NDA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	NDA 205422/S-011
Priority or Standard	Priority
Submit Date(s)	11/8/23
Received Date(s)	11/8/23
PDUFA Goal Date	5/8/24
Division/Office	Division of Psychiatry (DP)/Office of Neuroscience (ON)
Review Completion Date	5/8/24
Established/Proper Name	Brexpiprazole
Trade Name	Rexulti
Pharmacologic Class	Atypical antipsychotic
Code name	
Applicant	Otsuka Pharmaceutical Company, Ltd.
Dosage form	Tablets
Applicant proposed Dosing Regimen	N/A
Applicant Proposed Indication(s)/Population(s)	N/A
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Schizophrenia (disorder) SCTID: 58214004
Recommendation on Regulatory Action	Supplement approval—no new indication
Recommended Indication(s)/Population(s) (if applicable)	N/A
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	N/A
Recommended Dosing Regimen	N/A

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Abbreviations: 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-HT1a	serotonin subtype-1a
5-HT2a	serotonin subtype-2a
ABC	Aberrant Behaviors Checklist
ABC-I	Aberrant Behaviors Checklist – Irritability Subscale
ADI-R	Autism Diagnostic Interview - Revised
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ASD	Autism Spectrum Disorders
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
BP	blood pressure
BREX	brexpiprazole
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression of Severity
CI	confidence interval
CNS	central nervous system
CRF	case report form
D2	dopamine type 2
DBP	diastolic blood pressure
DMC	data monitoring committee
DSM-5	Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition
ECG	electrocardiogram
ET	early termination
FDA	Food and Drug Administration
HR	heart rate
IA	interim analysis
IND	Investigational New Drug
LOCF	Last Observation Carried Forward
LS	least squares
LSM	least squares mean
LSMD	least squares mean difference
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MDD	major depressive disorder
MI	multiple imputation
MMRM	Mixed-Effect Model for Repeated Measure
MNAR	Missing Not at Random
NDA	new drug application
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PK	pharmacokinetics
PRO	patient reported outcome
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Scale
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SI/B	suicidal ideation and behavior
sNDA	supplemental new drug application
TEAE	treatment emergent adverse event
US	United States

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 (also known together 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 is FDA-approved for the of schizophrenia in adults (NDA 205422; July 10, 2015) and adolescents (NDA 205422/S-010; December 27, 2021), adjunctive treatment of major depressive disorder (MDD) in adults (NDA 205422; July 10, 2015), and for the treatment of agitation associated with dementia due to Alzheimer's disease (NDA 205422/S-009; May 10, 2023). Brexpiprazole's mechanism of action in treating psychiatric conditions is unclear; however, the Applicant hypothesizes that partial agonist activity at 5-HT1a and D2 receptors in combination with noradrenaline (α1B) receptor antagonism may correlate with reduced irritability and impulsive behavior.

With this supplemental new drug application, the Applicant is submitting negative studies conducted to explore the potential indication of treatment of irritability associated with autism spectrum disorder (ASD). This product is currently available as tablets for oral administration, including dosage strengths of 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg. The proposed recommend target dosage range for subjects < 50 kg and ≥ 50 kg is 1 to 1.5 mg/day and 1.5 to 3 mg/day, respectively.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant conducted one randomized, double-blind, placebo-controlled, flexible-dose, 8-week clinical study (331-201-00148) in pediatric subjects 5 to 17 years of age with irritability associated with ASD. Brexpiprazole did not demonstrate a statistically significant effect on the primary endpoint, change from baseline in the Aberrant Behaviors Checklist – Irritability (ABC-I) subscale score, at Week 8. Although the Applicant is not seeking to expand the indicated population, relevant pediatric safety information from Study 331-201-00148 and findings from the long-term, open-label extension study (331-201-00191) will be incorporated into the product label. The product label will also state that the safety and effectiveness of brexpiprazole have not been established for the treatment of irritability associated with ASD in pediatric patients 5 to 17 years of age.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

ASD is a neurodevelopment disorder characterized by deficits in reciprocal social communication and restricted, repetitive behaviors. Symptoms initially present in early childhood and contribute to difficulties in developing, maintaining, and understanding relationships. In addition to core symptoms, children and adolescents with ASD often suffer from challenging behaviors, including symptoms of irritability, which may manifest as tantrums, self-injury, and aggressive behaviors. Although there are no pharmacological treatments for core symptoms associated with ASD, atypical antipsychotics (i.e., risperidone and aripiprazole) are commonly prescribed to treat irritability associated with ASD in children and adolescents.

Given that brexpiprazole is likely to be used as an off-label treatment for irritability associated with ASD in pediatric patients, the Agency highlighted the importance of evaluating efficacy and safety of brexpiprazole in this patient population. In response to the Agency's pediatric Written Request, the Applicant conducted a single randomized, double-blind, placebo-controlled phase 3 study (331-201-00148) and a long-term, open-label extension study (331-201-00191) to evaluate the efficacy and safety of brexpiprazole for the treatment of irritability associated with ASD in pediatric subjects 5 to 17 years of age. Results from Study 331-201-00148 did not demonstrate a statistically significant treatment effect relative to placebo on the primary endpoint, change from baseline in the ABC-I score at Week 8. Although there were no new safety signals in the pediatric population relative to adults, and the safety profile for brexpiprazole appeared to be generally consistent with the known safety profile of other atypical antipsychotics, there was a higher incidence of somnolence in pediatric subjects (16%) relative to adults (3 to 5%). Like other atypical antipsychotics, pediatric subjects also experienced clinically relevant increases in body weight and body mass index (BMI) on brexpiprazole.

Given the negative efficacy study, the Applicant is not requesting to expand brexpiprazole's indicated population; however, relevant safety information will be included in the product label to inform the risks associated with brexpiprazole in pediatric patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The estimated prevalence of ASD in 2020 was 27.6 per 1,000 children (approximately 1 in every 36 children). The prevalence of ASD is four times higher in boys than among girls. • The average age of onset ranges between 38 to 120 months;	Irritability is a clinically serious aspect of ASD and important target for treatment to decrease functional disability and improve long-term outcomes.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	however, a diagnosis can be established as early as 18 months of age • The range of symptoms and severity are highly heterogenous within and across age groups. Clinical presentation is typically correlated with age, cognitive and language abilities, co-morbid conditions, and access to external support. • Approximately 40% of pediatric patients with ASD experience symptoms of irritability that can be persistent and lifelong. Although there is no formal diagnostic criteria, identification of patients with irritability is based on frequency of symptoms relative to similar peers and whether symptoms interfere with daily functioning. • Irritability and other challenging behaviors cause significant caregiver distress and can limit an individual's involvement in the community. If not addressed, symptoms may become chronic and disabling.	
Current Treatment Options	• There are no pharmacological treatment options to treat core symptoms (i.e., social communication deficits and restricted behaviors) associated with ASD. Non-pharmacological treatments, including behavioral therapy, are first-line options to treat core symptoms and challenging behaviors. • Although various antipsychotics are commonly used off-label, risperidone and aripiprazole are the only FDA-approved treatments for irritability associated with ASD in pediatric patients.	There is a need for additional pharmacological treatment options for the treatment of irritability in pediatric patients with ASD.
Benefit	• The Applicant conducted a single adequate and well-controlled phase 3 study (331-201-00148) to evaluate the effectiveness of brexpiprazole in 119 pediatric subjects 5 to 17 years of age with irritability associated with ASD. Flexibly dosing with brexpiprazole (0.5 to 3 mg/day) did not demonstrate a statistically significant	Study 331-201-00148 was a negative study and, thus, did not support evidence of effectiveness for brexpiprazole in the treatment of irritability associated with ASD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	improvement relative to placebo on the primary endpoint, change from baseline in the ABC-I subscale score at Week 8.	
Risk and Risk Management	• In Study 331-201-00148, adverse events (AE) that occurred in ≥ 5% of subjects randomized to brexpiprazole and at greater frequency than placebo included: fatigue, headache, increased appetite, somnolence, and vomiting. The incidence of somnolence, including sedation, was 16% and approximately four-fold greater than the incidence reported in adults (3 to 5%). • During the 8-week double-blind period, subjects receiving brexpiprazole experienced greater clinically relevant increases in age- and gender-adjusted z-scores for body weight (19% vs. 5%) and BMI (40% vs. 9%) relative to placebo. In the 26-week, long-term study, 26% of subjects experienced clinically relevant increases in age- and gender-adjusted z-scores for both body weight and BMI. • Overall incidence of EPS-related AEs and clinically relevant changes in vital signs, laboratory measures, and ECG findings were low and within the range observed in adults.	Safety findings will be included in Section 8.4 of the product label to describe the higher incidence of somnolence and clinically relevant changes in weight among the pediatric population.

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		
		□	Patient reported outcome (PRO)	
		X	Observer reported outcome (ObsRO)	Section 8.1 (Aberrant Behaviors Checklist)
		X	Clinician reported outcome (ClinRO)	Section 8.1 (Clinical Global Impression of 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

Autism spectrum disorders (ASD) refer to a group of complex, pervasive, and multifactorial neurodevelopmental conditions defined by two core features: persistent deficits in social communication (e.g., issues with social reciprocity, non-verbal communication, and developing relationships) and restricted, repetitive sensory-motor behaviors (e.g., insistence on sameness, fixed interests, and hypersensitivity or hyposensitivity to sensory inputs). Table 1 below describes the current Diagnostic and Statistical Manual for Mental Disorders (DSM-5) diagnostic criteria for ASD (Hirota T, et al., 2023). Of note, diagnoses of autism, Asperger's syndrome, and pervasive developmental disorder-not otherwise specified established by prior versions of the DSM are now consolidated under the umbrella diagnosis of ASD (Lord C, et al., 2018). Based on data collected from the Centers for Disease Control and Prevention's Autism and Developmental Monitoring Network, the estimated prevalence of ASD in 2020 was 27.6 per 1,000 children (approximately 1 in every 36 children). ASD is reported to occur in all racial, ethnic, and socioeconomic groups; however, the prevalence of ASD is four times higher in boys than among girls (Maenner MJ, et al., 2023).

Although the neuropathophysiology of ASD is not fully understood, current research suggests that biologic, genetic, and environmental factors play a vital role in disease etiology (Kodak T, et al., 2020). The range of symptoms and severity of ASD are highly heterogenous within and across age groups; clinical manifestation is typically dependent on the patient's age, cognitive and language abilities, co-morbid conditions (e.g., epilepsy, sleep disorders, anxiety, depression, and attention deficit hyperactivity disorder), and external support (e.g., education, speech, language services). The average age of onset ranges between 38 to 120 months; however, a diagnosis of ASD can be made as early as 18 months of age (Hyman SL, et al., 2020). Longitudinal studies suggest that in the first 2 years of life, common features include poor acquisition of or decline in language skills and communicative gestures (Lord C, et al., 2006). As a child develops, behavioral or cognitive rigidity, lack of interest in socializing, and restricted interests become more apparent. In adolescents and adults, patients with AD may have difficulties developing and maintaining friendships, communicating with peers, and understanding expected behaviors (Hirota T, et al., 2023).

In addition to the core symptoms that characterize ASD, patients often exhibit other challenging behaviors that can be disruptive to daily life. Over 40% of patients with ASD have symptoms of irritability including aggression, tantrums, rapidly changing moods, or self-injurious behavior. Studies have suggested that the prevalence of these disruptive behaviors increases with age during childhood, reaches a peak during adolescence and young adulthood, and may decline into adulthood (Lord C, et al., 2020). Long-term longitudinal data shows that 40% of patients with ASD and irritability continue to exhibit similar behaviors a decade later in life; therefore, this suggests that irritability can be persistent and be lifelong if not overcome.

The frequency and severity of irritability are commonly associated with core symptom severity, levels of cognitive and language impairments, and medical comorbidity (Rattaz C, et al., 2018). Although there are no formal consensus diagnostic criteria, identification of patients with irritability associated with ASD is typically based on the frequency of symptoms relative to peers in the same setting, and whether symptoms regularly interfere with learning, functioning, relationships, or poses a risk to safety. Because these behaviors can cause significant caregiver distress and limit involvement in the community, irritability is clinically recognized as an important aspect of ASD and a potential target for treatment. If not addressed, symptoms of irritability may become chronic and disabling, and ultimately require long-term institutionalization (McGuire K, et al., 2016).

Table 1: DSM-5 Diagnostic Criteria for ASD

Criteria A: Social Communication and Interaction[1]	Must have persistent deficits in each of the three areas of social communication and interaction	1. Deficits in social-emotional reciprocity 2. Deficits in nonverbal communicative behaviors used for social interaction 3. Deficits in developing, maintaining, and understanding relationships
Criteria B: Restricted, repetitive behaviors[1]	At least two out of four types of restricted, repetitive behaviors	1. Stereotyped or repetitive motor movements, use of objects, or speech 2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior 3. Highly restricted, fixated interests that are abnormal in intensity or focus 4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment
Criteria C	Must meet all three criteria	Symptoms must be present in early developmental period (may not fully manifest until social demands exceed limited capacities, or may be masked by learned strategies later in life)
Criteria D		Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
Criteria E		Disturbances are not better explained by intellectual disability or global developmental delay (to make a co-morbid diagnosis of ASD and intellectual disability, social communication should be below that expected for general developmental level)

[1]Severity is based on social communication impairments and restricted, repetitive patterns of behavior. For either criterion, severity is described in three levels: Level 3 requires very substantial support; Level 2 requires substantial support, and Level 1 requires support.
Source: Reviewer-created table using DSM-5 criteria

2.2. Analysis of Current Treatment Options

The American Academy of Pediatrics therapeutic guidelines for ASD indicate that the goals of treatment are to: minimize core deficits and co-occurring associated impairments; maximize functional independence by facilitating learning and acquisition of adaptive skills; and eliminate, minimize, or prevent problem behaviors that may interfere with functional skills. Interventions are typically multimodal and individualized to target strengths and weaknesses of a child (Maenner MJ, et al., 2023).

Despite several decades of research in ASD, current evidence has only established behavioral (non-pharmacological) treatments as the mainstay of management to address core symptoms of ASD. Non-pharmacological approaches for both core symptoms and challenging behaviors are primarily based on the principles of learning and behavioral theory and are provided through educational practices, developmental therapies, and behavioral interventions. Studies evaluating early behavioral intervention have proposed several treatment models, including: applied behavior analytic interventions, developmental relationship-focused interventions, naturalistic developmental behavioral interventions, and parent-mediated training (Maenner MJ, et al., 2023). Behavioral interventions work most effectively when started at an early age to improve a child's functioning and outcome. Other approaches may also include speech and language, motor, sensory, and cognitive behavioral therapy (Masi A, et al., 2017).

To date, there are no FDA-approved pharmacologic options for treatment of core symptoms of ASD. However, pharmacologic treatments are often used to treat associated symptoms of inattention/hyperactivity, anxiety, repetitive behaviors, and irritability. Off-label treatments include antidepressants, anticonvulsants, stimulants, mood stabilizers, and alpha-2 adrenergic agonists (Robb AS, 2010). Given that aripiprazole (5 to 15 mg/day) and risperidone (0.5 to 3 mg/day) are FDA-approved for the treatment of irritability associated with ASD, antipsychotics are the most frequently prescribed psychotropic medication in this population. Drug utilization data indicate that approximately 20% of children and 40% of adults with ASD will receive treatment with typical or atypical antipsychotics (Park SY, et al., 2016).

Randomized, double-blind, placebo-controlled, 8-week clinical studies demonstrated that aripiprazole and risperidone were effective in reducing symptoms of irritability in pediatric subjects 5 to 17 years of age with ASD. However, use of atypical antipsychotics in pediatric patients relative to adults has also been associated with higher risk of extrapyramidal symptoms (EPS), sedation, weight gain and metabolic effects (e.g., hyperglycemia, diabetes mellitus, dyslipidemia), and hyperprolactinemia (Salazar de Pablo, et al., 2023). Given the potential for off-label use of brexpiprazole to treat symptoms of irritability, evaluation of brexpiprazole's efficacy and safety is important to potentially address a serious unmet medical need and to provide an additional treatment option in pediatric patients with ASD.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Brexpiprazole is FDA-approved for the of schizophrenia in adults (NDA 205422; July 10, 2015) and adolescents (NDA 205422/S-010; December 27, 2021), adjunctive treatment of major depressive disorder in adults (NDA 205422; July 10, 2015), and for the treatment of agitation associated with dementia due to Alzheimer's disease (NDA 205422/S-009; May 10, 2023).

3.2. Summary of Presubmission/Submission Regulatory Activity

On April 19, 2018, the Division issued a Written Request (WR) in response to the Applicant's Pediatric Study Request (submitted on December 18, 2017). Because pediatric patients with ASD are likely to receive off-label treatment with brexpiprazole, the Division indicated the importance of evaluating the efficacy and safety of brexpiprazole in this patient population. The WR outlined the following studies needed to investigate the potential use of brexpiprazole to treat irritability associated with ASD in pediatric patients ages 5 to 17 years: a safety, tolerability, and PK study in subjects 5 to 12 years of age; an adequate and well-controlled efficacy and safety study in subjects 5 to 17 years of age with irritability associated with ASD; and a pediatric long-term safety study. The following list summarizes key milestone meetings and regulatory activities under investigational new drug (IND) application 141257 and NDA 205422:

- October 18, 2018: Submission of an Initial Pediatric Study Plan (iPSP)

  - The Sponsor indicated that pharmacological treatment for irritability associated with ASD is rarely sought for children less than 5 years of age. Therefore, the Division agreed with a waiver in pediatric patients 0 to less than 5 years of age because necessary studies are highly impracticable.
  - The Sponsor's plan included the following studies (and associated timelines):
    - Study 331-10-233 (to be completed in January 2017): a phase 1, open-label, dose-escalation trial to assess safety, tolerability, and PK of brexpiprazole in adolescents with schizophrenia (b) (4)

      (b) (4)
    - Study 331-201-00148 (to be completed in January 2023): a phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate brexpiprazole in children and adolescents with irritability associated with ASD

  - Study 331-201-00191: a phase 3, open-label study to evaluate long-term safety and tolerability of brexpiprazole in children and adolescents with (b) (4) irritability associated with ASD

- November 1, 2018: The Division amended the WR (Amendment 1), which included a modification to the pharmacokinetic (PK) study design (removed the requirement for multiple-dosing) and age range (increased the lower age threshold from 5 to 6 years). The Division also required the Applicant to complete the PK study in subjects 6 to 12 years of age before initiating efficacy trials to inform dosing.

- June 6, 2019: The Applicant submitted protocols 331-201-00148 and 331-201-00191. The Division determined both studies were safe to proceed.

  - (b) (4)

- July 23, 2019: The Division noted that WR Amendment 1 only included one pediatric efficacy and safety study. Because a single study would not provide substantial evidence of effectiveness to support an indication, WR Amendment 2 included the need to conduct <u>two</u> adequate and well-controlled studies to evaluate efficacy and safety in pediatric subjects with irritability associated with ASD. The Division noted that if the first study was unsuccessful, the WR should be amended to remove the second study.

- (b) (4)

- April 12, 2023: The Applicant conducted a single adequate and well-controlled pediatric efficacy and safety study in subjects 5 to 17 years of age with irritability associated with ASD (Study 331-201-00148). As stated in WR Amendment 3, because efficacy findings from the study were negative, the Division removed the second efficacy and safety study from the WR (Amendment 4).

- January 3, 2024: The Division filed supplemental NDA (sNDA) 205422/S-011 and granted a priority review.

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

4.1. Office of Scientific Investigations (OSI)

The Applicant does not plan to use sNDA 205422/S-011 to support a labeled indication. Due to the negative findings of Study 331-201-00148, the Division did not consult OSI to conduct site inspections.

4.2. Product Quality

The Applicant did not submit any new product quality information. Refer to the original NDA for information on the drug product.

4.3. Clinical Microbiology

The Applicant did not submit any new clinical microbiology information. Refer to the original NDA for additional information.

4.4. Devices and Companion Diagnostic Issues

The Applicant did not submit any new information regarding companion devices. Refer to the original NDA for additional information.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant previously submitted two juvenile animal studies in rats and dogs on December 8, 2009, and February 5, 2010, to INDs 101871, 103958, (b) (4) for the indications of schizophrenia, major depressive disorder, (b) (4) respectively. These studies were reviewed under the INDs and were found to be adequate to support pediatric clinical trials with brexpiprazole.

The rat study entitled "Eight-week Repeated Oral Dose Toxicity Study of OPC-331 in Juvenile Rats with 4-week Recovery Test" (report number 023805) evaluated general toxicity endpoints, recovery, effects on fertility and reproduction, learning and behavior, and toxicokinetics in 21-day old Sprague-Dawley rats at doses of 3, 10, and 20 mg/kg/day. Three 20 mg/kg/day animals were found dead during the study, and prior to death had clinical findings of decreased body weight, decreased body temperature, hypoactivity, closed eyes, and hypothermia. Clinical signs observed in surviving animals, mainly at 20 mg/kg/day, included findings of tremor, closed eyes, hypoactivity, hunchback position, creeping, hypothermia, with the incidence of these signs decreasing as the study progressed. A decrease in body weight gain, which correlated with a decrease in food consumption, occurred doses of 10 and 20 mg/kg/day. Decreases in organ weights including reproductive organs compared to control were related to body weight gain decreases. Immaturity of male and female reproductive organs was also observed, consistent with the pharmacology of the drug, with evidence of partial recovery. There were no drug-related effects on learning performance or sensory reflex function, or any adverse effects on fertility and reproduction. The No Observed Adverse Effect Level (NOAEL) was determined to be 3 mg/kg/day for males and 10 mg/kg/day for females.

A second study entitled "Twenty-six-week Repeated Oral Dose Toxicity Study of OPC-331 in Juvenile Beagle Dogs with 8-week Recovery Test" (report number 024102) evaluated general toxicity endpoints and recovery in 8- to 9-week-old dogs at 1, 3, or 30 mg/kg/day. Drug-related findings observed at 30 mg/kg/day, in both males and females, included decreases in body weight, increases in heart rate on day 1 followed by decreases at weeks 13 and 26, and QTc prolongation up to 32 msec compared to predose in males and up to 27 msec compared to predose in females. Additionally, clinical signs observed at 30 mg/kg/day included lethargy, drowsiness, and relaxation of the nictitating membrane. Drug-related minimal or mild hypertrophy of adrenal cortical cells was noted in both sexes at 30 mg/kg/day. Partially reversible minimal to mild immaturity of the epididymis and prostate, as well as minimal to moderate immaturity of the testes was also seen at 30 mg/kg/day, likely due to drug action at the dopamine D2 receptor. The NOAEL was determined to be 3 mg/kg for both sexes.

6 Clinical Pharmacology

6.1. Executive Summary

In this supplement (NDA205422/S-011), no new clinical pharmacology studies have been submitted. The clinical pharmacology studies referred in this supplement have been reviewed by the Office of Clinical Pharmacology (OCP) in the previous supplement (NDA205422/S-007). Please refer to the previous clinical pharmacology review (NDA205422, S-007 archived in DARRTS on 12/27/2021) for additional information.

6.2. Summary of Clinical Pharmacology Assessment

The Applicant conducted a phase 1, single-dose, sequential cohort, non-randomized crossover trial (331-201-00103) designed to assess the PK, safety, and tolerability of oral brexpiprazole in children (6 to < 13 years old) with central nervous system (CNS) disorders (including, but not limited to, attention deficit/hyperactivity disorder, autism-spectrum disorders, bipolar I disorder, conduct disorder, oppositional defiant disorder, or any psychotic disorder). The Applicant enrolled two cohorts of subjects in this study: 6 to < 10 years and 10 to < 13 years. Two single oral doses of brexpiprazole were administered to each subject with a 14-day washout period between doses for PK sample collection. Subjects received single doses of 0.75 mg (6 to < 10 years) or 1.5 mg (10 to < 13 years) brexpiprazole on Day 1 and 1.5 mg or 3 mg brexpiprazole (double the original dose) on Day 15. A total of 43 subjects were screened and 24 subjects (12 subjects per cohort) were enrolled in the trial. PK of brexpiprazole and its major metabolite, DM-3411, were characterized in children with CNS disorders. Table 2 shows the PK parameters of brexpiprazole in pediatric patients after single oral dose.

Table 2: Brexpiprazole PK Parameters (Mean [SD]) After Single Oral Dose in Pediatric Subjects

Mean (SD) Brexpiprazole PK Parameters Following a Single-dose Administration of 0.75 mg, 1.5 mg, or 3 mg of Brexpiprazole in Children (6 to < 13 years old) With CNS Disorders				
PK Parameter	**Children (6 to < 10 years old)**		**Children (10 to < 13 years old)**	
	0.75 mg (n = 11)	**1.5 mg (n = 11)**	**1.5 mg (n = 12)**	**3 mg (n = 10)**
C_{max} (ng/mL)	27.7 (12.9)	41.8 (16.5)	30.8 (16.4)	69.8 (42.4)
t_{max} (h)[a]	2.00 [1.00 - 6.00]	4.00 [1.02 - 7.98]	3.98 [1.00 - 4.07]	4.02 [2.00 - 6.00]
AUC_t (h*ng/mL)	877 (325)	1630 (642)	1340 (839)	3090 (1840)
AUC_∞ (h*ng/mL)	938 (384)	1720 (725)	1590 (853)	3620 (1940)
$t_{1/2,z}$ (h)	39.5 (15.4)	39.1 (7.90)	46.2 (11.8)	42.2 (10.0)
CL/F (mL/min)	15.4 (5.89)	16.8 (6.37)	20.9 (12.7)	19.3 (13.0)
CL/F/kg ([mL/min]/kg)	0.598 (0.222)	0.663 (0.267)	0.480 (0.260)	0.489 (0.321)

[a]Median [minimum - maximum] is presented.
Source: Applicant's 331-201-00103 Study Report, Table 11.5.2.4.1-1.

Table 3 provided the PK parameter of DM-3411 in adolescents after single oral dose in pediatric patients with CNS disorders.

Table 3: DM-3411 PK Parameters (Mean [SD]) After Single Oral Dose in Pediatric Subjects

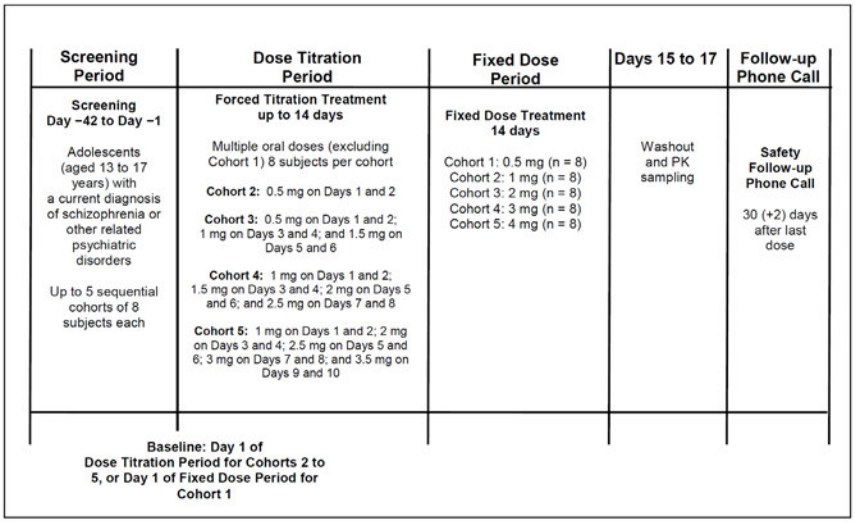
Table 11.5.2.4.2-1	Mean (SD) DM-3411 PK Parameters Following a Single-dose Administration of 0.75 mg, 1.5 mg, or 3 mg of Brexpiprazole in Children (6 to < 13 years old) With CNS Disorders			
PK Parameter	**Children (6 to < 10 years old)**		**Children (10 to < 13 years old)**	
	0.75 mg (n = 11)	**1.5 mg (n= 11)**	**1.5 mg (n = 11)**	**3 mg (n = 10)**
C_{max} (ng/mL)	10.1 (5.33)	16.1 (8.84)	9.96 (5.57)	19.9 (15.1)
t_{max} (h)[a]	8.00 [2.03 - 24.07]	12.00 [4.07 - 24.17]	11.95 [4.00 - 24.48]	12.01 [4.08 - 24.33]
AUC_t (h*ng/mL)	532 (229)	943 (441)	664 (408)	1330 (1020)
AUC_∞ (h*ng/mL)	565 (242)	1050 (454)	678 (438)	1680 (1090)
$t_{1/2,z}$ (h)	33.4 (7.70)	42.2 (15.3)	33.9 (4.40)	41.1 (10.6)

[a]Median [minimum - maximum] is presented.

Source: Applicant's 331-201-00103 Study Report, Table 11.5.2.4.2-1.

To support extrapolation of efficacy from adult to adolescent patients with schizophrenia, the Applicant conducted a phase 1, multicenter, open-label, sequential cohort, dose-escalation trial in adolescent subjects (age 13 to 17 years) with a diagnosis of schizophrenia or other related psychiatric disorders (331-10-233). The study consisted of five cohorts and evaluated dose levels from 0.5 mg to 4 mg with a titration dose schedule (Figure 1). The PK parameters in adolescents were compared to those reported for adults from Study 331-08-205. Table 4 shows the PK parameters of brexpiprazole in adolescent and adult patients at steady state.

Figure 1. Trail Design Schematic for Study 331-10-233



Source: Applicant's 331-10-233 Study Report, Figure 9.1-1.

Table 4: Brexpiprazole PK Parameters (Mean [SD]) After 14 days Once Daily Dosing in Adults and Adolescents (PK Evaluable Population)

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

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

The results suggest that children in the younger group (6 to < 10 years old) showed higher exposure (Cmax: ~60%; AUC: ~40%) and lower oral clearance (CL/F: ~20%) of 1.5 mg brexpiprazole as compared to children in the older group (10 to < 13 years old). In addition, the exposure of the major metabolite, DM-3411, also showed slightly higher exposure in younger group of children (~50%) compared to the older group. The clearance of brexpiprazole in children 10 to < 13 years old is comparable to those observed in adolescents and adults (21.3 mL/min following 2 mg single dose).

Overall, the PK of brexpiprazole and its major metabolite were adequately characterized in children 6 to <13 years old and adolescents with CNS disorders.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant's ASD development program (Table 5) consisted of one phase 3 efficacy and safety study (331-201-00148) and one long-term, open-label extension safety study (331-201-00191). At the initiation for both aforementioned studies, the Applicant also conducted two PK studies in pediatric subjects with schizophrenia and other CNS disorders to guide brexpiprazole dose selection in children and adolescents 5 to 17 years of age with ASD (refer to Section 6 for additional information).

Table 5: Listing of Clinical Trials Relevant to NDA 205422/S011

Trial Identity	NCT	Trial Design	Regimen/ schedule	Study Endpoints	Treatment Duration	No. of subjects randomized	Study Population	No. of Centers
Completed Efficacy and Safety Studies								
331-201-00148	NCT04174365	Randomized, double-blind, placebo-controlled, flexible-dose, 2-arm study	BREX 0.25 to 3 mg/day[1] Placebo daily	Primary: Change from baseline in the ABC-I subscale score at Week 8	8 weeks	BREX: 60 Placebo: 59	Subjects 5 to 17 years of age with a DSM-5 diagnosis of ASD (supported by the ADI-R) and with symptoms of irritability (ABC-I subscale score ≥ 18 and CGI-S scale score ≥ 4)	US: 29
331-201-00191	NCT04258839	Open-label, active-treatment, extension study	Prior BREX: same dose as in parent trial Prior Placebo: flexible BREX 0.5 to 3 mg/day	Frequency and severity of AEs and other safety parameters	26 weeks	Prior BREX: 49 Prior Placebo: 46	Subjects with ASD who completed Study 331-201-00148	US: 7

Source: Reviewer-created
[1]Target dose ranges for subjects with body weight < 50 kg and ≥ 50 kg were 1 to 1.5 mg and 1.5 to 3 mg, respectively. After Day 15, the Investigator could adjust the dose based on therapeutic effect or tolerability.
Abbreviations: ABC-I = Aberrant Behaviors Checklist – Irritability Subscale; ADI-R = Autism Diagnostic Interview - Revised ; BREX = brexpiprazole; CGI-S = Clinical Global Impression of Severity; DSM-5 = Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition; US = United States

7.2. Review Strategy

This review of efficacy focused on Study 331-201-00148 conducted in pediatric subjects 5 to 17 years of age with irritability associated with ASD. Although the study showcased characteristics of an adequate and well-controlled trial, results on the primary endpoint were not statistically significant and, therefore, did not provide evidence of effectiveness.

The review of safety primarily focuses on Study 331-201-00148 and a 26-week open-label extension study (Study 331-201-00191). Because previous clinical studies evaluating brexpiprazole did not include double-blinded, placebo-controlled data in children and adolescents, one aim for the safety review was to evaluate and compare adverse events (AEs), changes in laboratory findings, and other safety assessments to previous safety findings in adults reported in the product label.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 331-201-00148

8.1.1.1. Study Design of Study 331-201-00148

Trial Design

This study was a randomized, double-blind, placebo-controlled, multi-center, flexible-dose study intended to evaluate the efficacy, safety, and tolerability of brexpiprazole (0.25 to 3 mg/day) in pediatric subjects 5 to 17 years of age with irritability associated with ASD. This trial consisted of three periods (a schematic representation of the study design is presented in Figure 2):

- **Screening Period:** The total duration of the screening period was between 1 to 28 days. Investigators determined subject eligibility and required subjects to washout prohibited concomitant pharmacotherapy prior to randomization.

- **Double-blind Treatment Period:** The Applicant randomized subjects in a 1:1 ratio to receive either brexpiprazole or placebo once daily. Subjects with a total body weight < 50 kg initiated treatment at 0.25 mg on Days 1 to 3, followed by 0.5 mg for Days 4 to 7, and 1 mg for Days 8 to 14. Subjects with a total body weight ≥ 50 kg initiated treatment at 0.5 mg on Days 1 to 3, followed by 1.5 mg for Days 4 to 7, and 2 mg for Days 8 to 14. Day 15 was the earliest opportunity an investigator could increase the dosage to 1.5 mg/day and 3 mg/day for each dosing cohort, respectively.

  Decisions to increase or decrease the dose on or after Day 15 were based on tolerability and desire to achieve a therapeutic effect. All subjects must have received their final dose adjustment by Week 6; subjects that required a change in dose between Weeks 6 and 8 discontinued from the study. Investigators also discontinued subjects < 50 kg and ≥ 50 kg, if the subject was unable to tolerate the 1 mg/day or 1.5 mg/day dosage, respectively. Refer to Table 6 for a visual representation of the titration to target dose scheme. Investigators evaluated subjects at baseline, and at Weeks, 1, 2, 3, 4, 6, and 8. Visits at baseline, Week 2, and Week 8 occurred in clinic (subjects participated in all other visits virtually or in clinic).

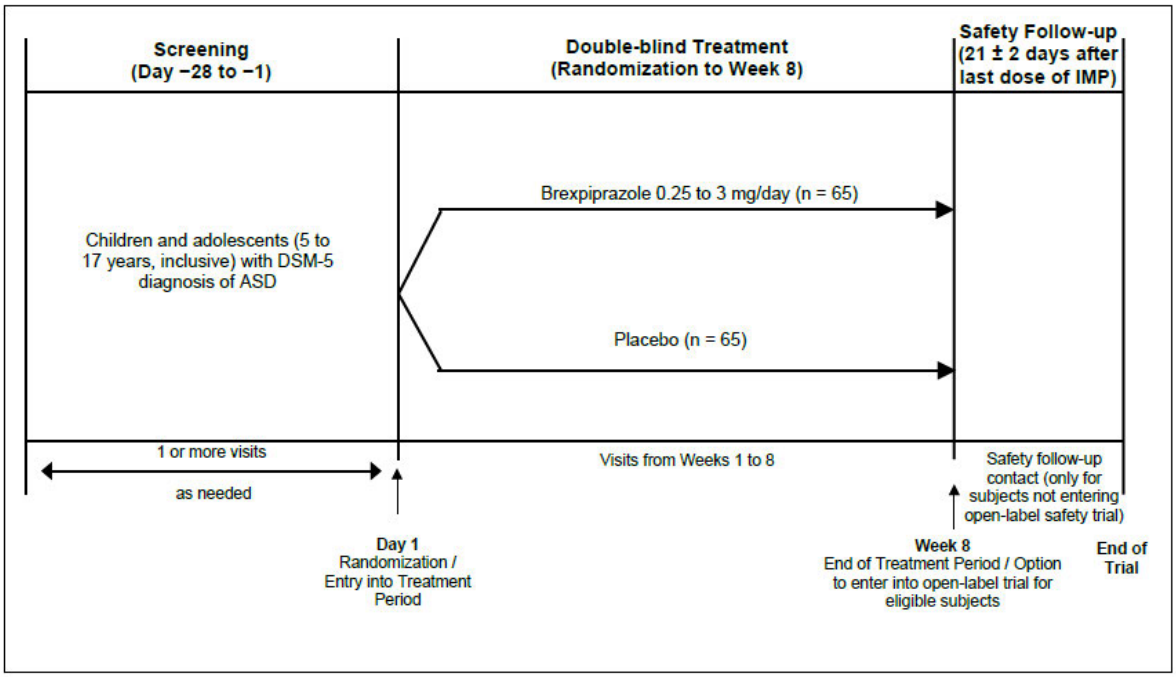
- **Safety Follow-up Period:** Investigators followed each subject by telephone for safety evaluation 21 days after receiving the last dose of the study medication.

Table 6: Flexible-dosing Scheme for Study 331-201-00148

Treatment Group	Daily Dose Administered			
	Days 1 to 3	Days 4 to 7	Days 8 to 15	Starting at Day 15[1]
Subjects < 50 kg receiving BREX	0.25 mg QD	0.5 mg QD	1 mg QD	1 mg or 1.5 mg QD
Subjects < 50 kg receiving BREX	0.5 mg QD	1.5 mg QD	2 mg QD	1.5 mg, 2 mg, or 3 mg QD
Matching placebo	<----------	----------	----------	---------->

Source: Applicant's 331-201-00148 Study Protocol, Table 3.2-1
[1]Earliest opportunity to increase to maximum dose within target dose range
Abbreviations: BREX = brexpiprazole; QD = once daily

Figure 2: Study Design Overview for Study 331-201-00148



Source: Applicant's 331-201-00148 Study Protocol, Figure 3.1-1

Study Eligibility Criteria

The target population consisted of pediatric subjects 5 to 17 years of age with ASD. The Applicant's comprehensive inclusion and exclusion criteria consisted of appropriate diagnostic and tolerability criteria, a list of prohibited and accepted concomitant medications, and acceptance thresholds for clinically significant abnormal laboratory values and medical history.

Key Inclusion Criteria:

- Current primary DSM-5 diagnosis of ASD, as determined by the investigator and supported by the Autism Diagnostic Interview – Revised (ADI-R)

- Aberrant Behavior Checklist – Irritability (ABC-I) subscale score ≥ 18 at screening and at baseline

- Clinical Global Impression of Severity (CGI-S) scale score ≥ 4 pertaining to irritability at screening and at baseline

- Mental age of ≥ 2 years, as determined by the investigator based on school participation, social history, or medical records

Key Exclusion Criteria:

- Current primary DSM-5 diagnosis of bipolar I disorder, including any DSM-5 current diagnosis of bipolar II disorder, schizophrenia, schizoaffective disorder, major depressive episode as determined by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version, or post-traumatic stress disorder.

- Current or historical diagnosis of Fragile-X Syndrome or Rett's Disorder

- History of neuroleptic malignant syndrome.

- Significant risk of committing violent acts, serious self-harm, or those who are homicidal or considered to be a high risk to others

- Subjects with an answer of "yes" on the Columbia Suicide Severity Rating Scale (C-SSRS) Ideation Item 4 or Item 5 at entry or within the past three months, or subjects with a response of "yes" on the C-SSRS Suicidal or a response of "yes" on any of the C-SSRS Suicidal Behavior Items at entry or within the past year

- Current or history of epilepsy, seizures (except for a single childhood febrile seizure or post-traumatic seizure), severe head trauma, or stroke

- Current or history of other unstable medical conditions that would expose the subject to undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial (e.g., hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease)

- Non-pharmacological therapy (e.g., psychotherapy, behavior modification) is not stable for 30 days prior to screening and is not likely to be consistent throughout the trial

- Current hypothyroidism or hyperthyroidism (unless stabilized with medication(s) for at least the past 90 days)

- Diagnosis of Type I or Type II diabetes if all of the following criteria are not met: glycosylated hemoglobin (HbA1c) ≤ 6.5%; screening fasting glucose is ≥ 70 mg/dL and ≤

100 mg/dL or non-fasting glucose is ≥ 70 mg/dL and ≤ 139 mg/dL; maintained on a stable regimen of non-insulin medication(s) for at least 28 days prior to screening; diabetes has been well-controlled by diet for at least 28 days prior to screening; no hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes; and diabetes is not newly diagnosed during screening

- Uncontrolled hypertension or symptomatic hypotension, or orthostatic hypotension (defined as a decrease of ≥ 15 mmHg in systolic blood pressure [SBP] or a decrease of ≥ 15 mmHg in diastolic blood pressure [DBP] after at least 3 minutes standing compared to the previous supine blood pressure, or development of symptoms)

- ≥ 13 years of age that engage in social activities with peers without adult supervision who test positive for drugs of abuse or with a positive blood alcohol test at screening

- Abnormal laboratory test or electrocardiogram (ECG) results (i.e., platelets ≤ 130 × 103/uL for ≤ 12 years of age or ≤ 140 × 103/uL for ≥ 13 years of age; hemoglobin ≤ 11.2 g/dL for ≤ 12 years of age or ≤ 11.6 g/dL for ≥ 13 years of age; absolute neutrophils ≤ 1.00 × 103/uL for ≤ 12 years of age or ≤ 1.35 × 103/uL for ≥ 13 years of age; aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥ 2 × upper limit of normal; serum creatinine ≥ 0.7 mg/dL for ≤ 12 years of age or ≥ 1.1 mg/dL for ≥ 13 years of age; creatine phosphokinase ≥ 2 × upper limit of normal; QTcF ≥ 450 msec for males and ≥ 470 msec for females)

Clinical Reviewer's Comments: *The Applicant's target population and eligibility criteria appear consistent with other development programs evaluating antipsychotics (i.e.,* (b) (4) (b) (4) *risperidone [020272], aripiprazole [021436]) in pediatric subjects for the treatment of irritability associated with ASD. Given the high degree of comorbidity between ADHD and ASD, the Applicant clarified that investigators could enroll subjects with ADHD, provided that ADHD was not the primary disorder and that the subject was clinically stable and adequately treated.*

Of note, other development programs used the DSM-IV-TR criteria for ASD, while the diagnostic criteria for this study was based on the DSM-5. The key difference relative to the older criteria is the removal of subtypes (e.g., Asperger syndrome, pervasive developmental disorder not otherwise specified), combining social and language deficits into a single measure, inclusion of sensory symptoms in the restrictive and repetitive behaviors component, and changing the specification of the age of onset from 3 years to "early childhood."

Procedures and Schedule of Events

Refer to Table 7 for the Applicant's schedule of procedures and study assessments.

Table 7: Abbreviated Schedule of Assessments for Study 331-201-00148

Assessment	Visit								
	Screening	Baseline (Day 1)	Wk 1 (± 2 days)	Wk 2 (± 2 days)	Wk 3 (± 2 days)	Wk 4 (± 2 days)	Wk 6 (± 2 days)	Wk 8/ ET (± 2 days)	Follow-Up (Day21)
Inclusion/exclusion criteria	X	X							
Medical and psychiatric history	X								
Prior medication washout, blood alcohol, and UDS	X								
ABC and CGI-S	X	X	X	X	X	X	X	X	
PedsQL and PARS		X						X	
Physical examination	X							X	
Vital signs	X	X	X	X	X	X	X	X	
Clinical laboratory tests	X	X						X	
Body weight and weight circumference	X	X						X	
Prolactin, ACTH, TSH, cortisol, and HbA1c	X							X	
ECG	X	X						X	
C-SSRS (child version)	X	X	X	X	X	X	X	X	X
AIMS, SAS, and BARS		X		X				X	
PK Sampling		X						X	
Pharmacogenomic sampling		X							

Source: Reviewer created using Applicant's Protocol Amendment 2, Table 3.7-1
Abbreviations: ABC = Aberrant Behaviors Checklist; ACTH = adrenocorticotropic hormone; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-S = Clinical Global Impression – Severity scale; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; HbA1c = glycosylated hemoglobin; PARS = Pediatric Anxiety Rating Scale; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetic; SAS = Simpson-Angus Scale; TSH = thyroid stimulating hormone; UDS = urine drug screen

Subject Completion, Discontinuation, or Withdrawal

The Applicant defined the treatment period as the time period during which investigators evaluated subjects for primary or secondary objectives of the trial irrespective of whether or not the subject was administered all doses of the study medication. The Applicant defined subjects who completed the Week 8 visit as trial completers. Investigators permitted subjects to withdraw from the study at any time for any reason without compromising their medical care. If a subject discontinued early before Week 8, investigators made attempts to complete all evaluations prior to administration of any new psychotropic medication. Subject-specific stopping criteria also included: occurrence of any AE, reasons unrelated to medical condition, treatment with prohibited concomitant medications, non-compliance (< 80%), or lack of tolerability with study medication.

Study Product Information and Compliance

The Applicant supplied the study medication as (b) (4) tablets and matching placebo (b) (4) tablets and provided (b) (4) containing sufficient tablets for the window visit. Responsible trial personnel dispensed the study medication and documented accountability and compliance verification in the subject's trial records.

Dose Selection

The Applicant selected the dosage range for this trial based on two PK studies: Study 331-10-223 evaluated multiple daily doses of brexpiprazole 0.5 to 4 mg/day in subjects 13-to-17 years old with schizophrenia and other CNS disorders; and Study 331-201-00103 evaluated single-doses of brexpiprazole 0.75 to 3 mg in subjects 6-to-13 years old (refer to Section 6 for additional information). To guide dose selection in children and adolescents 5 to 17 years of age, the Applicant developed a population PK model to identify target exposures that would match exposures observed in adults with MDD (0.5 to 3 mg/day). Based on simulation results, the Applicant selected a weight cutoff at 50 kg to ensure subjects received an appropriate dose.

Prior and Concomitant Therapy

Refer to Table 8 for a summarized list of prohibited medications. All subjects must have discontinued all prohibited medications during the screening period to meet the protocol-specified washout periods. Subjects must have discontinued all prohibited medications at least 24 hours prior to the first dose of the study medication. The Applicant also prohibited all CYP2D6 inhibitors and CYP3A4 inhibitors and inducers. The Applicant allowed oral benzodiazepine therapy, but limited administration to a maximum dose of 3 mg/day of lorazepam (or equivalent) and not within 8 hours prior to efficacy and safety assessments. The Applicant also permitted the use of anticholinergics for the treatment of EPS with as needed propranolol and up to 4 m/day benztropine, or its equivalent. New-onset psychotherapy was prohibited during the trial period.

Table 8: List of Prohibited Medications for Study 331-201-00148

Prohibited Medications	Required Washout
All psychotropic agents including, but not limited to the following: antipsychotics, antidepressants, mood stabilizers, benzodiazepines (except when used as rescue therapy), and stimulants (except when used for the treatment of ADHD).	Antipsychotics: 14 days for aripiprazole and 7 days for all other oral antipsychotics (long-acting injectables excluded) Antidepressants: 28 days for fluoxetine and 14 days for all other antidepressants Stimulants: minimum of five half-lives Mood stabilizers: 7 days Benzodiazepines: 8 hours before administration of efficacy and safety scales
Ramelteon and other non-benzodiazepine sleep aides, except for limited use of specific medications for the treatment of insomnia	Non-benzodiazepines: 8 hours before administration of efficacy and safety scales, but not on the same day as administration of a benzodiazepine
Varenicline	5 days
Other nutritional supplements and non-prescription herbal preparations with CNS effects	14 days prior to first dose of study medication
CYP2D6 inhibitors and CYP3A4 inhibitors and inducers	14 days prior to first dose of study medication

Source: Reviewer-adapted using Protocol 331-201-00148, Table 4.1-2

Clinical Reviewer's Comment*: The review team agreed that Study 331-201-00148 was adequate and well-controlled (e.g., placebo-controlled, adequate trial duration of 8 weeks, justified dose-selection, appropriate eligibility criteria). The study design was reasonable to evaluate the effects of brexpiprazole for the treatment of irritability associated with ASD. Because the COVD-19 global pandemic emerged in early 2020 and resulted in travel restrictions and service disruptions (i.e., on-site study visits, access to site facilities), the Applicant's plan to include remote site and monitoring visits was acceptable.*

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was mean change from baseline to Week 8 in the ABC-I subscale score.

The ABC is a parent-reported rating scale designed to assess treatment effects on problem behaviors in patients with intellectual disabilities. The ABC-I is a subscale of the ABC consisting of 15 items that measures severity of emotional and behavioral symptoms of ASD (4-point Likert scale), including aggression toward others, deliberate self-injuriousness, temper tantrums, and changing moods. The ABC-I subscale score is the sum of ratings from all 15 items. The possible total subscale score ranges between 0 and 45.

Secondary Efficacy Endpoint

The key secondary endpoint of this trial was mean change from baseline to Week 8 in the CGI-S scale score for irritability.

Other Secondary and Exploratory Endpoints

- Change from baseline in the ABC-I subscale score at each visit during the double-blind treatment period (other than at the Week 8 visit)

- Change from baseline in the CGI-S score at each visit during the double-blind treatment period (other than at the Week 8 visit)

- Response rate at Week 8 (response defined as having ≥ 25% improvement in the ABC-I subscale score and ≥ one point improvement in CGI-S score compared to baseline)

- Response rate at each visit during the double-blind treatment period (other than at the Week 8 visit)

- Change from baseline in other ABC subscales (social withdrawal, stereotypic behavior, hyperactivity or noncompliance, and inappropriate speech), Pediatric Quality of Life Inventory (PedsQL), PedsQL family impact total score, and the Pediatric Anxiety Rating Scale (PARS)

Statistical Analysis Plan

The Applicant defined the efficacy sample as all randomized subjects who received at least one dose of the study medication and had a baseline and at least one post-baseline assessment for the ABC-I subscale score. The primary efficacy analysis was based on observed cases (OC), which refers to the actual observations or assessments of the outcomes that the investigators recorded at each visit during the double-blind treatment phase, without imputation of any missing observations.

In clinical trial practice, due to instances of non-adherence such as treatment discontinuation, the Applicant selected the hypothetical strategy to define the primary estimand. The estimand, or target of estimation, followed the hypothetical strategy and represents the treatment effect observed assuming no withdrawals occurred. Subjects who withdrew from study treatment either could have lost their treatment effect (assuming no other treatments received after withdrawal) or could have had their treatment effect masked if the subject received other concomitant treatments after withdrawal. Therefore, observations made after the subject stops treatment will most likely not contribute relevant information about the treatment effect of the drug. Due to this strategy, the Applicant collected only one efficacy assessment after premature trial discontinuation at the early termination (ET) visit prior to administering any additional medications. In the case of terminal or lost to follow-up events, the Applicant did not plan to take ET evaluations.

The primary estimand is defined by the following attributes:

- Target Population: subjects who met eligibility criteria and were qualified for the Efficacy Sample
- Endpoint: change from baseline to Week 8 in the ABC-I subscale score
- Intercurrent Events: premature treatment discontinuation prior to Week 8 attributable to AEs, lack of efficacy, withdrawal of consent, or any other causes
- Measure of Intervention Effect: difference in endpoint means between the brexpiprazole and placebo arms

Based on the hypothetical strategy, the Applicant considered the event of withdrawing study medication as missing at random (MAR). Therefore, the primary endpoint of the trial was a combination of the responses of treatment completers at Week 8 and the imputation of the endpoint to Week 8 following the trend in each treatment group (using the mixed model for repeated measures [MMRM] method to impute missing data for subjects who withdrew). The Applicant used all data collected during the treatment period for each analysis. For the primary efficacy analysis, the Applicant estimated the treatment effect using the MMRM method. The MMRM analysis included fixed effect terms of treatment, trial center, baseline body weight stratum, visit, and treatment-by-visit interaction, with baseline-by-visit interaction included as a covariate. The Applicant pooled small centers to form pseudo-centers so that each treatment group included at least one evaluable subject within a center. The Applicant analyzed the OC dataset using a restricted maximum likelihood-based repeated measure approach and unstructured covariance to model the within-subject errors. If the analysis failed to converge, the Applicant tested the following structures in order: 1) heterogeneous Toeplitz; 2) heterogeneous autoregressive of order one; and 3) heterogeneous compound symmetry. The Applicant considered the first correlation structure to yield convergence as the primary analysis. The Applicant applied the Kenward-Roger approximation to estimate the denominator degrees of freedom and to adjust standard errors. Significance testing was based on least square means (LSM) using a two-sided 0.05 level and claimed if the test was nominally significant. The primary treatment comparison was the contrast (i.e., difference in LSMs) between brexpiprazole and placebo at Week 8. If a structured covariance was implemented, the Applicant planned to use the sandwich estimator of the standard error of the fixed effect parameters to account for possible model misspecification of the covariance matrix. Because the possibility of missing not at random (MNAR) cannot be ruled out, the Applicant conducted several sensitivity analyses to assess the robustness of the inferences to departures from model assumptions with respect to the missing data mechanism and normality of the response variable. The Applicant used pattern mixture models (PMM) based on multiple imputation (MI) with mixed missing data mechanisms to investigate the response profile of dropout patients by termination reason under the MNAR mechanism. The Applicant also applied delta-adjusted and placebo-based imputation methods and performed the nonparametric Van Elteren test to compare treatment effects at Week 8 on both last observation carried forward (LOCF) and MI

datasets for gross violation of normality assumption.

Sample Size and Power

The Applicant aimed to randomize approximately 102 subjects (51 per treatment arm). A sample size of 51 per treatment arm provides at least 85% power at a nominal two-sided alpha level of 0.05 to detect a 6.0-point reduction in change from baseline in ABC-I subscale score for brexpiprazole versus placebo, assuming a standard deviation (SD) of 10.

In July 2022, the Applicant conducted a blinded interim analysis with 81% of subjects having completed the Week 8 visit or prematurely discontinued from the trial. The estimated SD reported was 8.8, less than the assumed SD of 10. The results showed that the planned sample size (102 randomized subjects) would adequately maintain 85% study power. As a result, the Applicant did not increase the sample size.

Protocol Amendments

There were five global amendments to the protocol. Pertinent changes to the study protocol are highlighted below:

- Amendment 1 (August 14, 2019)
  - Revised the Week 2 visit to occur in-clinic and to include EPS scales
  - Updated ranges for laboratory test values to identify subjects with potentially clinically relevant shifts and abnormal values
  - Updated washout days for restricted medications based on Division comments

- Amendment 2 (November 22, 2019)
  - Included bicarbonate to the laboratory tests at screening, baseline, and Week 8 to identify any acid-base imbalances that could occur with treatment

- Amendment 3 (February 12, 2020)
  - Revised lower limit of adolescent SBP and potential clinically relevant ranges for HbA1c, adrenocorticotropic hormone, and cortisol

- Amendment 4 (July 6, 2020)
  - Introduced a COVID-19 addendum for any protocol-specified activities that the Applicant cannot perform due to COVID-19 considerations
  - Excluded simultaneous participation of siblings or unrelated members of the same residence
  - Extended the screening period to accommodate repeating clinical laboratory tests or ECGs

- Amendment 5 (July 7, 2022)
  - Revised the treatment effect assumption from 5.5 to 6.0 to align with the pediatric

WR, resulting in a reduction in the required sample size from 65 to 51 randomized subjects per treatment arm (assumed SD remains 10)
- Clarified that the 2-day window is applicable to the dose-titration schedule
- Included a detailed description of the estimand framework
- Added a series of structured covariances as an alternative strategy to mitigate the problem of non-convergence (if the Applicant used structured covariance matrices, the Applicant agreed to use a sandwich estimator of the standard error of the fixed effects parameters to account for possible model misspecification of the covariance matrix)

Statistical Reviewer's Comment:
In Protocol Amendment 5, the Applicant changed the magnitude of treatment effect from 5.5 to 6 units, with assumed SD 10 and reduced sample size from 65 to 51 maintaining 85% power. The Applicant conducted an interim analysis when 81% of the patients had completed week 8 or discontinued trial. Sample size increase was not necessary because the estimated SD was 8.8, which is less than 10. Other changes related to statistics were to address statistical comments.

Clinical Reviewer's Comment: *The review team previously determined that the proposed protocol changes incorporated in each amendment were reasonable. The majority of revisions appear to clarify study procedures and update the statistical analysis plan (SAP). None of the protocol revisions appear to negatively impact the interpretation of study results.*

8.1.1.2. **Study Results of Trial 331-201-00148**

Compliance with Good Clinical Practices

The Applicant conducted this study in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines. The Applicant states that the study protocol, amendments, informed consent form, and other appropriate study-related information were reviewed by an independent ethics committee or institutional review board prior to study initiation.

Financial Disclosure

Refer to Section 0 of this review for detailed financial disclosure information. There are no disclosed financial interests or arrangements or missing disclosures that raise questions about the integrity of study data.

Patient Disposition

The Applicant screened a total of 260 subjects and randomized 119 subjects into the double-blind treatment period. See Table 9 for an overview of patient disposition. In the Randomized Sample, 15 subjects (13%) discontinued during the trial (12% and 13% discontinued from the study in the placebo and brexpiprazole treatment groups, respectively). The Safety Sample comprised 115 subjects who received at least one dose of the study medication. Two subjects in each of the treatment arms did not receive at least one dose of the study medication. The Efficacy Sample did not include one randomized subject in the placebo group because the subject's baseline ABC-I assessment occurred 3 days after the date of the first dose. The most frequent reasons for discontinuation were due to loss to follow-up or AEs (2.5% each).

Table 9: Disposition of Subjects in Study 331-201-00148 (Randomized Sample)

Disposition	Placebo (N=59)	BREX (N=60)	Total (N=119)
Completed	52 (88%)	52 (87%)	104 (87%)
Discontinued	7 (12%)	8 (13%)	15 (13%)
Lost to follow-up	2 (3.4%)	1 (1.7)	3 (2.5)
Adverse events	1 (1.7%)	2 (3.3)	3 (2.5)
Subject withdrew	-	1 (1.7)	1 (0.8)
Subject withdrew by parent or guardian	1 (1.7%)	2 (3.3)	3 (2.5)
Protocol deviation	-	1 (1.7)	1 (0.8)
Lack of efficacy	2 (3.4%)	-	2 (1.7)
Disease relapse	-	1 (1.7)	1 (0.8)
Other	1 (1.7%)	-	1 (0.8)
Safety sample	57 (97%)	58 (97%)	115 (97%)
Efficacy sample	56 (95%)	58 (97%)	114 (96%)

Source: Reviewer-adapted using Applicant's Clinical Study Report 331-201-00148, Table 10.1-1

Protocol Violations/Deviations

Refer to Table 10 for an overview of the Applicant's listing of major protocol violations during the double-blind period. In general, the percentage of subjects with major protocol deviations was similar across both treatment groups. The Applicant categorized the majority of protocol deviations as related to procedural errors (i.e., virtual visit due to COVID-19; COVID-19 complications; actual visit was outside visit window; timing of assessments). During the study period, only one subject in the brexpiprazole treatment group discontinued due to a protocol deviation.

Table 10: Summary of Major Protocol Violations During the Double-Blind Period for Study 331-201-00148 (Safety Sample)

Protocol Deviations	Placebo (N=59)	BREX (N=60)
Number of subjects with major protocol deviations	10 (17%)	12 (20%)
Entry Criteria	1 (1.7%)	1 (1.7%)
Dosing	-	1 (1.7%)
Procedural	7 (12%)	10 (17%)
Concomitant medications	2 (3.4%)	4 (6.7%)

Source: Applicant's addv.xpt dataset

***Clinical Reviewer's Comment**: For an 8-week study conducted among pediatric subjects with ASD, the incidence of major protocol deviations appeared relatively low as compared to other studies in ASD (see the Multidisciplinary Reviews for risperidone, aripiprazole, (b) (4) (b) (4)). Given the balance of protocol deviations between treatment groups, it is unlikely that the study results would be biased towards demonstrating a positive treatment effect. Protocol deviations associated with the use of concomitant medications were numerically higher in the brexpiprazole group (two cases of ingesting antihistamines and two cases of receiving CYP2D6/CYP3A4 inhibitors) vs. placebo (one case describing use of oral contraception and stimulant, each, during the screening phase), although the overall difference is likely of negligible consequence.*

Table of Demographic Characteristics

Refer to Table 11 through Table 13 below for a summary of demographic, baseline disease characteristics, and prior medication-use history across treatment groups.

In general, demographic characteristics were similar between genders, age groups (≤ 12 vs. > 12 years), weight groups (< 50 kg vs. ≥ 50 kg), and racial groups across treatment arms. In the overall randomized population, there was a lower percentage of females (13%) vs. males (87%) and lower percentage of African Americans (11%) and Asians (4%) vs. White subjects (79%). Due to the Applicant's enrollment of subjects in only US study centers, an evaluation of regional differences was not necessary.

Table 11: Demographic and Baseline Characteristics for Study 331-201-00148 (Randomized Sample)

Demographic Characteristic	Placebo (N=59)	BREX (N=60)	Total (N=119)
Age (years)			
Mean (SD)	10.0 (3.2)	9.8 (2.9)	9.9 (3.0)
Median (Range)	9.0 (5, 16)	9.0 (5, 17)	9.0 (5, 17)
Age group (years), n (%)			
5 to 12	46 (78%)	50 (83%)	96 (81%)
13 to 17	13 (22%)	10 (17%)	23 (19%)
Gender, n (%)			
Male	50 (85%)	54 (90%)	104 (87%)
Female	9 (15%)	6 (10%)	15 (13%)
Race, n (%)			
White	45 (76%)	49 (82%)	94 (79%)
Black or African American	10 (17%)	3 (5.0%)	13 (11%)
Asian	3 (5.1%)	2 (3.3%)	5 (4.2%)
Native Hawaiian or Pacific Islander	-	1 (1.7%)	1 (0.8%)
Other	1 (1.7%)	5 (8.3%)	6 (5.0%)
Ethnicity, n(%)			
Hispanic or Latino	7 (12%)	8 (13%)	15 (13%)
Not Hispanic or Latino	52 (88%)	52 (87%)	104 (87%)
Weight (kg), mean (SD)	43.2 (19)	43.9 (24)	43.6 (22)
Height (cm), mean (SD)	142.9 (18)	142.9 (18)	142.9 (18)
BMI (kg/m^2), mean (SD)	20.0 (4.9)	20.0 (6.6)	20.0 (5.8)
Weight circumference (cm), mean (SD)	72.8 (15)	72.3 (16)	72.5 (16)

Source: Clinical Reviewer-created using adsl.xpt dataset
Abbreviations: BMI = body mass index; SD = standard deviation

Other Baseline Characteristics

Across both treatment groups, baseline disease characteristics and psychiatric history were similar based on subjects in the Randomized Sample (Table 12). Approximately 70% of subjects had at least one comorbid psychiatric condition—the highest incidence was reported for ADHD (68%). Assessment of mean ABC subscale scores and CGI-S score suggest that subjects exhibited moderate to severe symptoms.

Refer to Table 13 for a history of psychotropic medication prior to the double-blind period. There were no major differences in usage of psychotropic medications prior to study entry between treatment arms. Of the subjects receiving a psychotropic medication prior to study entry, slightly more than half of the subjects (54%) received a stimulant medication for the treatment of ADHD. Overall, the number of subjects that previously received antipsychotic treatment was 13% and similar between treatment groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant measured treatment compliance by dividing the total number of study medication tablets taken by the total number of scheduled tablets during the trial period. In

both treatment groups, the Applicant observed 90% study compliance in all subjects. During the double-blind treatment period, the majority of subjects that previously received treatment with a stimulant continued with their treatment; 48% and 54% of subjects in the brexpiprazole and placebo groups, respectively, concomitantly used a stimulant. The use of benzodiazepines as rescue therapy was rare between treatment arms (placebo = 3% vs. brexpiprazole = 1.8%). Only one subject in the brexpiprazole arm received propranolol for EPS-related symptoms. Of note, use of melatonin was approximately four times higher in the brexpiprazole group (20%) as compared to the placebo group (5%).

Table 12: Baseline Disease and Psychiatry History for Study 331-201-00148 (Randomized Sample)

Disease Characteristic	Placebo (N=59)	BREX (N=60)	Total (N=119)
Comorbid psychiatric conditions[1], n (%)			
Agitation	3 (5.1%)	-	3 (2.5%)
Anxiety	6 (10%)	7 (12%)	13 (11%)
ADHD	40 (68%)	41 (68%)	81 (68%)
Enuresis	2 (3.4%)	1 (1.7%)	3 (2.5%)
DMDD	5 (8.5%)	2 (3.3%)	7 (5.9%)
Insomnia	6 (10%)	12 (20%)	18 (15%)
OCD	2 (3.4%)	3 (5.0%)	5 (4.2%)
ODD	5 (8.5%)	3 (5.0%)	8 (6.7%)
ABC subscale scores, mean (SD)			
Hyperactivity/non-compliance	31.7 (11)	33.6 (8.9)	32.7 (9.8)
Inappropriate speech	5.7 (3.2)	6.7 (3.4)	6.2 (3.3)
Irritability	28.6 (7.6)	29.7 (8.0)	29.1 (7.8)
Social withdrawal	19.9 (11)	18.1 (9.7)	18.9 (10)
Stereotypic Behavior	8.5 (5.4)	8.7 (6.0)	8.6 (5.7)
CGI-S score, mean (SD)	4.7 (0.5)	4.9 (0.7%)	4.8 (0.7)
PARS total score, mean (SD)	11.4 (5.3)	11.0 (5.8)	11.2 (5.5)

Source: Reviewer-adapted using Applicant's Clinical Study Report 331-201-00148, Table 11.2.1-1
[1]Includes psychiatric comorbid conditions with total incidence > 2%
Abbreviations: ABC = Aberrant Behaviors Checklist; ADHD = attention deficit hyperactivity disorder; BMI = body mass index; CGI-S = Clinical Global Impression of Severity; DMDD = disruptive mood dysregulation disorder; OCD = obsessive compulsive disorder; OODD = oppositional defiant disorder; PARS = Pediatric Anxiety Rating Scale; SD = standard deviation

Table 13: Psychotropic Medication Use Prior to the Double-Blind Period in Study 331-201-00148 (Randomized Sample)

Indication/Drug, n (%)	Placebo (N=59)	BREX (N=60)	Total (N=119)
Subjects receiving at least one psychotropic	35 (60%)	39 (65%)	74 (62%)
Antipsychotics	7 (12%)	8 (13%)	15 (13%)
Stimulants	33 (56%)	29 (48%)	64 (54%)
Antidepressants	5 (8.5%)	4 (6.6%)	9 (7.6%)
Benzodiazepines	-	2 (3.3%)	2 (1.7%)
Sleep-aid (i.e., melatonin)	4 (6.8%)	11 (18%)	15 (13%)

Source: Clinical Reviewer-created using adcm.xpt and adsl.xpt dataset

Clinical Reviewer's Comment: *Overall assessment of demographic and baseline characteristics did not reveal any significant imbalances between the two treatment groups. Given that the*

Applicant enrolled subjects from US center sites only, there was lower representation of pediatric subjects of Asian and of African descent (prevalence of ASD known to be higher in non-White populations). The Applicant also did not provide any discussion on barriers to study enrollment. The current literature indicates that the majority of patients with ASD in the United States are male (four times higher prevalence relative to females), and 50 to 70% of patients present with comorbid ADHD (Hours C, et al., 2022). These proportions align with the enrolled study population. Although the Applicant did not report age of onset for irritability symptoms associated with ASD, the limited number of subjects receiving prior antipsychotic treatment (13%) suggest that the Applicant mainly enrolled a treatment-naïve study population. The lack of rescue treatments (e.g., benzodiazepines) and concomitant medications during the study period reduces concerns over potential bias in the estimated treatment effect.

Efficacy Results – Primary Endpoint

There was no statistically significant difference between the brexpiprazole and placebo groups for the primary efficacy endpoint, mean change from baseline to Week 8 in ABC-I subscale score (least squares mean difference [LSMD] = −1.22 [95% CI [confidence interval]: −4.49, 2.05], p = 0.4597; Table 14). There was a nominal reduction from baseline to Week 8 in mean ABC-I subscale score in both the brexpiprazole (LSM change= −10.1) and placebo (LSM change = −8.87) groups.

Table 14: Summary of Mean Change from Baseline to Week 8 in ABC- Irritability Subscale Score (MMRM; Efficacy Sample)

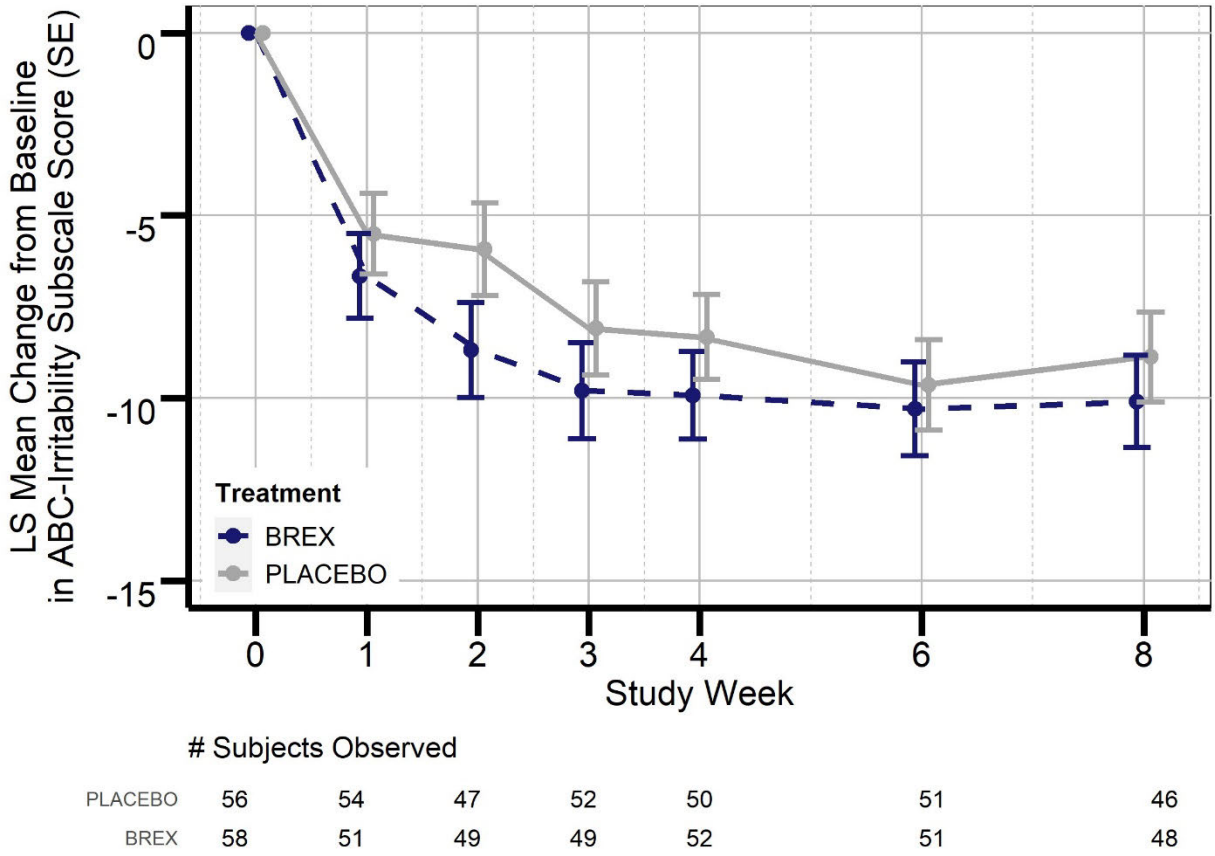
	Placebo (N=58)	BREX (N=56)
Mean ABC-I Total Score at Baseline (SD)	28.75 (7.69)	29.60 (8.05)
LSM Change from Baseline at Week 8 (SE)	-8.87 (1.25)	-10.1 (1.28)
Placebo-subtracted difference (95% CI)[1]		-1.22 (-4.49, 2.05)
P-value		0.4579

Source: Applicant's Study 331-201-00148 Clinical Study Report, Table 11.4.1.1.1-1 and confirmed by statistical reviewer
Abbreviations: ABC-I = Aberrant Behaviors Checklist – Irritability subscale; LSM = least squares mean; MMRM = mixed-effect model for repeated measures; SD = standard deviation; SE = standard error; 95% CI = unadjusted 95% confidence interval
[1]MMRM method with model terms: treatment, trial site, visit, baseline body weight stratum, visit, treatment by visit, and baseline by visit interaction

Time Plot

Figure 3 displays the mean change from baseline for each treatment group over 8 weeks. Although there was a slight nominal difference in the treatment at Week 2 (likely due to a deviation in the trajectory of the placebo response), there was no notable difference between treatment groups on the primary efficacy measure at any of the other study visits.

Figure 3: Study 331-201-00148 LS Mean Change from Baseline to Week 8 in the ABC-I Subscale Score by Week (MMRM; Efficacy Sample)



Source: Clinical Reviewer-adapted figure from Applicant's Clinical Study Report, Figure 11.4.1.1.2-1
[1]Dashed line represents the placebo treatment arm. Error bars are LS mean +/- one standard error.
Abbreviations: ABC-I = Aberrant Behaviors Checklist Irritability subscale; LS = least squares, MMRM = mixed-effect model repeated measures

Efficacy Results – Secondary Endpoint

Because the primary efficacy endpoint did not reach statistical significance, the Applicant did not conduct further formal statistical testing for the key secondary endpoint, mean change from baseline to Week 8 in CGI-S score. Table 15 provides the analysis results of the secondary efficacy endpoint. A numerical reduction from baseline to Week 8 in mean CGI-S score was seen in both the brexpiprazole (LSM change = −1.16) and placebo (LSM change = −1.09) groups; however, the treatment difference was negligible (LSMD = -0.07 [95% CI: -0.46, 0.32]).

Table 15: Summary of Mean Change from Baseline to Week 8 in CGI-S Score (MMRM; Efficacy Sample)

	Placebo (N=58)	BREX (N=56)
Mean CGI-S score at Baseline (SD)	4.68 (0.54)	4.86 (0.74)
LSM Change from Baseline at Week 8 (SE)	-1.09 (0.15)	-1.16 (0.15)
Placebo-subtracted difference (95% CI)[1]		-0.07 (-0.46, 0.32)
Nominal P-value		0.7315

Source: Applicant's Study 331-201-00148 Clinical Study Report, Table 11.4.1.2.1-1 and confirmed by statistical reviewer
Abbreviations: CGI-S = Clinical Global Impression of Severity; LSM = least squares mean; MMRM = mixed-effect model for repeated measures; SD = standard deviation; SE = standard error; 95% CI = unadjusted 95% confidence interval
[1]MMRM method with model terms: treatment, trial site, visit, baseline body weight stratum, visit, treatment by visit, and baseline by visit interaction

Dose/Dose Response

Given that this study 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. Evaluation of modal dosages after Day 15 (time at which subjects could receive a dosage within the target dose range) could provide insights into the potential dose-response relationship. Figure 4 provides the mean change from baseline in the ABC subscale scores by modal dosage in subjects who completed the 8-week double-blind treatment period. Because subjects with total body weight < 50 kg received lower dosages, it is expected that younger children likely received lower dosages relative to adolescents. Although mean change from baseline in the ABC subscale score was greater at higher dosages, the interpretation is limited due to the small sample size (approximately 20% of the study population consisted of adolescents who could have been eligible for higher dosages).

Durability of Response

Because brexpiprazole did not demonstrate a statistically significant treatment effect on the primary endpoint, this review did not evaluate durability of response with continued treatment.

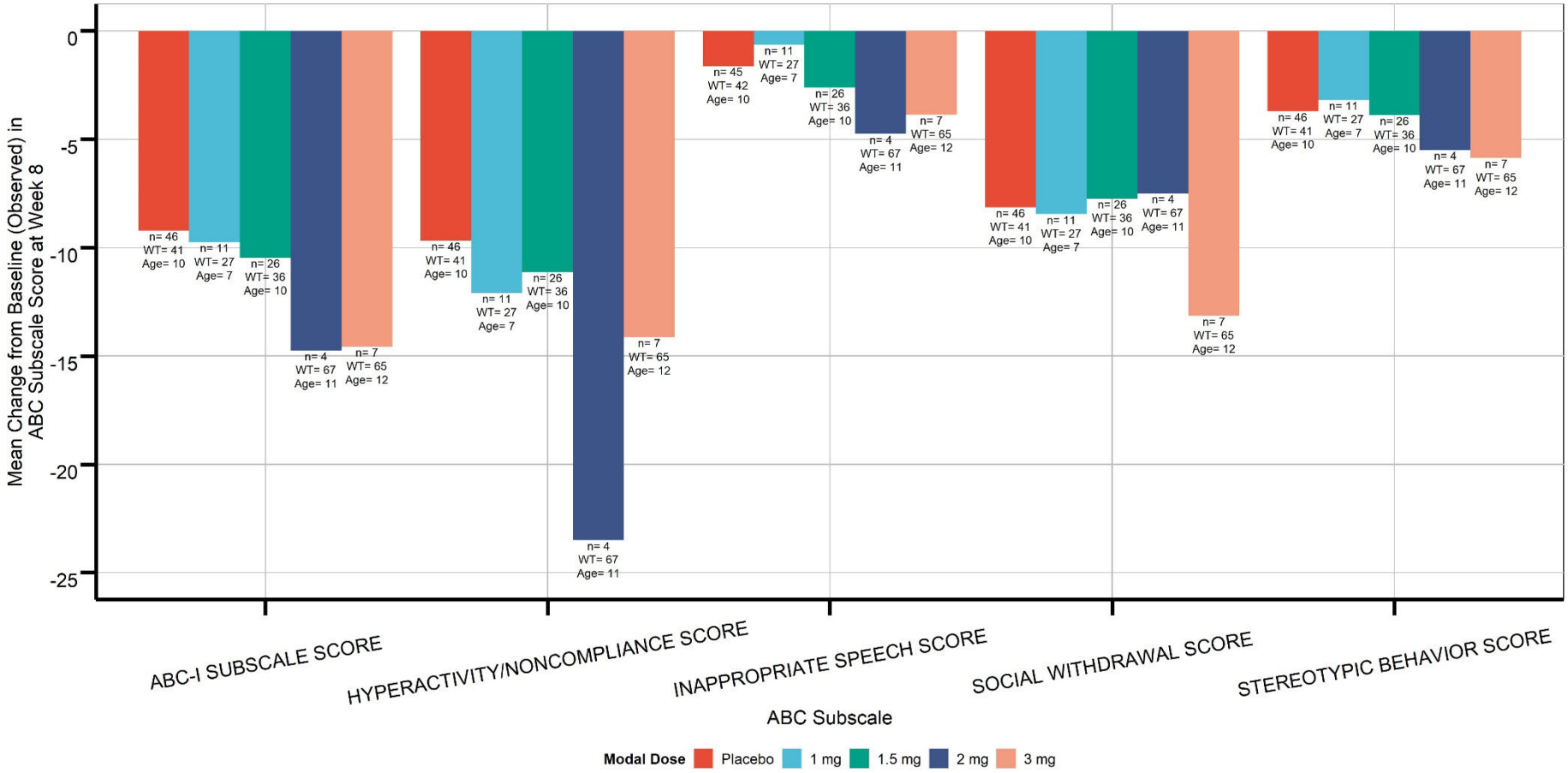
Persistence of Effect

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

Exploratory analysis on other secondary and exploratory endpoints (e.g., change from baseline in the PARS and PedsQL) also showed consistent results and a lack of numerical difference between treatment groups (PARS: LSMD = −0.07 [95% CI: −2.04, 1.91]; PedsQL generic core: LSDM = 5.22 [95% CI: −0.66, 11.11]).

Figure 4: Mean change from Baseline in ABC Subscale Scores by Modal Dose in Study Completers



Source: Clinical Reviewer-created using adsl.xpt and adabc.xpt datasets
Abbreviations: ABC = Aberrant Behaviors Checklist; WT = total body weight

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety evaluation for this supplemental application is based on one phase 3 double-blind, placebo-controlled study (331-201-00148) and data from an open-label, long-term extension study (331-201-00191). Details regarding the study design and patient population are provided in Section 8.1.1 and 8.2.7 of this review.

The current product label describes safety data in adults with major depressive disorder (based on short-term placebo-controlled and long-term, open label studies) and schizophrenia (based on short-term placebo-controlled and long-term, open label studies), adolescents with schizophrenia (based on a long-term, open label study), and elderly patients with agitation associated with dementia due to Alzheimer's disease (based on short-term placebo-controlled and long-term, open label studies). Safety data accumulated from the ASD development program will provide sufficient placebo-controlled data in adolescents and children and long-term data in children to fill in the gaps in the expected age-range of use for brexpiprazole and inform product labeling. Therefore, this review will also include analyses to evaluate brexpiprazole's safety profile in subjects 5 to 17 years of age relative to existing data in adults and adolescents.

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

- Adverse events (e.g., EPS, metabolic changes, orthostatic hypotension, infection)
- Physical examination and vital sign measurements
- ECG parameters
- Laboratory measurements
- C-SSRS assessments for SI/B
- EPS-related scales (i.e., Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], and Simpson-Angus Scale [SAS]).

Of note, Sections 8.2.2 through 8.2.6 will describe data from Study 331-201-00148. Section 8.2.7 will include a separate summary of the safety data from Study 331-201-00191.

8.2.2. Review of the Safety Database

Overall Exposure

A summary of the extent of exposure for Study 331-201-00148 is shown in Table 16. A total of 58 subjects were exposed to at least one dose of brexpiprazole. Approximately 70% of subjects received treatment for at least 8 weeks. There were no differences in mean exposure and

dosage by age, gender, or race. Among subjects who completed Study 331-201-00148, 95 subjects participated in Study 331-201-00191. In the Safety Sample of the long-term, open-label extension study, 24 subjects (25%) received brexpiprazole for at least 182 days (13 subjects [27%] in the prior brexpiprazole group and 11 subjects [24%] in the prior placebo group).

Table 16: Extent of Exposure in Study 331-201-00148 (Safety Sample)

Variable	Placebo (N=57)	BREX (N=58)	Total (N=115)
Days of exposure, n(%)			
1 to 7 days	-	1 (1.7%)	1 (0.9%)
8 to 14 days	3 (5.3%)	3 (5.2%)	6 (5.2%)
15 to 21 days	-	-	
22 to 28 days	1 (1.8%)	-	
29 to 35 days	-	-	
36 to 42 days	1 (1.8%)	2 (3.4%)	3 (2.6%)
43 to 49 days	-	1 (1.7%)	1 (0.9%)
50 to 56 days	10 (18%)	13 (22%)	23 (20%)
> 56 days	42 (74%)	38 (66%)	80 (70%)

Source: Applicant's 331-201-00148 Clinical Study Report Table 12.1-1

Adequacy of the Safety Database

Given that efficacy findings in Study 331-201-00148 were negative, the Applicant did not conduct a second phase 3 efficacy and safety study and did not pursue an indication for the treatment of irritability associated with ASD. Although the safety sample is limited (58 subjects from the short-term study and 95 subjects from the long-term study), comparisons of the available data in children and adolescents relative to adults can inform product labeling.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant provided original Case Report Forms for serious AEs (SAEs) and AEs leading to discontinuation (the Applicant did not report any deaths from either study). From a safety perspective, there are no issues regarding data integrity and submission quality.

Categorization of Adverse Events

The Applicant assessed for AEs at each study visit throughout the treatment period and categorized AEs by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA; version 25.0). The Applicant collected AEs as per the schedule provided in Section 8.1 of this review. The Applicant defined treatment-emergent adverse events (TEAEs) as AEs that were new in onset or increased in severity following treatment initiation, regardless of causality (all reported AEs were TEAEs; therefore, TEAEs are referred to as AEs throughout this review).

Clinical Reviewer's Comment: *The Applicant's AE monitoring, severity determinations, and*

mapping of verbatim-to-preferred terms are acceptable. The Applicant's categorization of AEs also align with their previous safety analysis for the original NDA. This reviewer grouped the following preferred terms together:

- *Decreased appetite: decreased appetite and food refusal*
- *Increased appetite: increase appetite, hyperphagia, appetite disorder (excessive hunger), and food craving*
- *Insomnia: initial insomnia and insomnia*
- *Fatigue: fatigue and lethargy*
- *Somnolence: sedation and somnolence.*

Routine Clinical Tests

The schedule of routine clinical tests for each study was presented in Section 8.1 of this review. The Applicant required all subjects to provide blood sample after fasting for a minimum of 8 hours at the scheduled visit. The scheduling of clinical tests appears similar across studies and adequate to support the review of clinical safety.

8.2.4. Safety Results

Deaths

No deaths occurred in the ASD development program.

Serious Adverse Events

The Applicant did not report any SAEs for Study 331-201-00148.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant discontinued study medication due to AEs in two subjects (3.4%) in the brexpiprazole group and one subject (1.8%) in the placebo group. All AE leading to treatment discontinuation were moderate in severity. In the brexpiprazole group, one subject discontinued treatment due to food refusal and emotional breakdown (self-blaming and guilt) and the second subject due to increased blood pressure (BP). The subject receiving placebo discontinued treatment due to aggressive outbursts at school (preferred term: aggression) and excessive hunger (preferred term: appetite disorder). Notably, all three subjects had co-morbid ADHD and reported concomitant use of a stable stimulant during the study period.

Treatment Emergent Adverse Events and Adverse Reactions

A summary of the incidence of AEs occurring in at least 2% of subjects in either the brexpiprazole or placebo groups is presented in Table 17. Although the total incidence of subjects reporting AEs were greater among subjects receiving brexpiprazole vs. placebo (52% vs. 35%, respectively), there were no observed dose-dependent trends (based on modal dosages). AEs reported in at least 5% of subjects in the total brexpiprazole group with an

incidence greater than in the placebo group included fatigue, headache, increased appetite, somnolence, and vomiting. The Applicant also did not identify any new AEs for brexpiprazole compared with AEs observed with prior brexpiprazole studies.

Table 17: Incidence of Adverse Events Reported by At least 2% of Subjects Receiving Brexpiprazole and Greater than Placebo in Study 331-201-00148

Adverse Event[1]	Placebo (N=57)	BREX (N=58)	Total (N=115)
Akathisia	-	2 (3.4%)	2 (1.7%)
Decreased appetite	-	2 (3.4%)	2 (1.7%)
Diarrhea	-	2 (3.4%)	2 (1.7%)
Fatigue	-	3 (5.2%)	3 (2.6%)
Headache	1 (1.8%)	6 (10%)	7 (6.1%)
Increased appetite	1 (1.8%)	4 (6.9%)	5 (4.3%)
Insomnia	3 (1.8%)	2 (3.4%)	5 (4.3%)
Pyrexia	-	2 (3.4%)	2 (1.7%)
Somnolence	3 (5.3%)	9 (16%)	12 (10%)
Tremor	-	2 (3.4%)	3 (2.6%)
Upper Respiratory Tract Infection	1 (1.8%)	2 (3.4%)	3 (2.6%)
Vomiting	1 (1.8%)	3 (5.2%)	4 (3.5%)

Source: Clinical Reviewer-created using adae.xpt dataset
[1]Subjects were counted once per AE grouping. Adverse events included only those that started after the start of the study drug or if the event was continuous from baseline and was serious, drug-related, or resulted in death, discontinuation, or interruption or reduction of study treatment.
Note: Decreased appetite included food refusal and decreased appetite preferred terms; Fatigue included fatigue and lethargy preferred terms; Increased appetite included food cravings, increased appetite, hyperphagia, and appetite disorder (coded for excessive hunger) preferred terms; Insomnia included insomnia and initial insomnia preferred terms; Somnolence included sedation and somnolence preferred terms.

Clinical Reviewer's Comment: *When comparing the observed incidences of AEs from Study 331-201-00147 relative to short-term, placebo-controlled studies described in the product label, AEs related to somnolence (16%) were significantly higher in pediatric subjects with ASD relative to adults (MDD studies: 4%; schizophrenia studies: 5%; agitation associated with dementia due to Alzheimer's disease: 3%). In a long-term, open-label study evaluating brexpiprazole in adolescents with schizophrenia, approximately 10% of subjects reported somnolence as AE. Of the nine cases of somnolence reported in Study 331-201-00148, seven cases occurred in subjects 5-to-12 years old. In an FDA meta-analysis of adult and pediatric safety studies evaluating 10 antipsychotics, results also suggested a consistently higher risk for somnolence in pediatric subjects relative to adults (Liu X, et al., 2020). Given the 3- to 4-fold higher incidence in children and adolescents relative to adults, this difference will be described in Section 8.4.*

Laboratory Findings

Refer to the schedule of events in Section 8.1 for details on the collection of laboratory measures. Table 18 describes the mean changes from baseline to last visit and incidences of potentially clinically relevant changes in laboratory measures for each treatment group. The Applicant appropriately included criteria for identifying laboratory values of potential clinical relevance specific to each age group in each of the study protocols. Overall, analysis of changes in laboratory measures, other than prolactin, did not indicate any clinically relevant differences

between brexpiprazole and placebo in the pediatric study population.

Table 18: Baseline and Mean Changes in Laboratory Assessments During the Treatment Period in Study 331-201-00148

Laboratory Measure[1]	Value	Placebo (N=57)	BREX (N=58)
Alanine aminotransferase (U/L)	Mean baseline (SD)	15.3 (7.7)	196 (14)
	Mean change (SD)	0.5 (6.5)	1.6 (14)
	Potentially clinically relevant changes, n (%)	-	1 (1.9%)
Alkaline phosphatase (U/L)	Mean baseline (SD)	230 (93)	247 (78)
	Mean change (SD)	-4.9 (32)	7.5 (38)
	Potentially clinically relevant changes, n (%)	-	-
Aspartate Aminotransferase (u/L)	Mean baseline (SD)	24.2 (6.3)	25.8 (8.1)
	Mean change (SD)	-1.0 (4.2)	0.3 (7.2)
	Potentially clinically relevant changes, n (%)	-	-
Bilirubin (mg/L)	Mean baseline (SD)	0.4 (0.2)	0.4 (0.2)
	Mean change (SD)	0.03 (0.2)	-0.01 (0.1)
	Potentially clinically relevant changes, n (%)	10 (26%)	9 (21%)
Bicarbonate (mEq/L)	Mean baseline (SD)	20.4 (2.4)	19.8 (2.0)
	Mean change (SD)	-0.3 (3.0)	-0.7 (2.7)
	Potentially clinically relevant changes, n (%)	9 (19%)	10 (20%)
Chloride (mEq/L)	Mean baseline (SD)	103 (2.2)	103 (2.3)
	Mean change (SD)	0.2 (2.6)	0.2 (2.6)
	Potentially clinically relevant changes, n (%)	-	2 (3.9%)
Cholesterol, fasting (mg/dL)	Mean baseline (SD)	156 (20)	162 (37)
	Mean change (SD)	-0.6 (17)	1.5 (18)
	Potentially clinically relevant changes, n (%)	1 (3.7%)	-
Cortisol	Mean baseline (SD)	7.3 (3.9)	6.9 (3.8)
	Mean change (SD)	-0.3 (3.9)	-0.1 (4.0)
	Potentially clinically relevant changes, n (%)	4 (8.3%)	4 (8.2%)
Creatinine (mg/dL)	Mean baseline (SD)	0.5 (0.1)	0.5 (0.1)
	Mean change (SD)	0 (0.1)	0.02 (0.1)
	Potentially clinically relevant changes, n (%)	1 (2.0%)	1 (1.9%)
Glucose, fasting (mg/dL)	Mean baseline (SD)	88.5 (7.4)	86.1 (8.4)
	Mean change (SD)	-0.9 (9.9)	6.6 (17)
	Potentially clinically relevant changes, n (%)	1 (3.8%)	2 (6.5%)
Potassium (mEq/L)	Mean baseline (SD)	4.3 (0.3)	4.4 (0.4)
	Mean change (SD)	0.04 (0.3)	-0.02 (0.4)
	Potentially clinically relevant changes, n (%)	-	1 (2.0%)
Sodium (mEq/L)	Mean baseline (SD)	141 (2.0)	140 (2.1)
	Mean change (SD)	0.4 (2.3)	0.6 (2.7)

Laboratory Measure[1]	Value	Placebo (N=57)	BREX (N=58)
	Potentially clinically relevant changes, n (%)	1 (2.1%)	2 (4.0%)
Triglycerides, fasting (mg/dL)	Mean baseline (SD)	74.5 (28)	95.1 (75)
	Mean change (SD)	7.6 (52)	0.65 (66)
	Potentially clinically relevant changes, n (%)	5 (19%)	3 (12%)
Hematocrit (%)	Mean baseline (SD)	38.6 (3.5)	38.3 (2.9)
	Mean change (SD)	0.2 (3.2)	0.3 (2.2)
	Potentially clinically relevant changes, n (%)	3 (6.1%)	3 (6.7%)
Hemoglobin (g/dL)	Mean baseline (SD)	13.2 (1.0)	13.2 (1.0)
	Mean change (SD)	-0.02 (1.0)	-0.05 (0.6)
	Potentially clinically relevant changes, n (%)	1 (2.0%)	-
Neutrophils (x10^9/L)	Mean baseline (SD)	3.5 (1.2)	3.6 (1.3)
	Mean change (SD)	-0.03 (1.9)	0.2 (1.4)
	Potentially clinically relevant changes, n (%)	-	1 (1.9%)
Platelets (x10^9/L)	Mean baseline (SD)	310 (75)	318 (92)
	Mean change (SD)	-4.9 (61)	-6.7 (69)
	Potentially clinically relevant changes, n (%)	-	-
Prolactin, females (ng/mL)	Mean baseline (SD)	8.1 (3.0)	8.7 (10)
	Mean change (SD)	1.7 (5.9)	8.1 (2.0)
	Potentially clinically relevant changes, n (%)	1 (11%)	-
Prolactin, males (ng/mL)	Mean baseline (SD)	6.2 (4.2)	7.3 (4.3)
	Mean change (SD)	0.1 (4.9)	1.8 (7.4)
	Potentially clinically relevant changes, n (%)	1 (2.4%)	3 (6.8%)

Source: Clinical Reviewer-created using adlb.xpt dataset
[1]Calculation of mean baseline and change from baseline for each parameter is based only on subjects with both baseline and evaluation at the last visit for each given parameter
Note: Potential clinically relevant changes include both abnormally low and high values based on the Applicant's age-specific criteria listed in the Clinical Study Report.

In both males and females, the mean change from baseline in prolactin was greater in the brexpiprazole group vs. placebo. Although the percentage of subjects with potentially clinically relevant changes were low in both treatment groups, interpretability of prolactin results in females is limited due to the small number of female subjects with collected prolactin measures.

There were no subjects in the brexpiprazole group that had an AE recorded as an abnormal laboratory result; one subject in the placebo group experienced elevated glucose that the Applicant recorded as hyperglycemia. There were also no cases that met pediatric criteria for metabolic syndrome.

Clinical Reviewer's Comment: *Overall, analysis of laboratory assessments did not reveal any new safety signals and were consistent with known prior adult findings for brexpiprazole. A*

comparison of clinically relevant shifts in fasting glucose and lipids in previous studies evaluating brexpiprazole in adults also described consistent results.

Vital Signs

Summaries for mean changes from baseline to the last study visit for supine SBP, DBP, and heart rate (HR) for Study 331-201-00148 are presented in Table 19. Mean changes in SBP and DBP were minimal and comparable between supine and standing measurements. Mean changes in HR were slightly increased in subjects receiving brexpiprazole versus placebo for both supine (3.0 mmHg vs. -2.0 mmHg) and standing (5.1 mmHg, vs. 1.8 mmHg) measurements, respectively. There was an increase in the percentage of subjects that had a potentially clinically relevant change in standing HR for the brexpiprazole group relative to placebo (16% vs. 9%, respectively).

Table 19: Changes in Heart Rate, Systolic Blood Pressure, and Diastolic Blood Pressure (Supine) in Study 331-201-00148

Vital Sign Measure	Value	Placebo (N=57)	BREX (N=58)
Supine			
HR (beats/min)	Mean baseline (SD)	84.0 (12)	83.6 (12)
	Mean change (SD)	-2.0 (12)	3.0 (14)
	Potentially clinically relevant changes, n (%)	3 (5.4%)	3 (5.7%)
SBP (mmHg)	Mean baseline (SD)	109 (11)	108 (11)
	Mean change (SD)	1.0 (11)	1.3 (7.8)
	Potentially clinically relevant changes, n (%)	3 (5.5%)	1 (1.8%)
DBP (mmHg)	Mean baseline (SD)	67.6 (12)	66.6 (9.1)
	Mean change (SD)	-1.2 (12)	-0.5 (10)
	Potentially clinically relevant changes, n (%)	2 (3.6%)	4 (7.2%)

Source: Applicant's 331-201-00148 Clinical Study Report Table 12.5.2-1
Note: Potential clinically relevant changes include both abnormally low and high values based on the Applicant's pre-specified criteria listed in the Clinical Study Report.

One subject in the brexpiprazole group each experienced AEs of increased BP (supine SBP was 133 mmHg) and diastolic hypotension (supine DBP was 55 mmHg). The Applicant did not report any cases of orthostatic hypotension.

***Clinical Reviewer's Comment**: Further evaluation of subjects with clinically relevant increases in standing HR indicated that most subjects (seven out of the nine in the brexpiprazole group and all subjects in the placebo group) were 5 to 12 years of age. However, none of these subjects experienced other clinical symptoms (e.g., clinical manifestations of neuroleptic malignant syndrome, autonomic instability, corrective response due to low BP) or reported AEs (e.g., tachycardia). It is also important to note that approximately 50% of subjects also received concomitant stimulants that could confound effects on vital sign measurements. Similarly, previous studies evaluating risperidone and* (b) (4) *in pediatric subjects similarly suggested*

minimal effects in HR (effect: 3.3 bpm) and BP (effect on SBP: 2.2 mmHg; effect on DBP: 2.8 mmHg).

Refer to Section 8.2.5 for information on brexpiprazole's effect on anthropometric measurements of growth.

Electrocardiograms (ECGs)

The Applicant collected resting 12-lead ECGs at screening, baseline, and Week 8 visits. Table 20 describes the mean baseline and mean change from baseline for each ECG parameter between treatment groups. In general, changes in each parameter were minimal and not considered to be clinically meaningful.

Table 20: Changes in ECG Parameters During the Treatment Period Across all 12-Week Phase 3 Studies

ECG Parameters	Value	Placebo (N=57)	BREX (N=58)
PR Interval	Mean baseline (SD)	137 (18)	136 (20)
	Mean change (SD)	-1.1 (8.4)	-0.7 (13)
QRS Interval	Mean baseline (SD)	84.5 (8.5)	82.8 (6.3)
	Mean change (SD)	0.7 (6.0)	1.0 (4.6)
RR Interval	Mean baseline (SD)	723 (114)	758 (138)
	Mean change (SD)	-2.0 (98)	-5.6 (101)
QT Interval	Mean baseline (SD)	346 (29)	353 (28)
	Mean change (SD)	-3.6 (23)	-9.0 (21)
QTcF Interval	Mean baseline (SD)	387 (20)	388 (16)
	Mean change (SD)	-3.5 (19)	-0.1 (16)
QTcN Interval	Mean baseline (SD)	393 (20)	392 (16)
	Mean change (SD)	-3.7 (20)	1.1 (16)

Source: Reviewer-adapted using Applicant's 331-201-00148 Clinical Study Report Table 12.5.3-1
Abbreviations: QTcB = corrected QT interval based on Bazett formula (QTcB = $QT/(RR)^{0.5}$); QTcF = corrected QT interval based on Fridericia formula (QTcF= $QT/(RR)^{0.33}$); QTcN = corrected QT interval based on the Office of Neurology/FDA formula (QTcN = $QT/(RR)^{0.37}$)

The most frequently observed clinically relevant ECG abnormality in the brexpiprazole and placebo groups was associated with cardiac rate (tachycardia; brexpiprazole: 7% vs. placebo: 8%) and rhythm (sinus tachycardia; brexpiprazole: 7% vs. placebo: 8%). ECG findings in one subject receiving placebo were indicative of a right bundle branch block. Only two subjects (4%) in the placebo group experienced a 30 to 60 msec change in the QTcF and QTcN interval. No subjects exhibited a QTc value > 500 msec by either correction method or reported an AE related to an ECG abnormality.

Clinical Reviewer's Comment: *The ECG results do not raise new safety concerns for brexpiprazole in the pediatric population.*

8.2.5. Analysis of Submission-Specific Safety Issues

Extrapyramidal Symptoms

The Applicant used solicited AE reporting and prospective evaluation of EPS-specific rating scale scores to inform the occurrence and severity of EPS-related symptoms. During the double-blind treatment period, two subjects (3%) in the brexpiprazole group and none in the placebo group reported mild EPS-related symptoms, excluding akathisia. Three subjects (5%) and two subjects (4%) receiving brexpiprazole and placebo, respectively, reported mild akathisia-related events including psychomotor hyperactivity and restlessness. Onset of EPS-related AEs generally occurred at Week 2 and 3 visits. Mean global scores captured using the BARS, SAS, and AIMS were consistent with AE reporting and described no clinically meaningful changes from baseline to the last study visit in either treatment group (SAS total score: brexpiprazole = 0 vs. placebo = 0.08; AIMS total score: brexpiprazole = -0.05 vs. placebo = -0.03; BARS: brexpiprazole = 0.02 vs. placebo = 0.1).

Clinical Reviewer's Comment: *The number of EPS-related events was relatively infrequent, and the overall incidence in the brexpiprazole group was similar to the incidence reported in adults (range: 3% to 6%).*

Changes in Body Weight, Height, and Body Mass Index

The Applicant collected weight, height, and waist circumference measurements at baseline and at Week 8 (or last study visit). Table 21 describes the mean change from baseline and the mean change in age- and gender-adjusted z-scores for each of the anthropometric measurements, including clinically relevant changes (i.e., changes in z-scores of > 0.5).

Although the difference in mean change in total body weight was approximately 1 kg between the brexpiprazole and placebo treatment groups, further evaluation of age- and gender-adjusted z-scores indicated a greater incidence of clinically relevant increases in body weight over 8 weeks among subjects receiving brexpiprazole vs. placebo (19% vs. 5%). One subject (2%) in the brexpiprazole group reported an AE of weight increase, while one subject (2%) in the placebo group reported an AE of weight decrease. Mean change from baseline in height was also similar between treatment groups; however, more subjects receiving brexpiprazole exhibited at least a 0.5 SD increase in age- and- gender-adjusted z-scores for height (21% vs. 12%). Changes in BMI followed a similar trend relative to changes in body weight; the between treatment difference in the mean change in BMI was approximately 0.7 mg/k^2 and the incidence of clinically relevant increases in age- and gender-adjusted BMI z-scores was greater among subjects receiving brexpiprazole vs. placebo (40% vs. 9%).

Refer to Section 8.2.7 for additional information on changes in body weight and BMI in the 26-week, open-label extension study (331-201-00191). Following the 8-week, double-blind treatment period from Study 331-201-00148, subjects who continued to receive brexpiprazole for 26 weeks experienced a 0.3 SD increase in age- and gender-adjusted z-scores for both body

weight and BMI (22% of subjects had an increase in body weight z-scores of at least 0.5 SD).

Table 21: Changes in Body Weight, Height, BMI, and Weight Circumference in Study 331-201-00148

Measure	Value[1,2]	Placebo (N=57)	BREX (N=58)
Body Weight (kg)	Mean baseline (SD)	41.6 (17)	42.0 (19)
	Mean change (SD)	0.4 (3.2)	1.5 (5.7)
	Mean z-score baseline (SD)	0.6 (1.3)	0.5 (1.4)
	Mean z-score change (SD)	0.05 (0.5)	0.3 (0.5)
	Increase > 0.5 SD, n (%)	3 (5.3%)	11 (19%)
	Decrease > 0.5 SD, n (%)	2 (3.5%)	2 (3.4%)
Height (cm)	Mean baseline (SD)	142 (17)	143 (18)
	Mean change (SD)	1.2 (2.2)	1.4 (3.0)
	Mean z-score baseline (SD)	0.3 (1.2)	0.4 (1.1)
	Mean z-score change (SD)	0.2 (0.3)	0.2 (0.5)
	Increase > 0.5 SD, n (%)	7 (12%)	12 (21%)
	Decrease > 0.5 SD, n (%)	2 (3.5%)	2 (3.4%)
BMI (kg/m^2)	Mean baseline (SD)	19.6 (4.6)	19.3 (5.1)
	Mean change (SD)	0.06 (1.1)	0.8 (1.3)
	Mean z-score baseline (SD)	0.5 (1.3)	0.4 (1.3)
	Mean z-score change (SD)	0 (0.5)	0.3 (0.6)
	Increase > 0.5 SD, n (%)	5 (9.3%)	22 (40%)
	Decrease > 0.5 SD, n (%)	7 (13%)	4 (7.3%)
Weight circumference (cm)	Mean baseline (SD)	71.6 (14)	71.0 (15)
	Mean change (SD)	-0.6 (4.0)	-0.7 (4.0)

Source: Reviewer-adapted using advs.xpt dataset
[1]Age- and gender-adjusted z-scores for body weight, height, and BMI were calculated using the Center for Disease Control and Prevention (CDC) approach (reference data from 2000)
[2]Change from baseline to last study visit; a change of 0.5 SD in z-scores previously described as clinically significant in product labels for other antipsychotics

Clinical Reviewer's Comment*: Due to the short duration of the double-blind period (8 weeks), changes in height were minimal, which was expected. However, the incidences of subjects with greater than 0.5 SD increase in age- and gender-adjusted z-scores for both total body weight and BMI were approximately four-fold greater in the brexpiprazole group vs. placebo. Of note, there was also a higher incidence of subjects with increased appetite among subjects receiving brexpiprazole vs. placebo (7% vs. 2%).*

It is also important to note that subjects who received brexpiprazole treatment for 26 weeks in Study 331-201-00191 (which will be discussed further in Section 8.2.7) also experienced a mean change in body weight of 4.5 kg (mean change in body weight z-score of 0.3; 26% of subjects with body weight z-score increases of at least 0.5 SD). In a long-term, open-label safety study in adolescents with schizophrenia (Study 331-10-236), subjects exposed to brexpiprazole for at least 6 months experienced a body weight z-scores increase of 0.1 SD (average weight increase of 3.8 kg), while 20% of subjects had an increase of at least 0.5 SD.

Changes in growth measures in pediatric subjects 5 to 17 years of age were also similar to those observed with other atypical antipsychotics. In short-term studies evaluating risperidone, mean weight change for risperidone-treated subjects over 8 weeks was 2 kg and approximately 30% of subjects had weight gain of at least 7%. In short-term studies evaluating aripiprazole, mean weight change for aripiprazole-treated subjects over 8 weeks was 1.6 kg and 26% of subjects had weight gain of at least 7%. For reference, 40% of brexpiprazole-treated subjects with ASD (Study 331-201-00148) experienced at least 7% increase in body weight over 8 weeks.

Given that the changes in body weight and BMI with brexpiprazole use appear to be clinically significant and comparable to other atypical antipsychotics, this reviewer recommends including additional language to describe observed changes in body weight and BMI during the short-term and long-term studies in the Section 8.4 (Pediatric Use) of the product label.

Suicidal Ideation and Behavior

The Applicant did not report any cases of SI/B as an AE or as an event prospectively captured using the C-SSRS.

8.2.6. Safety Analyses by Demographic Subgroups

Given the relatively small sample size of females, adolescents, and other non-White racial groups, interpretation of subgroup analyses by gender, age, and race is limited. Because the Applicant enrolled all subjects from US study sites, an evaluation of regional differences was not feasible.

8.2.7. Specific Safety Studies/Clinical Trials

Study 331-201-00191

The Written Request outlined the need to characterize the long-term safety profile in subjects diagnosed with ASD and exposed to brexpiprazole for at least 6 months. Study 331-201-00191 was a multicenter, open-label extension study intended to evaluate the long-term safety and tolerability of brexpiprazole in children and adolescents with irritability associated with ASD who previously completed the 8-week treatment period in Study 331-201-00148.

The Applicant excluded any rollover subjects with previous substantial protocol violations during Study 331-201-00148. Assessments from the last visit of Study 331-201-00148 served as the baseline measures for Study 331-201-00191. Eligible subjects received 26 weeks of open-label brexpiprazole once daily and participated in visits at Weeks 1, 2, 3, 4, 8, 14, 18, 22, and 26 (visits at baseline and Weeks 2, 14, and 26 occurred in the clinic). All subjects subsequently participated in a follow-up visit 21 days after their last dose of brexpiprazole. Identical to the titration scheme used in Study 331-201-00148, the dosing schedule was based on body weight. Investigators titrated subjects with a body weight < 50 kg and ≥ 50 kg to receive target doses

between 1 to 1.5 mg and 1.5 to 3 mg, respectively (refer to the flexible-dose titration scheme in Table 6).

The Applicant enrolled a total of 95 subjects who completed Study 331-201-00148 (49 subjects previously received brexpiprazole and 46 subjects previously received placebo). Approximately 26% of subjects discontinued from the study, 20% from the prior brexpiprazole group and 33% from the prior placebo group. The major reason for study discontinuation was due to withdrawal by caregiver (10% in the prior brexpiprazole group and 13% in the prior placebo group) and AEs (4% in the prior brexpiprazole group and 9% in the prior placebo group). Demographic and baseline disease characteristics were similar to the parent study. Among the subjects who received prior brexpiprazole treatment, 36 subjects (73%) continued to receive brexpiprazole for at least 26 weeks.

The Applicant did not report any deaths during the trial period. Serious AEs occurred in two subjects (4%) who received prior brexpiprazole treatment (dyskinesia and suicidal ideation occurring in one subject each) and one subject (2%) who received prior placebo treatment (aggression/affective disorder). The event of suicidal ideation started on Day 212 and occurred after the subject showed signs of irritability that required restraints. Based on the C-SSRS data, the Applicant reported suicidal ideation (wish to be dead or non-specific suicidal thought) in four subjects (8%) in the prior brexpiprazole group and two subjects (4%) in the prior placebo group.

Table 22: Incidence of Adverse Events Reported by At least 2% of all Subjects in Study 331-201-00191

Adverse Event[1]	Prior Placebo (N=46)	Prior BREX (N=49)	Total (N=95)
Weight increased	8 (17%)	5 (10%)	13 (14%)
Somnolence	1 (2.2%)	6 (12%)	7 (7.4%)
Increased appetite	4 (8.7%)	2 (4.1%)	6 (6.3%)
Gastroenteritis	2 (4.3%)	3 (6.1%)	5 (5.3%)
Irritability	-	3 (6.1%)	3 (3.2%)
Akathisia	3 (6.5%)	1 (2.0%)	4 (4.2%)
Influenza	-	4 (8.2%)	4 (4.2%)
Upper respiratory tract infection	4 (8.7%)	-	4 (4.2%)
Insomnia	2 (4.3%)	1 (2.0%)	3 (3.2%)
Headache	1 (2.2%)	2 (4.1%)	3 (3.2%)
Agitation	2 (4.3%)	1 (2.0%)	3 (3.2%)
Vomiting	1 (2.2%)	1 (2.0%)	2 (2.1%)
Pain in extremity	1 (2.2%)	1 (2.0%)	2 (2.1%)
Fatigue	2 (4.3%)	-	2 (2.1%)
Dizziness	1 (2.2%)	1 (2.0%)	2 (2.1%)
Anxiety	1 (2.2%)	1 (2.0%)	2 (2.1%)

Source: Clinical Reviewer-created using adae.xpt dataset
[1]Subjects were counted once per AE grouping. Adverse events included only those that started after the start of the study drug or if the event was continuous from baseline and was serious, drug-related, or resulted in death, discontinuation, or interruption or reduction of study treatment.
Note: Akathisia included: akathisia, restlessness, and psychomotor hyperactivity preferred terms; Gastroenteritis included gastroenteritis and gastroenteritis viral preferred terms; Somnolence included somnolence and sedation preferred terms; Upper respiratory tract infection included: nasopharyngitis, pharyngitis, and upper respiratory tract infection.

The overall percentage of subjects who experienced AEs was 47% in the prior brexpiprazole group vs. 52% in the prior placebo group. Incidence of AEs greater than 5% included: weight increased (14%), somnolence (7%), increased appetite (6%), and gastroenteritis (5%). Incidences of AEs occurring in at least 2% of the overall population is provided in Table 22. Most AEs were mild or moderate in severity; severe AEs occurred in two subjects (4%) in the prior brexpiprazole group (irritability and suicidal ideation each in one subject) vs. two subjects (4%) in the prior placebo group (weight increased and aggression/affective disorder each in one subject).

The incidence of EPS-related events (6%) was also similar to the incidence observed in Study 331-201-00148 and within the range of incidence observed in other studies evaluating brexpiprazole in adults (3 to 6%). None of the EPS-related AEs led to study discontinuation. Prospective evaluation of EPS-related symptoms (e.g., AIMS, BARS, SAS) so did not reveal any clinically significant changes and aligned with results from Study 331-201-00148.

Changes in vital signs, ECG parameters, and laboratory measures over the 26-week treatment period were also similar between treatment groups and similar to previous results from Study 331-201-00148. Fourteen subjects (15%) overall had experienced potentially clinically relevant increases in heart rate (standing), 10 subjects (21%) in the prior brexpiprazole group and four subjects (9%) in the prior placebo group (incidence of 16% among brexpiprazole-treated subjects in Study 331-201-00148). Although there were no AEs for ECG abnormalities, four subjects (5%) overall experienced an increased in the QTcF interval between 30 to 60 msec (no cases above 450 msec).

Mean changes in prolactin over time by gender did not suggest any new risk for brexpiprazole. The mean change from baseline to the last study visit was 0.22 ng/mL and -0.33 ng/mL, respectively. One subject (3.2%) had prolactin values greater than three times the upper limit of normal (ULN) in the prior placebo group. Overall, five subjects (6%) had prolactin values > one times the ULN (two subjects [6%] in the prior placebo group and two subjects [5%] in the prior brexpiprazole group).

Table 23 describes the mean change from baseline and the mean change in age- and gender-adjusted z-scores for each of the anthropometric measurements, including clinically relevant changes (i.e., changes in z-scores of > 0.5) over the 26-week treatment period. A total of 13 subjects (14%) experienced weight-gain related AEs; however, none of these AEs were serious and only one subject discontinued treatment. In general, there was an observed increase in body weight and BMI during the treatment period. Approximately 75% of subjects gained at least 7% of their body weight (mean increase in body weight of 5.1 kg) at Week 26 and 26% of subjects reported an increase in age- and gender-adjusted body weight and BMI scores at any post-baseline visit.

Table 23: Changes in Body Weight, Height, BMI, and Weight Circumference in Study 331-201-00191

Measure	Value[1,2]	Prior Placebo (N=46)	Prior BREX (N=49)
Body Weight (kg)	Mean baseline (SD)	44.2 (18)	41.6 (18)
	Mean change (SD)	5.2 (5.2)	4.5 (3.6)
	Mean z-score baseline (SD)	0.8 (1.3)	0.4 (1.3)
	Mean z-score change (SD)	0.2 (0.5)	0.3 (0.4)
	Increase > 0.5 SD, n (%)	13 (28%)	9 (18%)
	Decrease > 0.5 SD, n (%)	2 (4.3%)	-
Height (cm)	Mean baseline (SD)	144 (16)	145 (19)
	Mean change (SD)	3.4 (4.1)	3.5 (2.6)
	Mean z-score baseline (SD)	0.4 (1.1)	0.4 (1.0)
	Mean z-score change (SD)	0.2 (0.7)	0.2 (0.4)
	Increase > 0.5 SD, n (%)	7 (15%)	9 (18%)
	Decrease > 0.5 SD, n (%)	1 (2.2%)	2 (4.0%)
BMI (kg/m^2)	Mean baseline (SD)	20.6 (5.2)	19.1 (4.6)
	Mean change (SD)	1.3 (2.0)	1.2 (1.9)
	Mean z-score baseline (SD)	0.7 (1.2)	0.3 (1.4)
	Mean z-score change (SD)	0.2 (0.6)	0.3 (0.7)
	Increase > 0.5 SD, n (%)	12 (27%)	11 (24%)
	Decrease > 0.5 SD, n (%)	3 (6.8%)	3 (6.7%)
Weight circumference (cm)	Mean baseline (SD)	73.7 (15)	70.3 (14)
	Mean change (SD)	3.7 (7.9)	4.3 (5.7)

Source: Reviewer-adapted using advs.xpt dataset
[1]Age- and gender-adjusted z-scores for body weight, height, and BMI were calculated using the Center for Disease Control and Prevention (CDC) approach (reference data from 2000)
[2]Change from baseline to last study visit; a change of 0.5 SD in z-scores previously described as clinically significant in product labels for other antipsychotics

Clinical Reviewer's Comment: *In general, the safety profile of brexpiprazole administered over 26 weeks did not reveal any new safety signals that were not identified from Study 331-201-00148 or from other studies evaluating brexpiprazole in adults. Among the 11 subjects who previously received brexpiprazole in Study 331-201-00148 that experienced a body weight z-score increase of at least 0.5 SD, four subjects that participated in Study 331-201-00191 continued to experience a further increase in age- and gender-adjusted body weight z-score of 0.37 SD (cumulative increase from double-blind baseline of 0.98 SD). Only one subject that continued to receive brexpiprazole experienced a further increase in age- and gender-adjusted body weight z-score of at least 0.5 SD.*

In an open-label study evaluating long-term safety of aripiprazole, pediatric subjects 6 to 17 years of age with ASD had a mean change in age- and gender-adjusted z-scores of 0.26 SD after at least 9 months of treatment. In another open-label study evaluating risperidone in pediatric subjects with ASD and other psychiatric conditions, the mean change in age- and gender-adjusted z-scores after 12 months of treatment was 0.25 SD. Because the observed change in age- and gender-adjusted z-score for body weight (0.31 SD) after 6 months of brexpiprazole

treatment suggests that weight gain occurred at a faster rate relative to other antipsychotics, Section 8.4 of the product label should at least include additional language describing long-term changes in body weight following brexpiprazole treatment.

The Applicant also reported that six subjects (6%) experienced passive suicidal ideation during the study period. Although there was one AE of suicidal ideation in the parent study (331-201-00148), the observed incidence of suicidal ideation (6%) from the long-term study is significantly less than the background prevalence of suicidal ideation (25%) in children with ASD (Kodak T, et al., 2020). Therefore, additional language in product labeling is not warranted.

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The application did not include new human carcinogenicity studies.

Human Reproduction and Pregnancy

The application did not include new human reproduction or pregnancy data.

Pediatrics and Assessment of Effects on Growth

Refer to sections 8.2.5 and 8.2.7 for information on changes in body weight, height, and BMI for subjects participating in Studies 331-201-00148 and 331-201-00191, respectively.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

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

8.2.8. 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. In the latest annual Periodic Safety Update Report (submitted on September 13, 2023), the Applicant did not identify any new risks or reclassify any current risks for brexpiprazole in the pediatric population. In the Applicant's global safety database search for brexpiprazole use in pediatric subjects, there were 60 cases that included one or more AE events (represents approximately 3% of all AE reported during the annual report interval). Of the 60 cases, the Applicant confirmed only two cases in pediatric subjects with ASD. Common AEs included neurological and psychiatric effects (specific preferred terms not reported).

Expectations on Safety in the Postmarket Setting

Given that the Applicant did not provide evidence of effectiveness for the treatment of irritability associated with ASD, that indication will not be added to labeling. Consistent with requirements for studies conducted under a Pediatric Written Request, the product label will be updated to reflect the lack of efficacy findings from Study 331-201-00148 and brexpiprazole's observed safety profile in children and adolescents 5 to 17 years of age (i.e., higher incidence of somnolence and changes in body weight following acute and chronic use).

8.2.9. Integrated Assessment of Safety

Overall, brexpiprazole's safety profile in pediatric subjects with ASD appeared to be consistent with other atypical antipsychotics in pediatric patients. However, safety findings did suggest a higher incidence of somnolence and clinically relevant increases in body weight among pediatric subjects relative to adults and adolescents. The Division recommends additional language in Section 8.4 of the product label to describe these concerning safety results.

8.3. Statistical Issues

There are no statistical issues that impact the overall conclusions in this review.

8.4. Conclusions and Recommendations

The study results do not support the use of brexpiprazole for the treatment of irritability associated with ASD in pediatric patients ages 5 to 17 years. Section 8.4 of the brexpiprazole product label will reflect these findings, along with a summary of safety information (i.e., risk of somnolence and changes in body weight in this pediatric population).

9 Advisory Committee Meeting and Other External Consultations

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

10 Pediatrics

On April 19, 2018, the Division issued a pediatric Written Request that outlined studies needed to investigate potential use of brexpiprazole in the treatment of pediatric patients with schizophrenia (ages 13 to 17 years), acute manic or mixed episodes associated with bipolar I disorder (ages 10 to 17 years), and irritability associated with autism spectrum disorder (ASD; ages 5 to 17 years). The current Written Request (Amendment 4) outlined the following studies: a safety, tolerability, and PK study in pediatrics 6 to 12 years of age (Study 1); a safety and efficacy study in pediatric subjects 5 to 17 years of age with irritability associated with ASD (Study 2); and a long-term safety study in pediatric subjects with schizophrenia or ASD (Study 3). In response to the Written Request, the Applicant submitted results from the following studies:

- Study 331-201-00103 (response to Study 1): a phase 1, single-dose, sequential cohort, non-randomized crossover trial to assess the PK, safety, and tolerability of oral brexpiprazole (0.75 to 3 mg) in children 6 to less than 13 years of age with central nervous system disorder

- Study 331-201-00148 (response to Study 2): phase 3, multi-center, randomized, double blind, placebo-controlled trial of brexpiprazole (0.25 to 3 mg/day) in treatment of children and adolescents with irritability associated with ASD

- Study 331-201-00191 (response to Study 3): a phase 3, multicenter, open-label extension trial to evaluate the long-term safety and tolerability of brexpiprazole in the subjects who completed Study 331-201-00148

- Study 331-10-236 (response to Study 3): a phase 3, multi-center, open-label trial to evaluate the long-term safety and tolerability of flexible dose brexpiprazole (1 to 4 mg/day) as maintenance treatment in adolescents with schizophrenia

Because the Division concurred with the Applicant's response and agreed that terms of the Written Request were met, the Agency will grant pediatric exclusivity for this product.

11 Labeling Recommendations

Proposed language to include in Section 8.4 (Pediatric Use):

- The safety and effectiveness of brexpiprazole for the treatment of irritability associated with autism spectrum disorder have not been established in pediatric patients.

- In an 8-week, double-blind, placebo-controlled, flexible-dose clinical study, somnolence (including sedation) occurred at a higher rate than reported in other brexpiprazole studies evaluating adults and elderly patients (16% in brexpiprazole-treated pediatric patients versus 5% for placebo). (b) (4)
- The mean increase in age-and-gender adjusted body weight z-score from baseline to last visit was 0.3 for brexpiprazole-treated patients versus 0.1 for placebo-treated patients. Increases in age-and-gender adjusted body weight z-score of at least 0.5 SD from baseline was higher in brexpiprazole-treated patients versus placebo (19% versus 5%).
- Of the 119 patients from the (b) (4) study, 95 patients entered the open-label treatment study and received up to 26 weeks of daily treatment with brexpiprazole. During the open-label treatment period, 2% of patients discontinued the study due to weight increase. In patients previously treated with brexpiprazole for 8 weeks, the mean increase in weight from the open-label study baseline to their last visit was 4.5 kg, and 26% of patients had an increase in their age-and-gender-adjusted body weight z-score of at least 0.5 SD from baseline.

12 Risk Evaluation and Mitigation Strategies (REMS)

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

13 Postmarketing Requirements and Commitment

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

14 Division Director (DP) 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

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 331-201-00148

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 39		
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): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Dr. Jackson (Principal Investigator at site 115) received payments for speaking engagements on the Applicant's behalf. Dr. Jackson was designated as a back-up rater for administrating study measures. Given that site 115 randomized one subject, the Applicant considered the potential bias to be minimal.

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

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