	0.2 (1.82)	0.1 (1.61)
PLATELETS (10^9/L)					
Baseline	n	110	102	104	316
	Mean (SD)	-2.1 (52.61)	-1.5 (42.14)	5.3 (44.41)	0.5 (46.69)
Change from Baseline	n	104	98	99	301
	Mean (SD)	-2.1 (52.61)	-1.5 (42.14)	5.3 (44.41)	0.5 (46.69)
POTASSIUM (mEq/L)					
Baseline	n	110	102	104	316
	Mean (SD)	0.0 (0.41)	0.1 (0.37)	-0.1 (0.38)	0.0 (0.39)
Change from Baseline	n	105	98	98	301
	Mean (SD)	0.0 (0.41)	0.1 (0.37)	-0.1 (0.38)	0.0 (0.39)
PROLACTIN (ng/mL)*					
Baseline	n	109	101	104	314
	Mean (SD)	16.6	17.8	14.7 (16.94)	16.4 (18.26)
Change from Baseline	n	104	97	98	299
	Mean (SD)	1.1 (21.13)	-11.1 (18.69)	-1.5 (15.31)	-3.7 (19.25)
PROTEIN (g/dL)					
Baseline	n	110	102	104	316
	Mean (SD)	-0.1 (0.51)	0.0 (0.42)	-0.1 (0.48)	-0.1 (0.48)
Change from Baseline	n	105	98	98	301
	Mean (SD)	-0.1 (0.51)	0.0 (0.42)	-0.1 (0.48)	-0.1 (0.48)
RBC (10^12/L)					
Baseline	n	110	102	104	316
	Mean (SD)	-0.1 (0.31)	0.0 (0.27)	0.0 (0.36)	0.0 (0.32)
Change from Baseline	n	104	98	99	301
	Mean (SD)	-0.1 (0.31)	0.0 (0.27)	0.0 (0.36)	0.0 (0.32)
SODIUM (mEq/L)					
Baseline	n	110	102	104	316
	Mean (SD)	0.4 (2.17)	0.5 (2.54)	0.4 (2.33)	0.4 (2.34)
Change from Baseline	n	105	98	98	301
	Mean (SD)	0.4 (2.17)	0.5 (2.54)	0.4 (2.33)	0.4 (2.34)
THYROTROPIN (uIU/mL)					
Baseline	n	110	101	104	315
	Mean (SD)	0.0 (1.50)	-0.1 (1.18)	-0.2 (1.19)	-0.1 (1.30)
Change from Baseline	n	104	96	94	294
	Mean (SD)	0.0 (1.50)	-0.1 (1.18)	-0.2 (1.19)	-0.1 (1.30)

		Brexpiprazole 2-4 mg (N=110)	Aripiprazole 10-20 mg (N=102)	Placebo (N=104)	Total (N=316)
TRIGLYCERIDES, FASTING (mg/dL)					
Baseline	n	109	102	104	315
	Mean (SD)	1.0 (55.31)	-2.9 (42.85)	3.2 (49.62)	0.4 (49.50)
Change from Baseline	n	102	98	96	296
	Mean (SD)	1.0 (55.31)	-2.9 (42.85)	3.2 (49.62)	0.4 (49.50)
UREA NITROGEN (mg/dL)					
Baseline	n	110	102	104	316
	Mean (SD)	-0.6 (3.00)	0.0 (2.79)	0.3 (3.26)	-0.1 (3.04)
Change from Baseline	n	105	98	98	301
	Mean (SD)	-0.6 (3.00)	0.0 (2.79)	0.3 (3.26)	-0.1 (3.04)
WBC (10^9/L)					
Baseline	n	110	102	104	316
	Mean (SD)	0.0 (1.66)	0.0 (1.73)	0.3 (2.01)	0.1 (1.80)
Change from Baseline	n	104	98	99	301
	Mean (SD)	0.0 (1.66)	0.0 (1.73)	0.3 (2.01)	0.1 (1.80)

* Subjects who became pregnant during Study 331-10-234 (n=2, one in the brexipiprazole group and one in the aripiprazole group) were not included in the prolactin calculations)
Source: Clinical reviewer created using Applicant's adsl.xpt and adlb.xpt datasets

Clinical Reviewer's Comment: *Laboratory assessment results outlined above are based on the Safety Sample and were not filtered using the Applicant's Analysis Flag (ANL01FL), which excludes screening results and selects which result to use for subjects with more than one result per visit. Any minor differences between laboratory results reporting outlined in this review and the Applicant's Study Report for Study 331-10-234, where the Analysis Flag was used, are deemed insignificant. Of note, two subjects were removed from the prolactin results reported in Table 19 due to pregnancy. Therefore, minor differences in results compared to the Applicant's exist for the brexpiprazole and aripiprazole groups which each had one less subject included in the Clinical Reviewer's analyses.*

Vital Signs

Vital signs were measured at Screening, Day 1, and then weekly throughout the treatment period in Study 331-10-234. There were no clinically relevant heart rate values (<50 beats per minute or decrease of ≥ 15 beats per minute) for the brexpiprazole and placebo groups during treatment. For systolic blood pressure, there was one subject in the brexpiprazole group (0.9%) with a clinically relevant value (defined as <90 mmHg and decrease ≥ 20 mmHg) and two in the placebo group (1.9%). For diastolic blood pressure, there was one subject in the brexpiprazole group (0.9%) with a clinically relevant value (defined as <50 and decrease ≥ 15 mmHg) and none in the placebo group. For orthostatic hypotension readings, there were two subjects in the brexpiprazole group (1.8%) with a clinically relevant value (defined as ≥ 20 decrease in systolic bp and ≥ 25 increase in heart rate from supine to standing) and two subjects in the placebo group (1.9%). Overall, there were no clinically meaningful mean changes from baseline to last visit in heart rate and blood pressure between the brexpiprazole and placebo groups.

The mean increase in weight from baseline to the last visit in the brexpiprazole group was 0.8 kg, with no change observed in the placebo group. No mean change in z-score for weight (calculation that adjusts for normal growth) from baseline to last visit was observed for the brexpiprazole group. TEAEs for weight increase occurred in two brexpiprazole group subjects (1.8%) and four placebo group subjects (3.9%). A clinically relevant weight shift was defined as a change of at least 7%. For weight decrease, five brexpiprazole group subjects (4.5%) and four placebo group subjects (3.9%) experienced a clinically relevant shift. Notably, for weight increase, numerically more subjects in the brexpiprazole group (n=9, 8.2% of subjects) had a clinically relevant shift compared to the placebo group (n=5, 4.9% of subjects). Z-score weight increase of at least 0.5 SD from baseline to the last visit occurred in 4.5% (n=5) of brexpiprazole subjects and 3.9% (n=4) of placebo subjects. Weight gain is a known risk of brexpiprazole.

Electrocardiograms (ECGs)

ECGs were obtained at Screening, Day 1, and at Week 6 (end-of-treatment). Overall, ECG results in Study 331-10-234 did not reveal significant clinical or toxicity-related issues. There was one subject (0.9%) in the brexpiprazole group that experienced premature ventricular beat(s) versus none in the placebo group. Two subjects (1.8%) in the brexpiprazole group experienced a QTcN change between > 30 and ≤ 60 msec (between baseline and end-of-treatment) versus one subject in the placebo group (1.0%).

QT

QTc findings listed above. There were no QTc findings in Study 331-10-234 that would warrant changes to the current product label.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Extrapyramidal Symptoms (EPS)
EPS are known side effects of antipsychotic medications. EPS events in Study 331-10-234 are reflected in Table 20, below. Numerically more subjects in the brexpriprazole (6.4% of subjects) experienced EPS events compared to the placebo group (2.9% of subjects). Akathisia was experienced by numerically less subjects in the brexpipirazole group (3.6% of subjects) versus the placebo group (2.9% of subjects). Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Scale (SAS) did not demonstrate any notable difference in change from baseline to last visit means comparing brexpiprazole to the placebo group. For BARS (Global Clinical Assessment ≤2 was considered normal), 0.9% (n=1) of brexipiprazole subjects shifted from normal to abnormal on this measure during treatment versus 0% (n=0) of placebo subjects. For SAS (total score ≤3 was considered normal), 5.5% (n=6) of brexipiprazole subjects shifted from normal to abnormal on this measure during treatment versus 2.9% (n=3) of placebo subjects.

Table 20: Prevalence of Extrapyramidal Symptoms in Study 331-10-234 (Safety Sample)

		Brexpiprazole (N = 110)		*Aripiprazole (N = 102)*		*Placebo (N = 104)*		*Total (N = 316)*	
EPS Category	*Preferred Term*	*Events*	*n (% of subjects)*	*Events*	*n (% of subjects)*	*Events*	*n (% of subjects)*	*Events*	*n (% of subjects)*
Akathisia Events		**4**	**4 (3.6%)**	**9**	**7 (6.9%)**	**5**	**5 (4.8%)**	**18**	**16 (5.1%)**
	Akathisia	4	4 (3.6%)	9	7 (6.9%)	3	3 (2.9%)	16	14 (4.4%)
	Psychomotor hyperactivity	0	0 (0%)	0	0 (0%)	2	2 (1.9%)	2	2 (0.6%)
Dystonic Events		**4**	**3 (2.7%)**	**9**	**7 (6.9%)**	**1**	**1 (1.0%)**	**14**	**11 (3.5%)**
	Blepharospasm	1	1 (0.9%)	0	0 (0%)	0	0 (0%)	1	1 (0.3%)
	Dystonia	0	0 (0%)	2	2 (2.0%)	0	0 (0%)	2	2 (0.6%)
	Eye movement disorder	2	1 (0.9%)	1	1 (1.0%)	0	0 (0%)	3	2 (0.6%)
	Muscle rigidity	1	1 (0.9%)	5	4 (3.9%)	1	1 (1.0%)	7	6 (1.9%)
	Musculoskeletal stiffness	0	0 (0%)	1	1 (1.0%)	0	0 (0%)	1	1 (0.3%)
Parkinsonian Events		**4**	**4 (3.6%)**	**5**	**3 (2.9%)**	**0**	**0 (0%)**	**9**	**7 (2.2%)**
	Extrapyramidal disorder	2	2 (1.8%)	1	1 (1.0%)	0	0 (0%)	3	3 (0.9%)
	Hypokinesia	1	1 (0.9%)	0	0 (0%)	0	0 (0%)	1	1 (0.3%)
	Tremor	1	1 (0.9%)	4	3 (2.9%)	0	0 (0%)	5	4 (1.3%)

Source: Clinical reviewer created using Applicant's adsl.xpt and adae.xpt datasets

Clinical Reviewer's Comment: *The Applicant did not include blepharospasm or eye movement disorder in their preferred terms to group as EPS. This led to differences in the numbers reported by the Applicant in the Clinical Study Report and those reported here.*

Metabolic Changes

Glucose

Subjects with a fasting glucose reading >100 accounted for 17.3% (n=19) of brexpiprazole subjects and 11.5% (n=12) of placebo subjects. A fasting glucose reading of ≥ 126 (suggestive of diabetic range) occurred in 1.8% (n=2) of brexpiprazole subjects and 1.9% (n=2) of placebo subjects. The proportion of subjects with shifts in fasting glucose from normal (< 100 mg/dL) at baseline to high (≥ 126 mg/dL) during treatment was similar for the brexpiprazole (1.1%, n=1) and placebo (2.3%, n=2) groups (Table 21).

Table 21: Number of Subjects with Clinically Meaningful Shifts in Glucose, Fasting in Study 331-10-234 (Safety Sample)

		Glucose, Fasting (mg/dL) during Treatment		
Grouping Variable	**Glucose, Fasting (mg/dL) Baseline Visit**	**<100**	**100-125**	**≥126**
Brexpiprazole 2-4 mg (N = 102)	<100	75 (73.53%)	15 (14.71%)	1 (0.98%)
	100-125	7 (6.86%)	2 (1.96%)	0 (0%)
	≥126	1 (0.98%)	0 (0%)	1 (0.98%)
Aripiprazole 10-20 mg (N = 98)	<100	69 (70.41%)	14 (14.29%)	1 (1.02%)
	100-125	4 (4.08%)	9 (9.18%)	0 (0%)
	≥126	0 (0%)	1 (1.02%)	0 (0%)
Placebo (N = 96)	<100	78 (81.25%)	7 (7.29%)	2 (2.08%)
	100-125	5 (5.21%)	4 (4.17%)	0 (0%)
	≥126	0 (0%)	0 (0%)	0 (0%)

Source: Clinical reviewer created using Applicant's adsl.xpt and adlb.xpt datasets

Lipids

For total cholesterol, 4.7% (n=3) of subjects in the brexpiprazole group had a shift from in normal (< 170 mg/dL) at baseline to high (≥ 200 mg/dL) during treatment. For HDL, 7.7% (n=5) of brexpiprazole subjects had a shift from normal (>45 mg/dL) at baseline to low (< 40 mg/dL) during treatment. For LDL, 6.2% (n=5) of subjects in the brexpiprazole group had a shift from in normal (< 110 mg/dL) at baseline to high (≥ 130 mg/dL) during treatment. For triglycerides, 8.5% (n=4) of subjects in the brexpiprazole group had a shift from in normal (< 90 mg/dL) at baseline to high (≥ 130 mg/dL) during treatment. No subjects had severe hypertriglyceridemia (> 500 mg/dL) during treatment.

Weight

See above in Section 8.2.4 (Vital Signs) for results related to weight.

Prolactin

Prolactin findings are detailed below (Table 22). Of note, one subject in the brexpiprazole group had TEAE of galactorrhea without increased prolactin.

Males

For males in Study 331-10-234, a 1.4 ng/mL mean decrease (from baseline to last visit) was observed in the brexpiprazole group (versus 0.4 ng/mL mean decrease in the placebo group). More subjects in the brexpiprazole group (21.4%, n=9) compared to the placebo group (7.0%,

n=3) had shifts from normal (≤20 ng/mL) prolactin levels at baseline to abnormal >20 ng/mL) during the course of treatment (Table 23).

Females

For females in Study 331-10-234, a 3.3 ng/mL mean increase (from baseline to last visit) was observed in the brexpiprazole group (versus a 2.8 ng/mL mean decrease in the placebo group). More subjects in the brexpiprazole group (28.9%, n=13) compared to the placebo group (4.7%, n=2) had shifts from normal (≤30 ng/mL) prolactin levels at baseline to abnormal (>30 ng/mL) during the course of treatment (Table 24).

Table 22: Mean Change from Baseline to Last Visit in Prolactin (Safety Sample)

		Brexpiprazole 2-4 mg (N=110)	Aripiprazole 10-20 mg (N=102)	Placebo (N=104)
Males				
Baseline	n	52	45	53
	Mean (SD)	12.7 (15.60)	11.5 (11.63)	13.4 (17.86)
Last Visit	n	49	44	50
	Mean (SD)	12.0 (6.76)	5.3 (3.89)	12.4 (16.81)
Change from Baseline	Mean (SD)	-1.4 (16.08)	-6.3 (11.43)	-0.4 (10.73)
Females*				
Baseline	n	57	56	51
	Mean (SD)	20.2 (21.37)	22.9 (21.55)	16.1 (16.00)
Last Visit	n	55	53	48
	Mean (SD)	23.9 (14.70)	8.1 (4.85)	13.3 (13.24)
Change from Baseline	Mean (SD)	3.3 (24.72)	-15.0 (22.40)	-2.8 (18.99)

*1 female in the brexipiprazole group and 1 female in the aripiprazole group were excluded from prolactin analyses due to pregnancy
Source: Reviewer created using Applicant's adsl.xpt and adlb.xpt datasets

Table 23: Number of Male Subjects with Potentially Clinically Meaningful Shifts in Prolactin in Study 331-10-234 (Safety Sample)

		Treatment Visit Relative to Upper Limit of Normal (ULN)			
Group	**Baseline Visit Relative to ULN**	**≤ 1x**	**> 1x and ≤ 2x**	**> 2x and ≤ 3x**	**> 3x**
Brexpiprazole 2-4 mg (N = 49)	≤ 1x	33 (67.35%)	6 (12.24%)	2 (4.08%)	1 (2.04%)
	> 1x and ≤ 2x	4 (8.16%)	0 (0%)	0 (0%)	0 (0%)
	> 2x and ≤ 3x	0 (0%)	1 (2.04%)	1 (2.04%)	0 (0%)
	> 3x	1 (2.04%)	0 (0%)	0 (0%)	0 (0%)
Aripiprazole 10-20 mg (N = 44)	≤ 1x	37 (84.09%)	1 (2.27%)	0 (0%)	0 (0%)
	> 1x and ≤ 2x	5 (11.36%)	0 (0%)	0 (0%)	0 (0%)
	> 2x and ≤ 3x	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	> 3x	1 (2.27%)	0 (0%)	0 (0%)	0 (0%)
Placebo (N = 50)	≤ 1x	40 (80%)	2 (4%)	1 (2%)	0 (0%)
	> 1x and ≤ 2x	2 (4%)	1 (2%)	0 (0%)	0 (0%)
	> 2x and ≤ 3x	2 (4%)	0 (0%)	1 (2%)	0 (0%)
	> 3x	0 (0%)	0 (0%)	0 (0%)	1 (2%)

ULN = ≤20 ng/mL
Source: Clinical reviewer created using Applicant's adsl.xpt and adlb.xpt datasets

Table 24: Number of Female Subjects with Potentially Clinically Meaningful Shifts in Prolactin in Study 331-10-234 (Safety Sample)

		Treatment Visit Relative to Upper Limit of Normal (ULN)			
Group	**Baseline Visit Relative to ULN**	**≤ 1x**	**> 1x and ≤ 2x**	**> 2x and ≤ 3x**	**> 3x**
Brexpiprazole 2-4 mg (N = 55)	≤ 1x	32 (58.18%)	13 (23.64%)	0 (0%)	0 (0%)
	> 1x and ≤ 2x	1 (1.82%)	4 (7.27%)	1 (1.82%)	0 (0%)
	> 2x and ≤ 3x	2 (3.64%)	1 (1.82%)	0 (0%)	0 (0%)
	> 3x	1 (1.82%)	0 (0%)	0 (0%)	0 (0%)
Aripiprazole 10-20 mg (N = 53)	≤ 1x	40 (75.47%)	0 (0%)	0 (0%)	0 (0%)
	> 1x and ≤ 2x	6 (11.32%)	0 (0%)	0 (0%)	0 (0%)
	> 2x and ≤ 3x	7 (13.21%)	0 (0%)	0 (0%)	0 (0%)
	> 3x	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Placebo (N = 48)	≤ 1x	41 (85.42%)	2 (4.17%)	0 (0%)	0 (0%)
	> 1x and ≤ 2x	2 (4.17%)	1 (2.08%)	1 (2.08%)	0 (0%)
	> 2x and ≤ 3x	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	> 3x	1 (2.08%)	0 (0%)	0 (0%)	0 (0%)

*1 female in the brexipiprazole group and 1 female in the aripiprazole group were excluded from prolactin analyses due to pregnancy
ULN = ≤30 ng/mL
Source: Clinical reviewer created using Applicant's adsl.xpt and adlb.xpt datasets

Clinical Reviewer's Comment: *Differences in prolactin results with the Applicants are due to the Applicant not excluding pregnant subjects and using the laboratory's upper limit of normal (ULN) from the post-baseline being compared to the baseline as the ULN for the baseline visit. Results described above exclude pregnant females (there was one in the brexpiprazole group and one in the aripiprazole group) and using standard prolactin cut-offs for males (>20 ng/mL) and females (>30 ng/mL) as recommended by UpToDate. Laboratory cut-offs were not used as the ULN were considered too high or too low in many cases (for example, ULN >39 ng/mL in females and ULN >13.13 ng/ML in males).*

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

Not applicable to the safety assessments conducted in this development program.

8.2.7. Safety Analyses by Demographic Subgroups

Analysis of AEs by demographic groups is limited by the low numbers of commonly occurring individual or grouped AEs (Table 18) such that differences would not be interpretable.

Prolactin changes as outlined by sex are reported above in Section 8.2.5.

8.2.8. Specific Safety Studies/Clinical Trials

Given the high incidence of abnormal prolactin reported in the long-term, open-label, uncontrolled safety Study 331-10-236, the Agency required the study report and datasets for Study 331-10-234 to fulfill PMR 4205-1. See above for safety results from Study 331-10-234 (Sections 8.2.4 and 8.2.5, including results related to prolactin).

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The application did not include new human carcinogenicity studies.

Human Reproduction and Pregnancy

Two subjects (one in the brexpiprazole group and one in the aripiprazole group) became pregnant during Study 331-10-234. Both subjects were reported to give birth to healthy babies via c-section. The subject in the brexpiprazole group was found to be pregnant after the treatment period was over. The subject in the aripiprazole group was discontinued from the study after the Day 34 blood test indicated pregnancy. Notably, concomitant medications for this subject included a levonorgestrel-releasing intrauterine device (IUD) for birth control. In addition, a urine drug screen was positive for cannabinoids, and the subject was noted to have high blood pressure and respiratory problems prior to induction of labor. Prenatal tests did not identify any fetal defect or anomaly.

Pediatrics and Assessment of Effects on Growth

See Section 8.2.4 Vital Signs for Study 331-10-234 results related to weight.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The application did not include any formal assessments related to drug abuse potential, withdrawal, and rebound.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Although there is extensive experience with brexpiprazole in adults, there is limited post-marketing data available in pediatric patients.

Expectations on Safety in the Postmarket Setting

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

8.2.11. Integrated Assessment of Safety

Overall, brexpiprazole's safety profile in pediatric subjects with schizophrenia is consistent with that of other atypical antipsychotic medications.

8.3. Statistical Issues

No statistical issues that could impact the overall conclusions were identified.

8.4. Conclusions and Recommendations

The safety profile of brexpiprazole in pediatric subjects (age 13 to 17 years) with schizophrenia is consistent with the known safety profile for other atypical antipsychotic medications for pediatric use. Information will be added to the appropriate sections of labeling to reflect the efficacy and safety findings of Study 331-10-234. Prolactin findings will be added to the label. The data submitted are adequate to fulfill the 505(o) postmarketing requirement 4205-1.

9 Advisory Committee Meeting and Other External Consultations

Not applicable; the Division did not convene an advisory committee to discuss this application.

10 Pediatrics

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 subjects 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. 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. On June 30, 2021, the Applicant submitted S-007 seeking the addition of the indication for treatment of schizophrenia in pediatric patients ages 13 to 17 years based on an extrapolation approach. On December 27, 2021, S-007 was approved. On May 7, 2024, S-011 was approved, adding pediatric safety information to Section 8.4 of labeling; with that supplement, the Agency considered the terms of the PWR fulfilled and granted pediatric exclusivity.

The long-term, open-label, uncontrolled safety data from ongoing Study 331-10-236 in pediatric subjects with schizophrenia revealed that there was a high incidence of abnormal prolactin values. Therefore, the PMR Fulfillment letter from December 27, 2021, issued new PMR 4205-1 under Section 505(o)(3) of the FDCA:

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 13-17) with schizophrenia.

Final Protocol Submission: June 2016
Study Completion: October 2024
Final Report Submission: April 2025

This supplemental NDA provided the final study report and datasets for Study-331-10-234. PMR-4205-1 is considered fulfilled.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
New pediatric information will be added to the prescribing information in the following sections:
Highlights. ADVERSE REACTIONS

- Pediatric patients (13 to 17 years) with schizophrenia: Extrapyramidal symptoms, excluding akathisia (≥5% and at least twice the rate of placebo) was added.

5. WARNINGS AND PRECAUTIONS
    5.6 Metabolic Changes
        - Fasting glucose results from Study 331-10-234 were added.
        - Lipid level results from Study 331-10-234 were added.
            - (b) (4) the Applicant's proposed (b) (4) was removed.
        - Lipid level results from Study 331-10-236 (long-term open-label study) were updated to reflect more up-to-date information and use pediatric appropriate thresholds.
            - Percentages for HDL and triglyceride shifts were based on the Study 331-10-236 dataset submitted under Supplement 7.
        - Weight results from Study 331-10-234 were added.
            - (b) (4) were omitted from the label due to the limited interpretability for a 6-week study.

6. ADVERSE REACTIONS
    6.1 Clinical Trial Experience
        - Overall exposures and adverse reactions in adults and pediatric patients were added.
        - Adverse reactions occurring at an incidence of 2% of brexpiprazole treated patients and greater than placebo in Study 331-10-234 were added.
            - Although the TEAE tables for other indications such as adjunctive treatment in MDD, schizophrenia in adults, and agitation associated with dementia due to Alzheimer's disease do not include EPS at this time even though EPS results for these indications would qualify for inclusion in the TEAE tables based on current language in the EPS-specific section of Section 6.1, updating these tables to include EPS would require additional data validation. As the other indications were not the focus of this Supplement, they were not updated at this time.
        - Extrapyramidal symptoms results from Study 331-10-234 were added.
            - (b) (4) s proposed by the Applicant was not incorporated into the label (b) (4)

(b) (4)

- Hyperprolactinemia information from Study 331-10-234 was added.
  - As the prolactin results were deemed not clinically significant such that they would prompt specific monitoring from prescribers, hyperprolactinemia information was placed in Section 6 (versus the Warning and Precautions sections where hyperprolactinemia is typically listed in other antipsychotic medications).

14. CLINICAL STUDIES

14.2 Schizophrenia

- Description of and efficacy results from Study 331-10-234 were added.
  - All groups (brexpiprazole, active comparator, and placebo) were included in the description of Study 331-10-234 for completeness and accuracy.

Other Prescription Drug Labeling

The Medication Guide was updated with adverse reactions common in pediatric patients to include a comprehensive description of extrapyramidal symptoms observed in pediatric subjects in lay language.

12 Risk Evaluation and Mitigation Strategy (REMS)

Not applicable; this review did not identify any new significant safety issues that would warrant a REMS.

13 Postmarketing Requirements and Commitment

Not applicable; the Division does not plan to issue any new postmarketing requirements or commitments for this application.

14 Division Director (Clinical) Comments

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

15 Appendices

15.1. References

See footnotes throughout document.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 331-10-234

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 579 (102 principal investigators and 477 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: 2 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 2		
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) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Financial disclosure information for Study 331-10-234 was requested and the Applicant provided financial disclosure information on August 22, 2024 (and provided reasons for investigators with certification of due diligence on March 5, 2025).

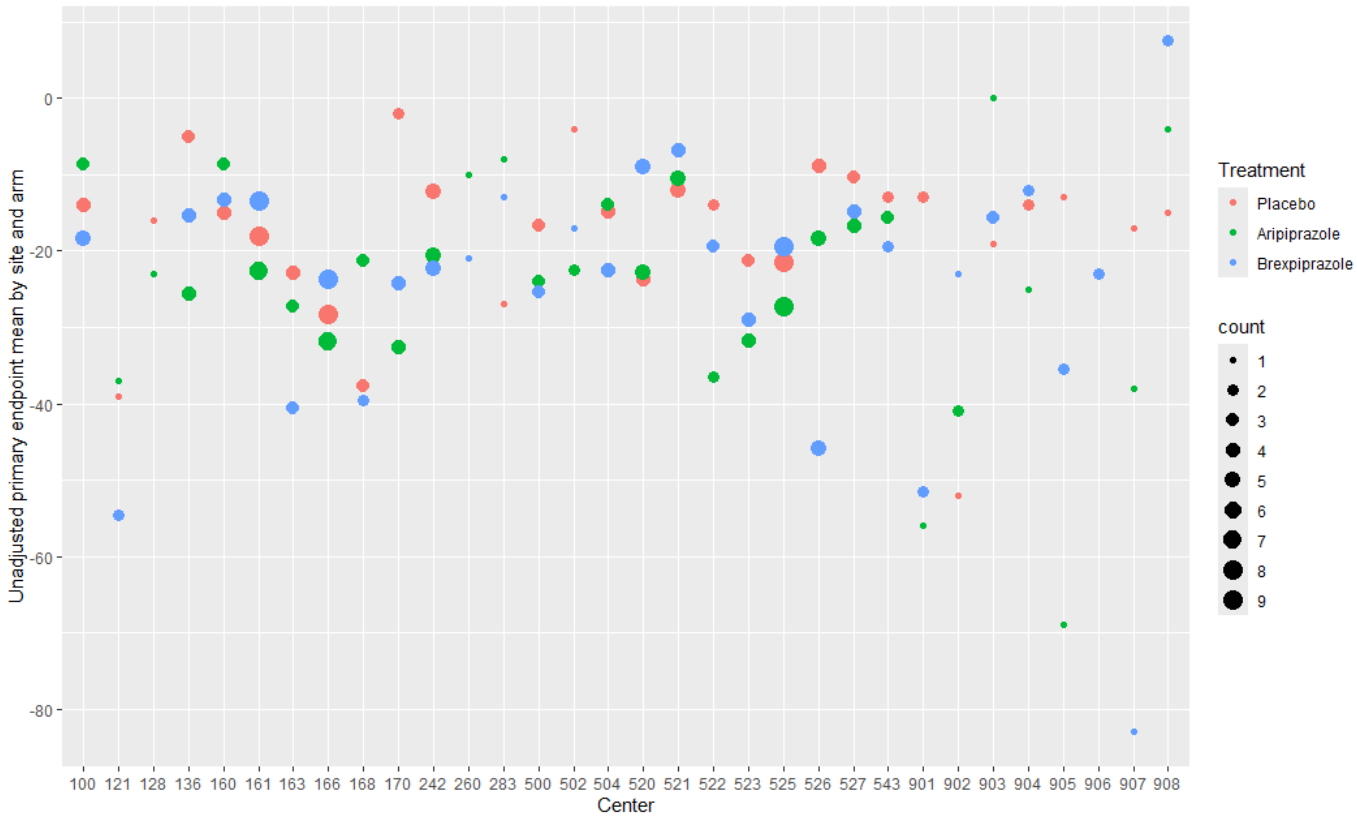
None of the investigators with disclosable financial interests were at study sites that enrolled any subjects in Study 331-10-234.

One of the investigators with certification of due diligence listed by the Applicant in their August 22, 2024, submission did not participate in the study. Therefore, seven is the number of investigators listed on initial Form FDA 1572 who were removed from site team prior to study initiation or did not participate in the study (instead of six as the Applicant originally listed). For the other investigator with certification of due diligence listed, the disclosure form was provided by the Applicant to the FDA on March 5, 2025, and the investigator had nothing to disclose.

15.3. Additional Statistical Analyses

The statistical reviewer explored PANSS total score differences across study centers. In the following analyses, the same pooling of small study sites as above is used. First, Figure 5 shows the (unadjusted) mean primary endpoint by study site and study arm. The size of the dots signifies the number of subjects. In this plot, no obvious outlier observations (study centers) were noted.

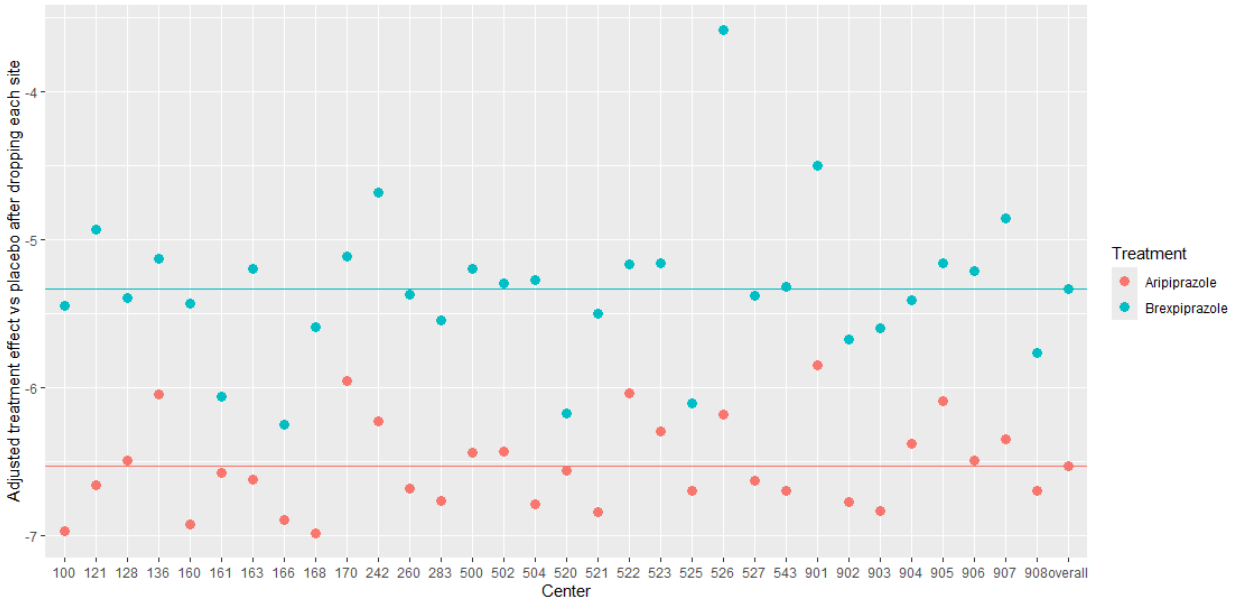
Figure 5: Exploratory Analysis: PANSS Total Score Unadjusted Mean Change from Baseline by Center in the Efficacy Sample (Study 331-10-234)



Source: Reviewer's results

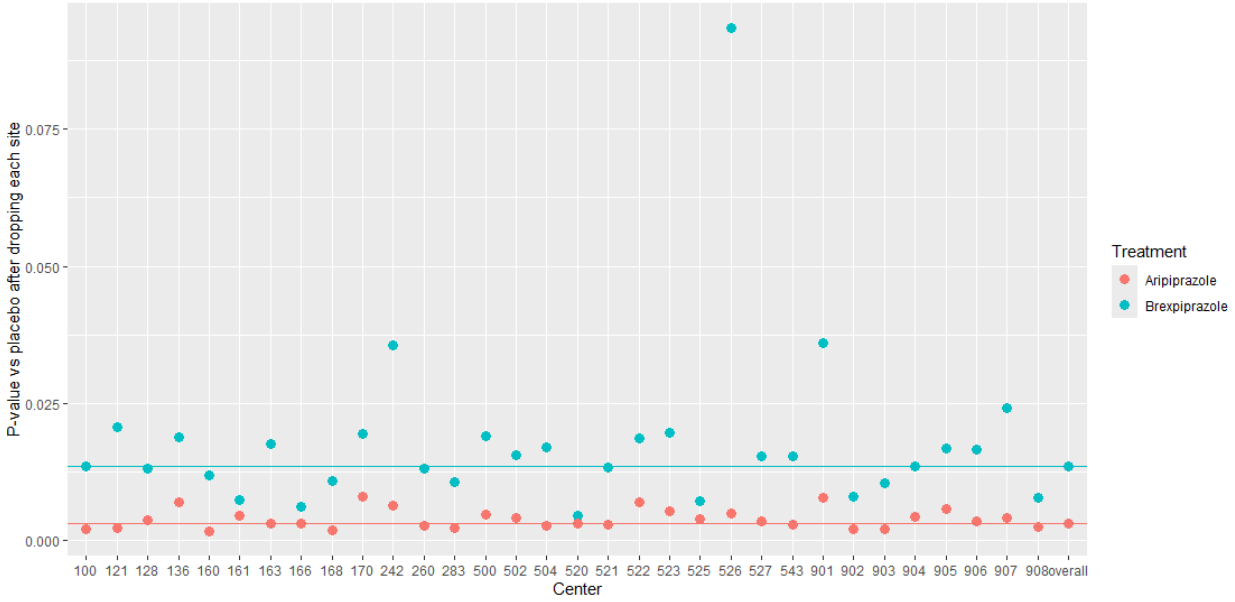
Next, an additional analysis of study sites was performed, this time exploring model-adjusted mean treatment effect and p-value in a model equivalent to the primary analysis model. In Figure 6 and Figure 7, adjusted treatment effect versus placebo and adjusted p-values are presented respectively. In these figures, each site is excluded from the primary analysis and results are yielded for the remaining sites. The impact on treatment effect and p-value then illustrates whether the study results were driven by any one study site in particular. In both figures, it appears no study sites have a strong effect on the results in the aripiprazole arm. One study site (site 526) appears to be the only study arm that when excluded, brexpriprazole arm no longer reaches statistical significance, although site 526 is not the largest study arm. Regardless, the presented analyses suggest general consistency of results between study sites.

Figure 6: Exploratory Analysis: PANSS Total Score Adjusted Treatment Effect vs Placebo, Excluding One Center at a Time in the Efficacy Sample (Study 331-10-234)



Source: Reviewer's results

Figure 7: Exploratory Analysis: PANSS Total Score p-value vs Placebo, Excluding One Center at a Time in the Efficacy Sample (Study 331-10-234)



Source: Reviewer's results

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