Table of Contents

Table of Contents..... 1

Study 331-201-00148 Protocol Amendment 5; 07 July 2022..... 2

CCI [redacted] 112

Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

REVISED CLINICAL PROTOCOL

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Brexpiprazole in Treatment of Children and Adolescents With Irritability Associated With Autism Spectrum Disorder

Protocol No. 331-201-00148
IND No. 141257
EudraCT No. 2019-000723-40

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase: 3

Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	CCI [redacted]
Issue Date:	26 Apr 2019
Date of Amendment 1:	14 Aug 2019
Date of Amendment 2	22 Nov 2019
Date of Amendment 3:	12 Feb 2020
Date of Amendment 4:	06 Jul 2020
Date of Amendment 5:	07 Jul 2022
Version No.:	6.0

Protocol 331-201-00148

Trial Conduct for COVID-19

All procedures and assessments in this protocol are to be followed to the fullest extent possible. The sponsor, in coordination with the trial sites, investigators, and medical monitor, will continuously monitor and evaluate the benefits and risks to subject participation in the clinical trial as it relates to COVID-19. If any protocol-specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, refer to the COVID-19 Addendum for the appropriate measures to be followed. Appropriate measures may include replacing in-person visits with virtual visits as deemed necessary by the investigator to ensure subject safety and maintain protocol requirements.

Protocol 331-201-00148

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-201-00148 IND No.: 141257 EudraCT No.: 2019-000723-40
Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Brexpiprazole in Treatment of Children and Adolescents With Irritability Associated With Autism Spectrum Disorder
Clinical Phase/Trial Type:	3/Therapeutic Use
Treatment Indication:	Irritability Associated with Autism spectrum disorder (ASD)
Objective(s):	Primary: To evaluate the efficacy, safety, and tolerability of brexpiprazole in reducing irritability in children and adolescents ages 5 to 17 years with a diagnosis of ASD.
Trial Design:	This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, 8-week trial designed to evaluate the effects of flexibly-dosed brexpiprazole (0.25 - 3 mg/day, weight based) compared with placebo on irritability in children and adolescent subjects, ages 5 to 17 years, with a diagnosis of ASD. The trial will consist of a 1 to 28 day screening period, followed by an 8-week double-blind treatment period, and a 21-day post-treatment safety follow-up period. Subjects who continue to meet entrance criteria at the baseline visit (Day 1) will be randomized 1:1 to receive brexpiprazole, or placebo daily. On Day 1 of the treatment period, subjects will begin titration to a target minimum dose of investigational medicinal product (IMP). The target dose range of IMP will be determined for each individual subject based on body weight. Those subjects with body weight < 50 kg will receive a target dose range of 1 to 1.5 mg, and those subjects with body weight ≥ 50 kg will receive a target dose range of 1.5 to 3 mg. Body weight at the time of randomization will determine dose/titration requirements throughout the trial. Subjects with body weight < 50 kg will receive brexpiprazole at a dose of 0.25 mg for Days 1 to 3, 0.5 mg for Days 4 to 7,

and 1 mg for Days 8 to 14. Day 15 is the earliest opportunity that the investigator has to increase to the maximum dose of 1.5 mg within the target dose range. The decision to increase the dose to 1.5 mg and when to increase the dose will be based on investigator judgment in order to reach a desired therapeutic effect. Subjects must be on their final dose at Week 6. Subjects that require a change in dose between Week 6 and Week 8 will be discontinued.

Subjects with body weight ≥ 50 kg will receive brexpiprazole at a dose of 0.5 mg for Days 1 to 3, 1.5 mg for Days 4 to 7, and 2 mg for Days 8 to 14. Day 15 is the earliest opportunity that the investigator has to increase to the maximum dose of 3 mg within the target dose range. The decision to increase the dose to 3 mg and when to increase the dose will be based on investigator judgment in order to reach a desired therapeutic effect. Subjects must be on their final dose at Week 6. Subjects that require a change in dose between Week 6 and Week 8 will be discontinued. Dose titrations will be performed in conjunction with a trial visit and therefore, trial visit windows are allowed for the titration schedule.

For all subjects, doses can be down-titrated due to tolerability based on investigator judgment. Subjects < 50 kg should receive a dose of 1.5 mg before decreasing the dose to 1 mg. Subjects ≥ 50 kg should receive a dose of 2 mg before decreasing the dose to 1.5 mg and a dose of 3 mg before decreasing to 2 mg.

Dosing Schedule During the Treatment Period

Trial Day	No. Days on IMP	Brexpiprazole Dose		Placebo
		< 50 kg	≥ 50 kg	
Days 1 to 3	3	0.25 mg QD	0.50 mg QD	placebo tablets QD
Days 4 to 7	4	0.50 mg QD	1.5 mg QD	placebo tablets QD
Days 8 to 14	7	1 mg QD	2 mg QD	placebo tablets QD
Starting at Day 15 (earliest opportunity to increase to maximum dose within target dose range)	Based on investigator discretion to change dose based on therapeutic effect or tolerability	1 mg, or 1.5 mg QD	1.5 mg, 2 mg, or 3 mg QD	placebo tablets QD

Protocol 331-201-00148

	If a subject < 50 kg is unable to tolerate the 1 mg dose, the subject will be discontinued. If a subject ≥50 kg is unable to tolerate the 1.5 mg dose, the subject will be discontinued. During the double-blind treatment phase, evaluations are planned on Day 1 (baseline) and at Weeks 1, 2, 3, 4, 6, and 8. Visits at baseline, Week 2, and Week 8 will occur at the clinic. All other visits may be conducted either virtually or in clinic. Where the investigator and caregiver make the decision to conduct a visit virtually, the visit will be conducted by means of telecommunications technology. For these virtual visits, the caregiver and subject will remain in their own home and complete trial assessments and questionnaires via an online technology. The caregiver and subject will interact with trial personnel using online communication tools which incorporate telemedicine. During virtual interactions (and at any other time), the trial personnel will be able to assess the subject and determine if an additional in-office visit for a physical evaluation is required at the discretion of the investigator. Eligible subjects who complete the 8-week double-blind phase may have the option to enroll into an open-label safety trial of brexpiprazole. Subjects who do not enroll in the open-label safety trial (Trial 331-201-00191) will have a follow-up contact 21 ± 2 days after the last dose of IMP to assess adverse events (AEs). This trial will be monitored by an independent Data Monitoring Committee (DMC). The DMC will monitor safety based on a predetermined schedule as outlined in the DMC charter.
Subject Population:	The trial population will include male and female subjects between 5 and 17 years of age, inclusive, at the time of informed consent/assent with a *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) diagnosis of ASD. Subjects will have irritability associated with ASD as defined by a score of ≥ 18 on the Aberrant Behavior checklist - Irritability (ABC-I) subscale and score ≥ 4 on the Clinical Global Impressions - Severity (CGI-S) scale for irritability.

Protocol 331-201-00148

Inclusion/Exclusion Criteria:	Subjects must meet the inclusion criteria at both baseline and screening. Key inclusion criteria include the following: • Male and female subjects 5 to 17 years of age, with a current primary DSM-5 diagnosis of ASD, as determined by the investigator and supported by the Autism Diagnostic Interview - Revised (ADI-R). • Subjects with an ABC-I subscale score ≥ 18 and with a CGI-S scale score ≥ 4 pertaining to irritability at screening and at baseline (Day 1). • Subjects must have a mental age of ≥ 2 years, as determined by the investigator based on school participation, social history, or medical records. Key exclusion criteria include the following: • Subjects with a current primary DSM-5 diagnosis of bipolar disorder, including any DSM-5 current diagnosis of bipolar II disorder, schizophrenia, schizoaffective disorder, major depressive episode as determined by clinical instrument (Kiddie-Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version [K-SADS-PL]), or post-traumatic stress disorder (PTSD). Subjects with comorbid attention deficit/hyperactivity disorder (ADHD) are permitted to enroll in the trial, provided that ADHD is not the primary disorder, the subject is adequately treated, and based on the investigator judgment the disorder is clinically stable.
Trial Site(s):	The trial is expected to enroll subjects at approximately 30 sites in the United States.

Protocol 331-201-00148

Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Brexpiprazole will be supplied by the sponsor or designated agent in child-resistant blister cards, each containing sufficient tablets for 7 (+ 2) days. Treatment assignments will be obtained by accessing eSource. Based on computer-generated randomization, eligible subjects will be allocated in a 1:1 ratio at randomization to 1 of the following 2 treatment groups: • Brexpiprazole • Placebo Neither the investigator nor the subject will be aware of the treatment assignment. All doses of brexpiprazole and matching placebo will be taken orally once daily, preferably in the morning, and will be administered without regards to meals. Brexpiprazole (or matching placebo) should be taken at approximately the same time each day.
Trial Assessments:	Efficacy: ABC-I and other subscales, CGI-S, CCI [redacted] and CCI [redacted] Pharmacokinetics (PK)/pharmacogenomic (PGx): 3 PK samples will be taken: Day 1 postdose, and Week 8/early termination (ET) predose and postdose. A PGx sample will also be collected to assess CYP2D6 genotype status CCI [redacted] Safety: AEs and concomitant medications, clinical laboratory tests, vital signs, electrocardiogram (ECG), physical examination, body weight, height, waist circumference, extrapyramidal scales (Simpson Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale [BARS]), and suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS, child version). Screening/Other: K-SADS-PL, ADI-R, demography, medical history, psychiatric history, prior and concomitant medications, pregnancy test, and urine drug and blood alcohol test in children ≥ 13 years of age that engage in social activities with peers without adult supervision.
Criteria for Evaluation	**Primary Endpoint:** The primary efficacy endpoint of this trial will be the mean change from baseline to Week 8 in the ABC-I subscale score.

Secondary Endpoint(s):

Efficacy: The key secondary endpoint of this trial will be the mean change from baseline to Week 8 in CGI-S score.

Safety: Safety will be assessed by the following standard endpoints for clinical trials and trials of antipsychotic drugs:

- Frequency and severity of AEs, serious AEs (clinical and laboratory), and discontinuation from the trial due to AEs
- Weight, height, body mass index (BMI), and waist circumference
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Vital signs and ECG parameters
- EPS scale scores: AIMS, BARS, and SAS
- Potential suicide events recorded on suicidality scale scores

CCI

[redacted]

Protocol 331-201-00148

Statistical Methods:	A sample size of 51 subjects per arm will provide at least 85% power at a nominal 2-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) = 10. The primary efficacy endpoint is the change from baseline to Week 8 in the ABC-I subscale score. The primary statistical comparison of interest is the difference between brexpiprazole and placebo at Week 8, analyzed using a mixed-model repeated measures analysis with an unstructured variance-covariance matrix for within-subject variation. The model will include fixed-class effect terms of treatment, trial center, visit week, and an interaction term of treatment-by-visit week, and includes the interaction term of baseline values of ABC-I subscale score by visit week as a covariate. The primary comparison between brexpiprazole and the placebo arm at Week 8 will be estimated as the difference between least squares means. To ensure that trial is adequately powered, the estimate of the trial variability will be obtained in a blinded fashion upon approximately 75% of the subjects having completed or discontinued from the trial. The variability will be estimated based on a blinded and pooled analysis of all treatment arms and sample size could be further increased. For full details please refer to the Statistical Analysis Plan.
Trial Duration:	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 28 months, of which 24 months are allotted for recruitment of subjects. Individual participation for subjects who complete the trial without early withdrawal will range from 11 to 15 weeks, consisting of a 1 to 28-day screening period, 8-week double-blind treatment, and a 21 (± 2 day) safety follow-up period.

Protocol 331-201-00148

Table of Contents

Trial Conduct for COVID-19 2
Protocol Synopsis 3
Table of Contents 10
List of In-text Tables 15
List of In-text Figures 16
List of Appendices 17
List of Abbreviations and Definitions of Terms 18
1 Introduction 21
1.1 Nonclinical Data 22
1.1.1 Efficacy Pharmacology 22
1.1.2 Safety Pharmacology 23
1.2 Clinical Data 23
1.2.1 Pharmacokinetics/Pharmacodynamics 23
1.2.2 Schizophrenia 25
1.2.3 Major Depressive Disorder 25
1.2.4 Other Indications 25
1.3 Known and Potential Risks and Benefits 26
2 Trial Rationale and Objectives 28
2.1 Trial Rationale 28
2.2 Dosing Rationale 29
2.3 Trial Objectives 30
3 Trial Design 30
3.1 Type/Design of Trial 30
3.2 Trial Treatments 33
3.3 Trial Population 35
3.3.1 Number of Subjects and Description of Population 35
3.3.2 Subject Selection and Numbering 35
3.4 Eligibility Criteria 35
3.4.1 Informed Consent/Informed Assent 35

Protocol 331-201-00148

3.4.2 Inclusion Criteria 37
3.4.3 Exclusion Criteria 37
3.5 Endpoints 40
3.5.1 Primary Endpoint 40
3.5.1.1 Efficacy Endpoint 40
3.5.2 Secondary Endpoints 40
3.5.2.1 Efficacy Endpoint 40
3.5.3 Safety Endpoints 40
CCI [redacted] 40
3.6 Measures to Minimize/Avoid Bias 41
3.6.1 Randomization 41
3.6.2 Blinding 41
3.7 Trial Procedures 41
3.7.1 Schedule of Assessments 45
3.7.1.1 Screening Period 45
3.7.1.2 Baseline/Day 1 (Randomization) 45
3.7.1.3 Double-blind Treatment Phase (Weeks 1, 2, 3, 4, and 6) 46
3.7.1.4 Week 8 (End of Treatment) 47
3.7.1.5 Early Termination 47
3.7.1.6 Follow-up 47
3.7.2 Efficacy Assessments 47
3.7.2.1 Aberrant Behavior Checklist 47
3.7.2.2 Clinical Global Impressions - Severity of Illness Scale 48
CCI [redacted]
[redacted]
3.7.3 Safety Assessments 49
3.7.3.1 Adverse Events 49
3.7.3.2 Clinical Laboratory Assessments 49
3.7.3.3 Physical Examination and Vital Signs 53
3.7.3.3.1 Physical Examination 53
3.7.3.3.2 Vital Signs 54
3.7.3.4 Electrocardiogram Assessments 55

Protocol 331-201-00148

3.7.3.5 Other Safety Assessments 56
3.7.3.6 Other Assessments 58
3.7.3.6.1 Autism Diagnostic Interview - Revised 58
3.7.3.6.2 Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version 58
3.7.4 Prior and Concomitant Medications 58
3.7.5 Pharmacokinetic/Pharmacogenomic Assessments 59
CCI [redacted]
3.7.7 End of Trial 60
3.7.8 Independent Data Monitoring Committee 60
3.8 Stopping Rules, Withdrawal Criteria, and Procedures 60
3.8.1 Entire Trial or Treatment Arm(s) 60
3.8.2 Individual Site 60
3.8.3 Individual Subject Discontinuation 61
3.8.3.1 Treatment Interruption 61
3.8.3.2 Treatment Discontinuation 61
3.8.3.3 Documenting Reasons for Treatment Discontinuation 61
3.8.3.4 Withdrawal of Consent/Assent 62
3.8.3.5 Procedures to Encourage Continued Trial Participation 63
3.9 Screen Failures 63
3.10 Definition of Completed Subjects 63
3.11 Definition of Subjects Lost to Follow-up 64
3.12 Subject Compliance 64
3.13 Protocol Deviations 64
4 Restrictions 65
4.1 Prohibited Medications 65
4.1.1 Restricted Therapies and Precautions 69
4.2 Other Restrictions 69
5 Reporting of Adverse Events 70
5.1 Definitions 70
5.2 Eliciting and Reporting Adverse Events 72
5.3 Immediately Reportable Events 73

Protocol 331-201-00148

5.4 Potential Serious Hepatotoxicity 73
5.5 Pregnancy 73
5.6 Procedure for Breaking the Blind 75
5.7 Follow-up of Adverse Events 75
5.7.1 Follow-up of Nonserious Adverse Events 75
5.7.2 Follow-up of Serious Adverse Events 75
5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring after Last Scheduled Contact 76
6 Pharmacokinetic Analysis 76
7 Statistical Analysis 76
7.1 Sample Size 76
7.2 Datasets for Analysis 77
7.3 Handling of Missing Data 77
7.4 Primary and Secondary Endpoint Analyses 77
7.4.1 Primary Endpoint Analysis 77
7.4.2 Secondary Endpoint Analysis 80
CCI [redacted] 80
7.4.4 Interim Analysis 80
7.5 Analysis of Demographic and Baseline Characteristics 80
7.6 Safety Analysis 81
7.6.1 Adverse Events 81
7.6.2 Clinical Laboratory Data 81
7.6.3 Physical Examination and Vital Signs Data 81
7.6.4 Electrocardiogram Data 82
7.6.5 Other Safety Data 82
7.6.5.1 Extrapyramidal Symptoms 82
7.6.5.2 Suicidality 82
8 Management of Investigational Medicinal Product 82
8.1 Packaging and Labeling 82
8.2 Storage 83
8.3 Accountability 83

Protocol 331-201-00148

8.4 Returns and Destruction 83
8.5 Reporting of Product Quality Complaints 83
8.5.1 Eliciting and Reporting Product Quality Complaints 84
8.5.2 Information Required for Reporting Purposes 84
8.5.3 Return Process 84
8.5.4 Assessment/Evaluation 85
9 Records Management 85
9.1 Source Documents 85
9.2 Data Collection 85
9.3 File Management at the Trial Site 86
9.4 Records Retention at the Trial Site 86
10 Quality Control and Quality Assurance 87
10.1 Monitoring 87
10.2 Auditing 87
11 Ethics and Responsibility 88
12 Confidentiality 88
13 Amendment Policy 88
14 Publication Authorship Requirements 89
15 References 91

Protocol 331-201-00148

List of In-text Tables

Table 3.2-1 Dosing Schedule During the Treatment Period[a] 33

Table 3.4.2-1 Inclusion Criteria 37

Table 3.4.3-1 Exclusion Criteria 38

Table 3.7-1 Schedule of Assessments 42

Table 3.7.3.2-1 Clinical Laboratory Assessments 51

Table 4.1-1 List of Washout of Prohibited Medications 66

Table 4.1-2 List of Medications Prohibited During the Trial 67

Table 4.1-3 Oral Benzodiazepine Rescue Therapy During the Trial 68

Table 4.1-4 Selected CYP2D6 Inhibitors and CYP3A4 Inhibitors and Inducers Prohibited During the Trial 68

Protocol 331-201-00148

List of In-text Figures

Figure 3.1-1 Trial Design Schematic.....32

Protocol 331-201-00148

List of Appendices

Appendix 1	Criteria for Identifying Vital Signs Outside of Normal Range Values and of Potential Clinical Relevance[a]	94
Appendix 2	Criteria for Identifying Laboratory Values of Potential Clinical Relevance	95
Appendix 3	Criteria for Identifying ECG Measurements of Potential Clinical Relevance	97
Appendix 4	Protocol Amendment(s)/Administrative Change(s)	98

Protocol 331-201-00148

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AAD	Agitation associated with dementia of the Alzheimer's type
ABC-I	Aberrant Behavior checklist – Irritability
ACTH	Adrenocorticotropic hormone
ADHD	Attention-deficit/hyperactivity disorder
ADI-R	Autism Diagnostic Interview – Revised
ADOS	Autism Diagnostic Observation Schedule
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
APO	Apomorphine
aPTT	Activated partial thromboplastin time
ARH1	Heterogeneous autoregressive of order 1
ASD	Autism Spectrum Disorder
AST	Aspartate aminotransferase
AUC_{0-24h}	Area under the plasma concentration-time curve from time 0 hours to time 24 hours
AUC_{tau}	Area under the concentration curve at steady state during a 24-hour dosing interval
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BUN	Blood urea nitrogen
CGI-S	Clinical Global Impressions - Severity
CL/F	Apparent clearance of drug from plasma after extravascular administration
CNS	Central nervous system
CPK	Creatine phosphokinase
CRO	Clinical Research Organization
CSH	Heterogeneous compound symmetry
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
D_2	Dopamine D_2
D_{2L}	Dopamine D_{2L}
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, 5th edition*
ECG	Electrocardiogram
EPS	Extrapyramidal symptoms
ET	Early termination
EudraCT	European Clinical Trial Data Base
CCI	[redacted]
FDA	(United States) Food and Drug Administration

FOCBP	Female of childbearing potential
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMR	Geometric means ratio
HbA1c	Glycosylated hemoglobin
HDL	High density lipoprotein
IAF	Informed assent form
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International normalized ratio
IR	Immediate-release
IRB	Institutional review board
IRE	Immediately reportable event
IRT	Interactive research technology
K-SADS-PL	Kiddie-Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version
LDH	Lactic dehydrogenase
LDL	Low density lipoprotein
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed model repeated measures
MNAR	Missing not at random
MTD	Maximum tolerated dose
OC	Observed cases
OPC	Otsuka Pharmaceutical Co.
OTC	Over the counter
QD	Once daily
QTcF	QT interval as corrected for heart rate by Fridericia's formula
CCI	[redacted]
PD	Pharmacodynamic
PE	Physical examination
CCI	[redacted]
PGx	Pharmacogenomic
PK	Pharmacokinetic
PQC	Product quality complaint

PT	Prothrombin time
PTSD	Post-traumatic stress disorder
PWR	Pediatric Written Request
RBC	Red blood cell
RDW	Red cell distribution width
SAE	Serious adverse event
SAS	Simpson Angus Scale
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TOEPH	Heterogeneous toeplitz
t_{max}	Time to maximum (peak) plasma concentration
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UN	Unstructured
US or USA	United States or United States of America
WBC	White blood cell

1 Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) criteria as deficits in reciprocal social communication and social interaction (verbal and nonverbal).[1] The severity of ASD is defined by the degree of restricted, repetitive patterns of behavior, interests, and activities. Symptoms are present from early childhood and contribute to difficulties in developing, maintaining, and understanding relationships.

In addition to the core symptoms that characterize the disorder, children and adolescents with ASD often suffer from problem behaviors such as symptoms of irritability and aggression, which may manifest as tantrums, self-injury, and aggressive behaviors toward others.[2] Approximately 20% of people with ASD exhibit irritability and aggression[3] with > 50% exhibiting significant emotion dysregulation.[4] Irritability and aggression often negatively affect the lives of people with ASD and their families.

The prevalence of ASD in the pediatric population in the United States (US) has increased over the past decade from estimates of 1 in 150 (0.67%) in 2000 to 1 in 68 (1.46%) in 2012, with increases occurring in all racial, ethnic, and socioeconomic groups (Autism and Developmental Disabilities Monitoring Network, 11 sites).[5] In 2011, the total costs per year for children with ASD in the United States (US) were estimated at between $11.5 billion and $60.9 billion which could be attributed to medical care, special education, and lost parental productivity.[6]

Two atypical antipsychotics (risperidone and aripiprazole) are currently approved by the US FDA for the treatment of irritability associated with ASD. With regard to the safety profile of atypical antipsychotics, available data across indications suggest that children and adolescents are at higher risk than adults for experiencing sedation, acute extrapyramidal symptoms (EPS), withdrawal dyskinesia, and significant weight gain during treatment.[7,8] For patients with ASD, the common side effects of these medications[9] are likely to further isolate children and adolescents from social interaction. Thus, there is a need to identify additional efficacious agents for children with psychiatric disorders, especially considering the safety and tolerability issues that may be associated with the use of selected antipsychotics in children and adolescents.[10]

Brexpiprazole (also referred to as OPC-34712 and Lu AF41156) is an atypical antipsychotic synthesized by Otsuka that is being codeveloped by Otsuka and Lundbeck for a number of indications. Brexpiprazole is currently approved in the US as

monotherapy for the treatment of schizophrenia and for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults. In addition, there are currently 2 ongoing phase 3 clinical trials in adolescent subjects with schizophrenia. While the precise mechanism of action of brexpiprazole in treating psychiatric conditions is unknown, the pharmacology of brexpiprazole is believed to be mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors. This trial is being conducted to evaluate the efficacy, safety, and tolerability of brexpiprazole for acute treatment of irritability in children and adolescents who meet the DSM-5 criteria for ASD.

1.1 Nonclinical Data

Efficacy and safety pharmacology are summarized in Section 1.1.1 and Section 1.1.2, respectively. A complete description of the available data from nonclinical studies, including pharmacokinetic (PK) and toxicology studies in different animal species, can be found in the Investigator's Brochure (IB).[11]

1.1.1 Efficacy Pharmacology

Brexpiprazole functions as a partial agonist at the D_2 receptor. In in vitro assay systems based on forskolin-induced cyclic adenosine monophosphate accumulation and calcium mobilization in human dopamine D_{2L} receptor-expressing cells, its intrinsic activity at the D_2 receptor was slightly lower than that of aripiprazole, another D_2 receptor partial agonist. Brexpiprazole inhibited apomorphine (APO)-induced hyperlocomotion, APO-induced stereotyped behavior, and conditioned avoidance response in rats, which are predictive animal models for antipsychotic-like efficacy. The inhibitory effects of brexpiprazole were more potent than those of aripiprazole. Moreover, in contrast to the D_2 receptor antagonist risperidone, brexpiprazole did not increase plasma prolactin levels in reserpine-treated rats, thus demonstrating a D_2 receptor partial agonistic profile in vivo. Despite its lower intrinsic activity at the D_2 receptor, the in vivo catalepsy liability of brexpiprazole, an index of EPS, was similar to that of aripiprazole, but still lower than that of the typical antipsychotic haloperidol. Furthermore, brexpiprazole showed high binding affinity for the 5-HT_{2A} receptor and dose-dependently inhibited (±)-2,5-dimethoxy-4-iodoamphetamine-induced head twitch response in rats, indicating that the compound has 5-HT_{2A} receptor antagonistic activity; the effect of brexpiprazole was more potent than that of aripiprazole. In addition, brexpiprazole exhibited high

binding affinities for the D_3 and 5-HT_{1A} receptors, acting as a partial agonist at these receptors.

1.1.2 Safety Pharmacology

In safety pharmacology studies in rats at an oral dose of 30 mg/kg or higher, brexpiprazole induced pharmacologically mediated clinical signs considered to be due to depression of the central nervous system (CNS) and dose-dependent decreases in body temperature. When orally administered at up to 30 mg/kg in conscious male beagle dogs, brexpiprazole showed no effect on respiratory parameters or heart rate at any dose tested. Brexpiprazole decreased blood pressure at doses of 3 mg/kg or higher and prolonged both QT interval and corrected QT interval ([QTc], by Van de Water's formula) at 30 mg/kg. Brexpiprazole inhibited human *ether-a-go-go* related gene current in Chinese hamster ovary cells at concentrations of 10^{-8} mol/L or higher, with a 50% inhibitory concentration of 1.17×10^{-7} mol/L. The mechanism for the blood pressure decreasing effect of brexpiprazole was suggested to result from a blockade of the α1-adrenoceptor in peripheral blood vessels, which is a part of the compound's pharmacological profile. Proarrhythmic risk was also evaluated by examining the effects of brexpiprazole on monophasic action potential parameters in halothane-anesthetized dogs. Brexpiprazole did not affect the terminal repolarization period even at an intravenous dose of 3 mg/kg, suggesting a low potential for proarrhythmic effects. In general, the changes in the CNS, respiratory, and cardiovascular systems observed with brexpiprazole occurred at doses or exposure levels higher than those at which efficacy was confirmed in rats (3 mg/kg), and similar changes were shown to occur after administration of risperidone at similar or lower doses.

1.2 Clinical Data

Pharmacokinetic and pharmacodynamic (PD) data, as well as data from schizophrenia, MDD, and other indications are summarized below. A complete description of the available data from clinical trials can be found in the IB.[11]

1.2.1 Pharmacokinetics/Pharmacodynamics

The PK of single and multiple doses of brexpiprazole was studied in healthy subjects and in subjects with MDD, attention-deficit/hyperactivity disorder (ADHD), and schizophrenia or schizoaffective disorder. Based on preclinical data and human clinical trials, brexpiprazole (OPC-34712) and one metabolite, DM-3411, were identified as the major analytes that are present in human plasma. In vitro, the activity of DM-3411 is

17 times lower than that of brexpiprazole and thus is considered as an inactive metabolite. Both brexpiprazole and DM-3411 PK were linear following single oral doses of brexpiprazole 0.2 to 8 mg to healthy subjects. The mean terminal phase elimination half-life of brexpiprazole and DM-3411 was 79.3 hours and 73.6 hours, respectively. The median time to maximum (peak) plasma concentration (t_{max}) occurred at approximately 4 hours post dose for brexpiprazole and at approximately 12 hours post dose for DM-3411. In healthy subjects, administration of single-dose brexpiprazole with a high-fat meal did not affect its rate and extent of absorption.

Steady state PK also appeared to be linear following multiple daily doses of brexpiprazole in the range of 0.5 to 2 mg to healthy subjects. The accumulation factor based on maximum (peak) plasma concentration and area under the concentration-time curve calculated to the last observable concentration at time t was approximately 4 times. After multiple dose administration of brexpiprazole (1 to 12 mg/day) to subjects with schizophrenia or schizoaffective disorder, brexpiprazole and DM-3411 mean terminal elimination half-life at steady state was 91.4 and 85.7 hours, respectively; median t_{max} was 3.0 and 5.0 hours, respectively.

In drug interaction trials in healthy subjects, brexpiprazole was shown to be metabolized by cytochrome P450 (CYP) 3A4 and CYP2D6 isozymes and was not an inhibitor of CYP3A4, CYP2B6, CYP2D6, or P-glycoprotein. Co-administration of potent CYP3A4 or CYP2D6 inhibitors with brexpiprazole resulted in about a 2-fold higher exposure and about a 1.5-fold increase in the terminal elimination half-life of brexpiprazole.

In a single-dose trial in healthy subjects, approximately 46.0% and 24.6% of administered radioactivity following an oral dose of ^{14}C-brexpiprazole was excreted in feces and urine, respectively. In this same trial, brexpiprazole did not preferentially bind to red blood cells. Brexpiprazole showed high protein binding in human serum (≥ 99.8%) in vitro.

In Trial 331-201-00103, a phase 1 pediatric trial to assess PK and safety of oral brexpiprazole in children age 6 to < 13 years old with CNS disorders, mean apparent clearance of drug from plasma after extravascular administration (CL/F) of brexpiprazole of 1.5 or 3 mg in children 10 to < 13 years old was comparable with that observed in adults following a single dose of brexpiprazole 2 mg. Dose proportionality was observed within treatment cohorts (ie, within the same age range) and children in the younger age group (6 to < 10 years old) appeared to have slightly higher brexpiprazole and DM-3411

exposure and lower brexpiprazole CL/F as compared with children in the older group (10 to < 13 years old).

1.2.2 Schizophrenia

The efficacy of brexpiprazole as monotherapy for the treatment of adults with schizophrenia has been studied in 2 completed placebo-controlled trials (Trials 331-10-230 and 331-10-231), a long term maintenance trial (Trial 331-10-232), and a long-term safety trial (Trial 331-10-237), and was approved for the treatment of schizophrenia in adults (ages 18 to 65) by the US Food and Drug Administration (FDA) on 10 Jul 2015. Brexpiprazole is currently being studied for the treatment of schizophrenia in adolescents 13 to 17 years old in the double-blind Trial 331-10-234 and open-label Trial 331-10-236.

In Trial 331-10-233, overall systemic exposure was measured by dose-normalized maximum concentration at steady state and area under the plasma concentration-time curve to the last observable concentration, and was slightly higher (geometric mean ratio [GMR] adult/adolescent: 0.765 and 0.904, respectively), and CL/F was slightly lower (GMR adult/adolescent: 1.11) in adolescents compared to adults in the more important PK evaluable population. For the less important PK population, slightly lower dose-normalized $AUC_{0\text{-}24h}$ (GMR adult/adolescent: 1.05), and slightly higher dose-normalized C_{max} (GMR adult/adolescent: 0.904) were observed in adolescents when compared to adults. The difference in the results for the two populations may be due to potential noncompliance, especially in the lower dose groups (0.5 and 1.0 mg), when dosing was not under medical supervision.

1.2.3 Major Depressive Disorder

The efficacy of brexpiprazole as adjunctive therapy for the treatment of MDD has been studied in 4 completed placebo-controlled trials (Trials 331-10-227, 331-10-228, 331-13-214, and 331-12-282) and a long-term, open-label safety trial (Trial 331-10-238). A double-blind, placebo-controlled trial to evaluate the safety, efficacy, and tolerability of brexpiprazole (Trial 331-201-00079) is currently ongoing. Brexpiprazole was approved in the US on 10 Jul 2015 in adult patients for use as an adjunctive therapy to antidepressants for the treatment of MDD.

1.2.4 Other Indications

Brexpiprazole was investigated in a proof-of-concept trial in adult ADHD (Trial 331-08-213). This was a multicenter, randomized, double-blind, placebo-

controlled, flexible dose trial in which adults with ADHD who had an incomplete/partial response to stimulant therapy in a prospective treatment phase were randomized to double-blind treatment with either brexpiprazole-plus-stimulant or placebo-plus-stimulant. This trial showed no statistically significant improvement with brexpiprazole compared to placebo. Brexpiprazole is also currently being investigated in 2 ongoing double-blind trials (Trials 331-201-00080 and 331-201-00081) and 1 ongoing open-label trial (Trial 331-201-00083) in adult subjects with bipolar disorder.

1.3 Known and Potential Risks and Benefits

As of 17 Apr 2021 (ie, the current IB cutoff date), the brexpiprazole clinical development program consisted of a total of 97 clinical trials conducted in North America, Latin America, Europe, and Asia (77 completed and 20 ongoing). This total includes 77 trials conducted under US Investigational New Drug applications (INDs) (65 completed and 12 ongoing) for schizophrenia, adjunctive treatment of MDD, adjunctive treatment of ADHD, agitation associated with dementia of the Alzheimer's type (AAD), post-traumatic stress disorder (PTSD), or bipolar disorder; and 20 non-US IND trials (12 completed and 8 ongoing in China, Japan, and Canada) conducted in healthy subjects, subjects with schizophrenia, subjects with MDD, and subjects with AAD.

There are currently 2 ongoing phase 3 clinical trials in adolescent subjects with schizophrenia as of the cutoff date (Trials 331-10-234 and 331-10-236). Trial 331-10-234 will evaluate the efficacy and safety of brexpiprazole monotherapy over a 6-week controlled treatment period in adolescents with schizophrenia, while Trial 331-10-236 is an open-label trial to evaluate the long-term (24 months) safety and tolerability of brexpiprazole.

Safety data are available from the 76 completed clinical trials. The total number of subjects exposed to either single or multiple doses of brexpiprazole is composed of 9831 subjects in trials conducted under US IND applications and 876 subjects (collectively) in non-US IND trials conducted in Japan, China, and South Korea.

Combined data from the completed phase 1 clinical trials indicate that the maximum tolerated dose (MTD) for healthy adult subjects was determined to be 6 mg after single-dose administration and 2 mg after once-daily, multiple-dose (14 days) administration. The MTD of brexpiprazole in subjects with schizophrenia, MDD, AAD, ADHD, or bipolar disorder has not been established. Data from completed phase 1 clinical trials indicate that brexpiprazole is tolerated at multiple oral doses up to 12 mg/day in subjects with schizophrenia or schizoaffective disorder; up to 4 mg/day when coadministered with

marketed antidepressant therapy in subjects with MDD; up to 3 mg/day in elderly subjects (70 - 85 years of age) with MDD; and up to 4 mg/day when coadministered with marketed stimulant therapy in subjects with ADHD.

Overall, 69.6% of subjects who received brexpiprazole either alone or coadministered with another marketed medication reported at least 1 treatment-emergent adverse event (TEAE, with ≥ 2% incidence in total brexpiprazole and more than placebo). The most frequently reported TEAEs (incidence ≥ 5% of the total brexpiprazole group and more than total placebo) in all subjects who received brexpiprazole were increased weight (11.7%), headache (8.9%), insomnia (7.5%), akathisia (7.3%), somnolence (6.0%), and dizziness (5.2%). In the total placebo group, headache (8.4%) was the most frequently reported TEAE (incidence ≥ 5% of subjects). The majority of TEAEs reported in 61 pooled completed brexpiprazole clinical trials under US INDs were mild or moderate in severity.

A total of 33 deaths have been reported in the brexpiprazole interventional clinical trials as of the cutoff date of 17 Apr 2021: 30 deaths in the US IND trials and 3 deaths in the non-US IND trials. Nine deaths occurred in schizophrenia trials, 12 deaths in MDD trials, 9 deaths in the AAD trials, and 3 deaths in PTSD trials. One death, a completed suicide, was considered by the investigator to be related to investigational medicinal product (IMP).

Serious TEAEs have been reported for 415 subjects who received brexpiprazole (either alone or coadministered with another medication) in the 61 completed trials conducted under the US INDs, and in 58 subjects in the 12 completed non-US IND trials.

Overall, 9.3% of subjects who received brexpiprazole (either alone or coadministered with another medication) and 4.5% of subjects who received placebo (either alone or coadministered with another medication) discontinued from IMP due to TEAEs in 61 pooled completed brexpiprazole trials conducted under the US INDs as of the cutoff date of 17 Apr 2021. Overall, 10.6% of subjects who received brexpiprazole discontinued from IMP due to TEAEs in completed non-US IND trials.

In the phase 1, pediatric Trial 331-201-00103, brexpiprazole was safe and well tolerated at single oral doses of 0.75 to 1.5 mg in subjects 6 to < 10 years old and 1.5 to 3 mg in subjects 10 to < 13 years old with CNS disorders including, but not limited to, ADHD, autism-spectrum disorders, bipolar I disorder, conduct disorder, oppositional defiant disorder, or any psychotic disorder. The most frequently reported TEAE (> 1 subject) was nausea. Additionally, in Trial 331-10-233, multiple oral doses of 0.5 to 4 mg/day

brexpiprazole in subjects 13 to 17 years old with schizophrenia or other related psychiatric disorders were safe and well tolerated. The observed IMP-related TEAEs were similar in both trials.

The recommended dose ranges are as follows: 2 to 4 mg/day for the treatment of schizophrenia in adults and 2 to 3 mg/day in adult subjects with MDD. The following dose ranges of brexpiprazole were selected for evaluation in additional clinical trials (by indication): 0.5 to 3 mg/day in adult subjects with AAD, 1 to 3 mg/day in adult subjects with PTSD, and 2 to 4 mg/day in adult subjects with bipolar disorder.

Please refer to the current IB for a detailed summary of available nonclinical and clinical safety data.[11]

2 Trial Rationale and Objectives

2.1 Trial Rationale

Autism Spectrum Disorder is a neurodevelopmental disorder characterized by DSM-5 criteria as deficits in reciprocal social communication and social interaction (verbal and nonverbal).[1] Severity of ASD is defined by the degree of restricted, repetitive patterns of behavior, interests, and activities. Symptoms are present from early childhood and contribute to difficulties in developing, maintaining, and understanding relationships.

In addition to the core symptoms that characterize the disorder, children and adolescents with ASD often suffer from problem behaviors, such as symptoms of irritability and aggression, which may manifest as tantrums, self-injury, and aggressive behaviors toward others.[2] Approximately 20% of people with ASD exhibit irritability and aggression[3] with > 50% exhibiting significant emotion dysregulation.[4] Irritability and aggression often negatively affect the lives of people with ASD and their families.

The prevalence of ASD in the pediatric population in the US has increased over the past decade from estimates of 1 in 150 (0.67%) in 2000 to 1 in 68 (1.46%) in 2012, with increases occurring in all racial, ethnic, and socioeconomic groups (Autism and Developmental Disabilities Monitoring Network, 11 sites).[12] In 2011, the total costs per year for children with ASD in the US were estimated at between $11.5 billion and $60.9 billion which could be attributed to medical care, special education, and lost parental productivity.[6]

The atypical antipsychotics risperidone and aripiprazole are the only medications currently approved by the US Food and Drug Administration for the treatment of

irritability associated with ASD.[13] The common side effects of these medications are sedation, extrapyramidal side effects and weight gain[9], which are likely to further isolate children and adolescents from social interaction. Thus, there is a need to identify additional efficacious agents, especially considering the safety and tolerability issues that may be associated with use of selected antipsychotics in children and adolescents.[10]

2.2 Dosing Rationale

Two clinical trials have been conducted to investigate the PK, safety, and tolerability of brexpiprazole in children and adolescent patients with schizophrenia or other CNS disorders: in Trial 331-10-233, subjects 13 to 17 years old received multiple daily doses of brexpiprazole 0.5 to 4 mg; and in Trial 331-201-00103, subjects 6 to 13 years old received single doses of brexpiprazole 0.75, 1.5, or 3 mg.

In order to guide dose selection of brexpiprazole in children and adolescents 5 to 17 years of age with irritability associated with ASD, a population PK model was developed using pharmacokinetic data from the 2 PK trials in children and adolescents (Trial 331-10-233 and Trial 331-201-00103) and 3 PK trials in healthy adults or adults with schizophrenia (Trials 331-07-201, 331-08-205, and 331-08-206). In this model, clearance and volume of distribution were allometrically scaled by body weight (raised to the power of 0.75 for clearance, and 1 for volume of distribution); poor and ultra-rapid cytochrome P450 (CYP) 2D6 metabolizers were excluded in the analysis data; when needed for simulation, effect of CYP2D6 metabolic status on clearance can be imputed using the value reported in the adult population PK model previously submitted.[14] The allometrically scaled PK model adequately described the PK data in adults, children, and adolescents. Pharmacokinetic simulations were performed using this model to predict systemic exposure of brexpiprazole given different doses in adults (6000 virtual subjects with body weight resampled from two phase 3 trials), children, and adolescents (6240 virtual subjects with body weight simulated from the Centers for Disease Control growth chart for 5 - 17 year olds). Target exposure used for the simulations of ASD in subjects 5 to 17 years of age was similar to that of the adult subjects with MDD (0.5 - 3 mg/day).

Brexpiprazole systemic exposure, represented by area under the concentration curve at steady state during a 24-hour dosing interval (AUC_{tau}), were simulated and the 5th, median, and 95th percentiles were compared between children or adolescents 5 to 17 years of age and adult subjects with MDD. Based on the simulation result and clinical considerations, a weight cutoff at 50 kg was suggested to make sure subjects receive appropriate dose; and the following was observed:

- AUC_{tau} following 0.25 mg in children and adolescents < 50 kg and AUC_{tau} following 0.5 mg in children and adolescents ≥ 50 kg are comparable (based on 5th and 95th percentile of predicted exposure) with that following 0.5 mg in adult subjects.
- AUC_{tau} following 1.5 mg in children and adolescents < 50 kg and AUC_{tau} following 3 mg in children and adolescents ≥ 50 kg are comparable (based on 5th and 95th percentile of predicted exposure) with that following 3 mg in adult subjects.

The dosing schedule for this trial is shown in Table 3.2-1

2.3 Trial Objectives

The primary objective of this trial is to evaluate the efficacy, safety, and tolerability of brexpiprazole in reducing irritability in children and adolescents ages 5 to 17 years with a diagnosis of ASD.

3 Trial Design

3.1 Type/Design of Trial

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, 8-week trial designed to evaluate the effects of flexibly-dosed brexpiprazole 0.25 to 3 mg/day, compared with placebo on irritability in children and adolescent subjects, ages 5 to 17 years, with a diagnosis of ASD according to DSM-5; score ≥ 18 on the Aberrant Behavior checklist - Irritability (ABC-I) subscale; and score ≥ 4 on the Clinical Global Impressions - Severity (CGI-S) scale.[15,16] The trial will consist of a 1 to 28 day screening period, followed by an 8-week double-blind treatment period, and a 21-day post-treatment safety follow-up period. The trial will be conducted on an outpatient basis.

Subjects who continue to meet entrance criteria at the baseline visit (Day 1) will be randomized 1:1 to receive brexpiprazole or placebo daily. If fasting or nonfasting blood and clinical laboratory tests (chemistry, hematology, and urinalysis) and ECG were obtained at screening with results within normal ranges and collected less than 28 days before baseline, blood and urine samples and ECG do not need to be repeated at the baseline visit.

On Day 1 of the treatment period, subjects will begin titration to a target minimum dose of investigational medicinal product (IMP). The target dose range of IMP will be determined for each individual subject based on body weight.

During the double-blind treatment phase, evaluations are planned on Day 1 (baseline) and at Weeks 1, 2, 3, 4, 6, and 8. Visits at baseline, Week 2, and Week 8 will occur at the clinic. All other visits may be conducted either virtually or in clinic. Where the investigator and caregiver make the decision to conduct a visit virtually, the visit will be conducted by means of telecommunications technology. The caregiver and subject will remain in their own home and complete trial assessments and questionnaires via an online technology. The caregiver and subject will interact with trial personnel using online communication tools which incorporate telemedicine. During virtual interactions (and at any other time), the trial personnel will be able to assess the subject and determine if an additional in-office visit for a physical evaluation is required at the discretion of the investigator.

Eligible subjects who complete the 8-week double-blind phase may have the option to enroll into an open-label safety trial (Trial 331-201-00191) of brexpiprazole. Subjects who do not enroll in the open-label safety trial will have a follow-up contact 21 ± 2 days after the last dose of IMP to assess adverse events (AEs).

A schematic of the trial design is provided in Figure 3.1-1.

Protocol 331-201-00148

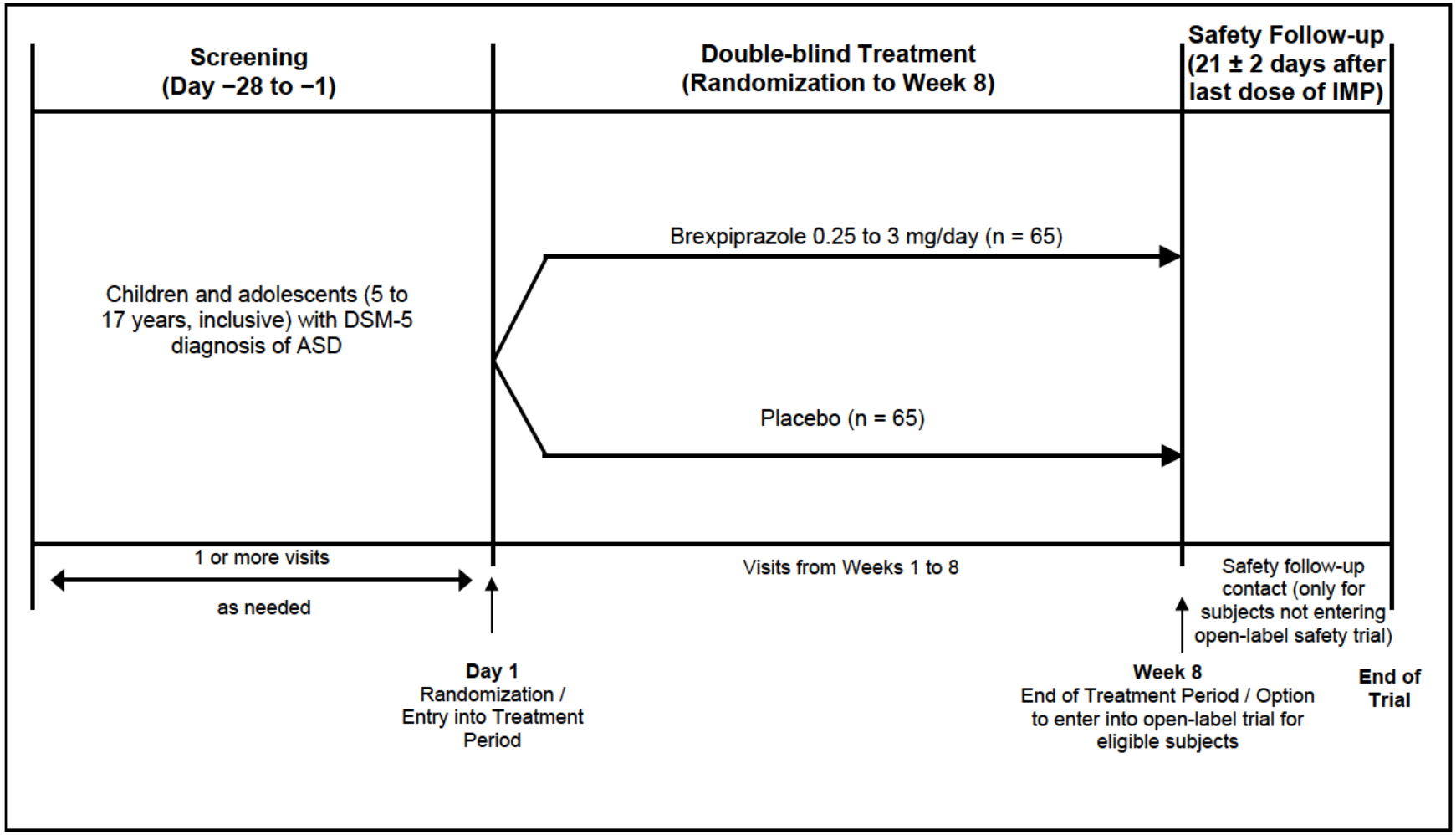

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

Brexpiprazole will be supplied by the sponsor or designated agent in child-resistant blister cards, each containing sufficient tablets for 7 (+ 2) days. Treatment assignments will be obtained by accessing eSource. Based on computer-generated randomization, eligible subjects will be allocated in a 1:1 ratio at randomization to 1 of the following 2 treatment groups:

- Brexpiprazole
- Placebo

Neither the investigator nor the subject will be aware of the treatment assignment. All doses of brexpiprazole and matching placebo will be taken orally once daily, preferably in the morning, and will be administered without regards to meals. Brexpiprazole (or matching placebo) should be taken at approximately the same time each day.

Subjects will follow a titration schedule, depending on their assigned treatment group, see Table 3.2-1.

Table 3.2-1 Dosing Schedule During the Treatment Period[a]

Trial Day	No. Days on IMP	Brexpiprazole Dose		Placebo
		< 50 kg	≥ 50 kg	
Days 1 to 3	3	0.25 mg QD	0.50 mg QD	placebo tablets QD
Days 4 to 7	4	0.50 mg QD	1.5 mg QD	placebo tablets QD
Days 8 to 14	7	1 mg QD	2 mg QD	placebo tablets QD
Starting at Day 15 (earliest opportunity to increase to maximum dose within target dose range)	Based on investigator discretion to change dose based on therapeutic effect or tolerability	1 mg or 1.5 mg QD	1.5 mg, 2 mg, or 3 mg QD	placebo tablets QD

QD = once daily.

[a]Dose titrations will be performed in conjunction with a trial visit and therefore, trial visit windows are allowed for the titration schedule.

The target dose range of IMP will be determined for each individual subject based on body weight. Those subjects with body weight < 50 kg will receive a target dose range of 1 to 1.5 mg, and those subjects with body weight ≥ 50 kg will receive a target dose range of 1.5 to 3 mg. Body weight at the time of randomization will determine dose/titration requirements throughout the trial.

Subjects with body weight < 50 kg will receive brexpiprazole at a dose of 0.25 mg for Days 1 to 3, 0.5 mg for Days 4 to 7, and 1 mg for Days 8 to 14. Day 15 is the earliest opportunity that the investigator has to increase to the maximum dose of 1.5 mg within the target dose range. The decision to increase the dose to 1.5 mg and when to increase the dose will be based on investigator judgment in order to reach a desired therapeutic effect. Subjects must be on their final dose at Week 6. Subjects that require a change in dose between Week 6 and Week 8 will be discontinued.

Subjects with body weight ≥ 50 kg will receive brexpiprazole at a dose of 0.5 mg for Days 1 to 3, 1.5 mg for Days 4 to 7, and 2 mg for Days 8 to 14. Day 15 is the earliest opportunity that the investigator has to increase to the maximum dose of 3 mg within the target dose range. The decision to increase the dose to 3 mg and when to increase the dose will be based on investigator judgment in order to reach a desired therapeutic effect. Subjects must be on their final dose at Week 6. Subjects that require a change in dose between Week 6 and Week 8 will be discontinued.

For all subjects, doses can be down-titrated due to tolerability based on investigator judgment. Subjects < 50 kg should receive a dose of 1.5 mg before decreasing the dose to 1 mg. Subjects ≥ 50 kg should receive a dose of 2 mg before decreasing the dose to 1.5 mg and 3 mg before decreasing to 2 mg.

If a subject < 50 kg is unable to tolerate the 1 mg dose, the subject will be discontinued. If a subject > 50 kg is unable to tolerate the 1.5 mg dose, the subject will be discontinued.

Dose titrations will be performed in conjunction with a trial visit and therefore, trial visit windows are allowed for the titration schedule.

To accommodate maximum flexibility in dosing for the autism subjects, more than 1 dose decrease or increase may be allowed based on the dosing schedule by weight. Any increase or decrease, however, should happen in a stepwise fashion based on investigator discretion to change dose based on therapeutic effect or tolerability according to Table 3.2-1.

IMP will be dispensed by the site or delivery will be made to a subject's home. IMP for dose increases or decreases occurring between scheduled visits will be dispensed as an unscheduled visit and accommodations arranged to have IMP received by the subject/caregiver, either by home delivery or pickup at the site. Instructions will be supplied to the subject/caregiver by study/team support staff regarding any dosing changes.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

The trial population will include male and female subjects between 5 and 17 years of age, inclusive, at the time of informed consent/assent with a DSM-5 diagnosis of ASD. Subjects will have irritability associated with ASD as defined by a score of ≥ 18 on the ABC-I and ≥ 4 on the CGI-S.

Approximately 102 subjects will be randomized (51 per treatment arm).

3.3.2 Subject Selection and Numbering

At screening, subjects will be assigned a unique subject identification (ID) number upon completion of the consent/assent process.

3.4 Eligibility Criteria

3.4.1 Informed Consent/Informed Assent

Informed consent/assent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). Consent and assent will be documented on an electronic or written informed consent form (ICF) and informed assent form (IAF). The ICF/IAF will be approved by the same institutional review board/independent ethics committee (IRB/IEC) that approves this protocol. Subjects who are too young to sign an ICF/IAF either via wet signature or electronic signature (e-signature) will provide informed assent per local law, and the subject must be able to understand that he or she can withdraw from the trial at any time and for any reason.

Each ICF/IAF will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[17] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written site-specific ICF/IAF used in the trial before submission to the IRB/IEC.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent/assent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the subject and/or his/her parent/legal guardian or legally acceptable representative, as applicable by the investigator (or a qualified designee), and it has been documented that the subject and his/her parent/legal guardian or legally acceptable representative has had the opportunity to ask questions, the IRB/IEC approved written ICF/IAF will be signed and dated by the subject, the subject's legally acceptable representative (eg, guardian) and the person obtaining consent/assent (investigator or designee), as well as by any other parties required by the IRB/IEC. The subject will receive a copy of the signed ICF/IAF; the original shall be kept on file by the investigator.

At sites where the electronic ICF/IAF application is used, prospective trial participants will be provided with controlled access to the application by trial site staff. When the trial site staff and the participant agree that the participant has enough information to make an informed decision to participate, the participant will electronically sign the ICF or assent form in the electronic ICF application and an electronic date and timestamp will be applied to the signature. The subject will be given a printed, signed copy of the ICF and assent form. Any other parties required by the IRB/IEC (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the electronic ICF/IAF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied. At sites where the electronic ICF/IAF application is not used, paper consent and assent forms will be signed after trial site staff and the participant agree that the participant has enough information to make an informed decision to participate. Any other parties required to provide signatures will also sign the paper forms, and the forms will be stored in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines.

Subjects or their parent/legal guardian or legally acceptable representative, as applicable for local laws, may be asked to sign additional ICFs/IAFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on trial participation.

Subjects who are not started on treatment after the ICF/IAF is signed are permitted to be rescreened under the conditions specified in Section 3.9 (Screen Failures). In the event that the subject is rescreened for trial participation, a new ICF/IAF must be signed and a new ID number obtained.

If a subject is legally emancipated, informed consent must be sought directly from the subject. Subjects who turn age 18 (or the age of adulthood as specified by local laws or regulations) during the trial must sign a new ICF at that time.

In addition to the English version of the ICF/IAF, the documents may also be translated into local languages for use in this trial. Translation with back-translation for confirmation will be utilized to ensure accuracy.

CCI

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1.	Written informed consent, assent, or both obtained from a legally acceptable representative (eg, guardian) or subject prior to the initiation of any protocol-required procedures. In addition, the subject must provide informed assent at screening and must be able to understand that he or she can withdraw from the trial at any time. All informed consent/assent procedures must be in accordance with the trial site's IRB/IEC and local regulatory requirements (Section 3.4.1).
2.	Male and female subjects 5 to 17 years of age, inclusive, at the time of informed consent/assent.
3.	Subjects with a current primary DSM-5 diagnosis of ASD, as determined by the investigator and supported by the ADI-R.
4.	Subjects with an ABC-I subscale score $\geq$ 18 at screening and at baseline (Day 1).
5.	Subjects with a CGI-S scale score $\geq$ 4 pertaining to irritability at screening and at baseline (Day 1).
6.	Subjects with a mental age of $\geq$ 2 years, as determined by the investigator based on school participation, social history, or medical records.
7.	Ability, in the opinion of the principal investigator, of the subject or the subject's legally acceptable representative (eg, guardian) or caregiver(s) to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet ingestion, and discontinuation of prohibited concomitant medications, to read and understand the written word in order to be reliably rated on assessment scales and participate in virtual visits.

ADI-R = Autism Diagnostic Interview - Revised.

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Protocol 331-201-00148

Table 3.4.3-1 Exclusion Criteria	
1.	Sexually active males or FOCBP who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide.
2.	Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
3.	Subjects with a 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 clinical instrument (K-SADS-PL), or PTSD. Subjects with comorbid ADHD are permitted to enroll in the trial, provided that ADHD is not the primary disorder, the subject is adequately treated and based on the investigator judgment the disorder is clinically stable.
4.	The subject has a current or historical diagnosis of Fragile-X Syndrome or Rett's Disorder.
5.	The subject has a history of neuroleptic malignant syndrome.
6.	Subjects who have a significant risk of committing violent acts, serious self-harm, or suicide based on history or routine psychiatric status examination, or those who are homicidal or considered to be a high risk to others, or subjects with an answer of "yes" on C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) at entry or within the past three months, OR Subjects with a response of "yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) at entry or within the past three months, OR Subjects with a response of "yes" on any of the 5 C-SSRS Suicidal Behavior Items(actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) at entry or within the past year.
7.	Subjects who have epilepsy, a history of seizures (except for a single childhood febrile seizure or post-traumatic seizure), or a history of severe head trauma or stroke, or have a history or current evidence of other unstable medical conditions that would expose them to undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the trial, including but not limited to hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the investigator (eg, history of myocardial infarction or ischemic heart disease, arrhythmia, congestive heart failure, or cancer); subjects with a comorbid serious systemic illness that requires pharmacotherapy; subjects with a history of electroconvulsive therapy.
8.	Non-pharmacological therapy (eg, psychotherapy, behavior modification) is not stable for 30 days prior to screening and is not likely to be consistent throughout the trial.
9.	Subjects with current hypothyroidism or hyperthyroidism (unless the condition has been stabilized with medications for at least the past 90 days). Eligibility of subjects that have an abnormal free T_4 result that is considered not clinically significant can be discussed with the medical monitor prior to randomization.
10.	Subjects with Type I or Type II diabetes are excluded if all of the following criteria are not met: • HbA1c ≤ 6.5%, • Screening fasting glucose is ≥ 70 mg/dL and ≤ 100 mg/dL or nonfasting glucose is ≥ 70 mg/dL and ≤ 139 mg/dL. If the nonfasting glucose is ≥ 139 mg/dL, subjects must be retested in the fasting state. At retest, fasting glucose must be ≤ 100 mg/dL • Subject has been maintained on a stable regimen of non-insulin medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening, • Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, **AND** • Subject's diabetes is not newly diagnosed during screening for the trial.

Protocol 331-201-00148

Table 3.4.3-1 Exclusion Criteria	
11.	Subjects with uncontrolled hypertension or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 15 mmHg in SBP or a decrease of ≥ 15 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure, **OR** development of symptoms.
12.	Subjects ≥ 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 are excluded. A positive test for amphetamines, barbiturates, opiates, benzodiazepines may not result in exclusion of the subjects if the investigator determines that the positive test is a result of prescription medicine(s). When a subject tests positive for cannabinoids (tetrahydrocannabinol) at screening, the investigator is required to evaluate the subject's ability to abstain from using this substance during the trial and to discuss his/her evaluation with the Medical Monitor prior to randomization.
13.	The following laboratory test and ECG results are exclusionary: 1) Platelets ≤ 130 × 10^3/uL for ≤ 12 years of age, ≤ 140 × 10^3/uL for ≥ 13 years of age 2) Hemoglobin ≤ 11.2 g/dL for ≤ 12 years of age, ≤ 11.6 g/dL for ≥ 13 years of age 3) Neutrophils, absolute ≤ 1.00 × 10^3/uL for ≤ 12 years of age, ≤ 1.35 × 10^3/uL for ≥ 13 years of age 4) AST ≥ 2 × upper limit of normal 5) ALT ≥ 2 × upper limit of normal 6) Creatinine ≥ 0.7 mg/dL for ≤ 12 years of age, ≥ 1.1 mg/dL for ≥ 13 years of age 7) HbA1c ≥ 6.5% 8) CPK ≥ 2 × upper limit of normal 9) QTcF ≥ 450 msec for males and ≥ 470 msec for females using the QTcF correction
14.	The subject weighs < 15 kg.
15.	Subjects who would be likely to require prohibited concomitant therapy during the trial.
16.	Subjects who have been exposed to brexpiprazole (eg, prior clinical trial or prescription).
17.	Subjects with a history of true allergic response (ie, not intolerance) to more than one class of medications.
18.	Inability to tolerate oral medication or swallow tablets.
19.	Subjects who participated in any clinical trial within the last 30 days prior to screening.
20.	Any subject who, in the opinion of the investigator, should not participate in the trial.
21.	Subjects who are siblings, or are unrelated and live in the same household, cannot simultaneously participate in the trial.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; C-SSRS = Columbia-Suicide Severity Rating Scale; CYP = cytochrome P450; DBP = diastolic blood pressure; ECG = Electrocardiogram; FOCBP = females of childbearing potential; HbA1c = glycosylated hemoglobin; IM = intramuscular; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version; PTSD = post-traumatic stress disorder; QTcF = QT interval as corrected for heart rate by Fridericia's formula; SBP = systolic blood pressure; T_4 = thyroxine; WBC = white blood cell.

Subjects must agree to restrictions to medications as described in Section 4.

Subjects excluded for positive drug/alcohol screen are not eligible to be rescreened for participation in the trial. However, subjects excluded for any other reasons may be rescreened at any time if the exclusion characteristic has changed. In the event that the subject is rescreened, a new ICF/IAF must be signed and a new ID number assigned.

Protocol 331-201-00148

3.5 Endpoints

3.5.1 Primary Endpoint

3.5.1.1 Efficacy Endpoint

The primary efficacy endpoint of this trial will be the mean change from baseline to Week 8 in the ABC-I subscale score.

The estimand of the primary efficacy endpoint is described in Section 7.4.1.

3.5.2 Secondary Endpoints

3.5.2.1 Efficacy Endpoint

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

3.5.3 Safety Endpoints

Safety will be assessed by the following standard endpoints for clinical trials and trials of antipsychotic drugs:

- Frequency and severity of AEs, serious AEs (clinical and laboratory), and discontinuation from the trial due to AEs
- Weight, height, body mass index (BMI), and waist circumference
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Vital signs and electrocardiogram (ECG) parameters
- EPS scale scores: Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Scale (SAS)
- Potential suicide events recorded on suicidality scale scores

CCI

3.6 Measures to Minimize/Avoid Bias

3.6.1 Randomization

Treatment assignments will be obtained by accessing eSource. Based on computer-generated randomization, eligible subjects will be allocated in a 1:1 ratio at randomization to receive either brexpiprazole or placebo. The randomized treatments will be administered in a double-blind fashion and stratified by clinical site. Treatment assignments will be based on a computer-generated randomization code provided by the Otsuka Pharmaceutical Development & Commercialization, Inc. Biometrics Department.

Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, operating the interactive web response system, and reporting serious TEAEs to regulatory agencies.

3.6.2 Blinding

Placebo tablets are identical in appearance to active IMP and all dose strength brexpiprazole tablets are visually indistinguishable.

3.7 Trial Procedures

Trial assessment time points are summarized in Table 3.7-1.

Table 3.7-1 Schedule of Assessments

	Screening	Double-blind Treatment							Follow-up	
Assessment	**Day -28 to -1** **In office**	**Baseline (Day 1)** **In office**	**Week 1 (Day 7 ± 2 days)** **Virtual or In office**	**Week 2 (Day 14 ± 2 days)** **In office**	**Week 3 (Day 21 ± 2 days)** **Virtual or In office**	**Week 4 (Day 28 ± 2 days)** **Virtual or In office**	**Week 6 (Day 42 ± 2 days)** **Virtual or In office**	**Week 8/ET (Day 56 ± 2 days)** **In office**	**21 ± 2 days) after last dose of IMP** **By Telephone**	**Notes**
Trial Entrance and History										
Informed consent/assent	X									Section 3.4.1
Inclusion/exclusion criteria	X	X								Section 3.4.2
Demography	X									
Medical history	X									Section 3.7.1
Psychiatric history	X									Section 3.7.1
ADI-R[a]	X									Section 3.7.3.6.1
Prior medications and washout, if applicable	X									Section 4.1
K-SADS-PL[b]	X									Section 3.7.3.6.2
Randomization		X								Section 3.7.1.2
Efficacy Assessments										
ABC	X	X	X	X	X	X	X	X		Section 3.7.2.1
CGI-S	X	X	X	X	X	X	X	X		Section 3.7.2.2
CCI										
Safety Assessments										
Physical examination	X							X		Section 3.7.3.3.1
Vital signs	X	X	X	X	X	X	X	X		Section 3.7.3.3.2
Height	X							X		Section 3.7.3.3.1
Body weight and waist circumference	X	X						X		Section 3.7.3.3.1

Protocol 331-201-00148

Table 3.7-1 Schedule of Assessments

	Screening	Double-blind Treatment							Follow-up	
Assessment	**Day -28 to -1** **In office**	**Baseline (Day 1)** **In office**	**Week 1 (Day 7 ± 2 days)** **Virtual or In office**	**Week 2 (Day 14 ± 2 days)** **In office**	**Week 3 (Day 21 ± 2 days)** **Virtual or In office**	**Week 4 (Day 28 ± 2 days)** **Virtual or In office**	**Week 6 (Day 42 ± 2 days)** **Virtual or In office**	**Week 8/ET (Day 56 ± 2 days)** **In office**	**21 ± 2 days) after last dose of IMP** **By Telephone**	**Notes**
Clinical laboratory tests (hematology, serum chemistry, and urinalysis)	X[c]	X[d]						X		Section 3.7.3.2
Prolactin (blinded)	X							X		Section 3.7.3.2
Pregnancy test	X							X		Section 3.7.3.2
ECG	X[c]	X[d]						X		Section 3.7.3.4
C-SSRS (child version)	X	X	X	X	X	X	X	X	X	Section 3.7.3.5.4
Extrapyramidal symptoms scales (SAS, AIMS, and BARS)		X		X				X		Section 3.7.3.5
Urine drug screen	X									Section 3.7.3.2
Blood alcohol test	X									Section 3.7.3.2
ACTH	X							X		Section 3.7.3.2
Cortisol	X							X		Section 3.7.3.2
HbA1c	X							X		Section 3.7.3.2
TSH with reflex to free T_4 if abnormal	X							X		Section 3.7.3.2
Coagulation parameters	X							X		Section 3.7.3.2
Adverse events	X	X	X	X	X	X	X	X	X	Section 5
Concomitant medications	X	X	X	X	X	X	X	X	X	Section 3.7.4
Pharmacokinetic and Pharmacogenomic Assessments										
Pharmacokinetic sampling[e]		X						X		Section 3.7.5

Protocol 331-201-00148

Table 3.7-1 Schedule of Assessments

	Screening	Double-blind Treatment							Follow-up	
Assessment	**Day -28 to -1** **In office**	**Baseline (Day 1)** **In office**	**Week 1 (Day 7 ± 2 days)** **Virtual or In office**	**Week 2 (Day 14 ± 2 days)** **In office**	**Week 3 (Day 21 ± 2 days)** **Virtual or In office**	**Week 4 (Day 28 ± 2 days)** **Virtual or In office**	**Week 6 (Day 42 ± 2 days)** **Virtual or In office**	**Week 8/ET (Day 56 ± 2 days)** **In office**	**21 ± 2 days) after last dose of IMP** **By Telephone**	**Notes**
Pharmacogenomic sampling[f]		X								Section 3.7.5
[redacted] CCI [redacted]		[redacted]								[redacted]
Other Procedures										
IMP dispensing		X	X	X	X	X	X			
IMP accountability			X	X	X	X	X	X		Section 8.3

Adrenocorticotropic hormone = ACTH; CRO = clinical research organization; ET = early termination; TSH = thyroid-stimulating hormone.

[a]Assessment must be done unless previously completed within the last 3 years. Assessment with the Autism Diagnostic Observation Schedule (ADOS) can also serve as documentation for ADI-R rating provided that it was completed within the last 3 years.

[b]If a subject is rescreened for participation in the trial, the K-SADS-PL does not need to be repeated at the screening visit.

[c]The screening period may be extended in order to repeat clinical laboratory tests and ECGs; if an extension is required, the site should contact the medical monitor.

[d]Baseline clinical laboratory tests (hematology, serum chemistry, and urinalysis) and ECGs are not collected if screening clinical laboratory tests/ECGs were obtained within 28 days prior to the baseline visit and within normal ranges.

[e]One PK sample will be collected 1 to 4 hours postdose on Day 1. Two PK samples will be collected at the Week 8 visit (predose and 1-4 hours postdose). The actual time of the PK sample will be recorded as well as the dosing time prior to the PK sample collection. The longest time possible within the 1 to 4 hour range is preferred but should be no less than 1 hour.

[f]Pharmacogenomic and CCI sampling (if done), are to be taken with the postdose PK draw to avoid additional blood draws.

3.7.1 Schedule of Assessments

3.7.1.1 Screening Period

The screening period begins after written informed consent/assent has been obtained and will take place between Day −28 and Day −1 prior to enrollment. All required assessments will be performed as described in the schedule of assessments (Table 3.7-1). Although the screening period continues up to administration of the first dose of IMP, screening procedures should be initiated with a sufficient amount of time allotted in order to obtain laboratory results and ECG results from the central reader prior to randomization. The screening period may be extended in order to repeat fasting or nonfasting blood and clinical laboratory tests (chemistry, hematology, and urinalysis) and ECGs; if an extension is required, the site should contact the medical monitor. After a subject has provided consent/assent, an ID number will be provided via eSource. Completion of screening activities may require more than 1 visit; however, only the initial visit will be registered. The screening period maximum of 28 days may be extended after discussion with the medical monitor.

The following should also be noted:

- Subjects will assent and the subject's legally acceptable representative (eg, guardian) will sign an ICF/IAF to participate in this trial prior to initiation of any trial-related procedures. After signing the ICF/IAF, subjects will be assigned a unique subject screening identification number through the eConsent system that is transferred to both the eSource and interactive response technology (IRT).
- Trial personnel will enter subject data into eSource to register all trial visits.
- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- Medical and psychiatric history will be recorded, including the DSM-5 diagnosis of ASD that will be made by an adequately trained clinician and supported by the Autism Diagnostic Interview - Revised (ADI-R).
- Previous and concomitant medications taken within 30 days of screening will be recorded. Lifetime antipsychotic use will be recorded. Washout from prohibited concomitant medications will begin after consent/assent has been obtained, if applicable.

3.7.1.2 Baseline/Day 1 (Randomization)

If the subject is found to be eligible for the trial during the screening period, all required baseline assessments will be performed according to the Schedule of Assessments (Table 3.7-1). The following should also be noted:

- Inclusion/exclusion criteria will be verified.
- Baseline clinical laboratory tests (hematology, serum chemistry, and urinalysis) and ECGs are not collected if the screening clinical laboratory tests/ECGs were obtained within 28 days prior to the baseline visit and within normal ranges.
- If the subject remains eligible for the trial after completion of the baseline evaluations, trial personnel will capture trial data within the eSource and randomize the subject to obtain an IMP assignment. The subject will receive the first dose of IMP from the assigned double-blind card and the date and time of the first dose will be recorded in eSource. The subject should take the IMP at approximately the same time each day, preferably in the morning, without regard to meals. It is acceptable, however, based on timing of the clinic visit that the first dose may not be at the same approximate time as all subsequent doses.
- A blood sample for PK will be collected postdose.
- A blood sample for pharmacogenomics analysis will be collected (with the postdose PK draw to avoid additional blood draws).
- If the subject has signed a separate ICF/IAF, blood may be drawn for CCI (with the postdose PK draw to avoid additional blood draws).

3.7.1.3 Double-blind Treatment Phase (Weeks 1, 2, 3, 4, and 6)

All subjects will be assessed at scheduled visits. Week 2 visit will be conducted as an in-office visit. Visits at Weeks 1, 3, 4, and 6 may be conducted either virtually or in clinic. Where the investigator and caregiver make the decision to conduct a visit virtually, the visit will be conducted by means of telecommunications technology. For these virtual visits, the caregiver and subject will remain in their own home and complete trial assessments and questionnaires via an online technology. The caregiver and subject will interact with trial personnel using online communication tools which incorporate telemedicine. During virtual interactions (and at any other time), the trial personnel will be able to assess the subject and determine if an additional in-office visit for a physical evaluation is required at the discretion of the investigator. The telecommunication equipment is supplied to all caregivers and subject pairs. The equipment will be returned at the end of trial participation.

Visits are to occur within ± 2 days of the target visit date. All required evaluations will be performed as described in the Schedule of Assessments (Table 3.7-1). The following should also be noted:

- The IMP will be dispensed to the subject/caregiver. The subject will begin taking the IMP from the assigned blister card. Instructions will be supplied to the subject/caregiver by study team/support staff regarding any dosing changes. The

subject should take the IMP at approximately the same time each day, preferably in the morning, without regard to meals.

- IMP accountability will be performed.

3.7.1.4 Week 8 (End of Treatment)

The treatment period will conclude at the Week 8 in clinic visit. The visit is to occur within ± 2 days of the target visit date. Subjects should take the last dose of IMP during the Week 8 visit in order to be able to complete a PK lab draw (predose and postdose). All required evaluations will be performed as described in the Schedule of Assessments (Table 3.7-1). The following should also be noted:

- Blood samples for PK will be collected at Week 8 (predose and postdose).
- Trial personnel will register completion or discontinuation from the trial in eSource.
- IMP accountability will be performed.

Eligible subjects who complete this 8-week trial may have the option to enroll into an open-label safety trial of brexpiprazole (Protocol 331-201-00191).

3.7.1.5 Early Termination

If a subject discontinues early before Week 8, procedures noted for Week 8 must be completed at the ET visit. Attempts should be made to complete all evaluations, particularly efficacy assessments, prior to the administration of any new psychotropic medications.

3.7.1.6 Follow-up

All subjects who do not enroll in the open-label rollover trial (Protocol 331-201-00191) will be followed up by either a telephone or other acceptable means of contact 21 (± 2) days after the last dose of IMP to assess any new or ongoing AEs and to record any concomitant medications. Depending upon the type of follow-up required, other evaluations or tests may be conducted or performed.

3.7.2 Efficacy Assessments

3.7.2.1 Aberrant Behavior Checklist

The ABC is a standardized parent-reported rating scale originally designed to assess treatment effects on problem behavior in people with intellectual disabilities. The irritability subscale of the ABC (ABC-I) is the primary efficacy endpoint of this trial. The

ABC-I measures emotional and behavioral symptoms of ASD, including aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. Since its use in the seminal studies with risperidone, the ABC-I has been accepted as a standard in medication trials for ASD.[15,16] CCI [redacted]

CCI [redacted]

CCI [redacted]

3.7.2.2 Clinical Global Impressions - Severity of Illness Scale

The severity of illness for subjects with ASD will be rated using the CGI-S[18] with a focus on symptoms of irritability. To perform this assessment, the rater or investigator will answer the following question: "Considering your total clinical experience with this particular population, how ill is the patient at this time with regard to symptoms of irritability?" Response choices include: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.

CCI [redacted]

CCI [redacted]

Protocol 331-201-00148

CCI [redacted]

CCI [redacted]

CCI [redacted]

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.3.2 Clinical Laboratory Assessments

Table 3.7.3.2-1 presents the protocol-required clinical laboratory test for all subjects in this trial. A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up laboratory tests, if needed). In cases where an immediate result is required for a particular laboratory test, the sample should be divided and sent to both a local laboratory and the designated central laboratory. Urine will be collected and blood will be drawn from each subject during screening prior to treatment with IMP and then at the scheduled visits designated in Table 3.7-1. The results of these tests must be reviewed by the investigator prior to initiation of IMP. Additional urine and blood samples may be collected for further evaluation of safety as warranted by the investigator's judgment.

Subjects should be fasting for a minimum of 8 hours prior to blood draws, if at all possible. If fasting blood samples are not feasible, nonfasting blood samples may be obtained initially. If a subject is not fasting at a visit, the blood draw should still be performed and the status documented as nonfasting on the laboratory requisition sheet. If fasting or nonfasting blood and clinical laboratory tests (chemistry, hematology, and urinalysis) were obtained at screening with results within normal ranges and collected less than 28 days before baseline, blood and urine samples do not need to be repeated at the baseline visit. Reports from the central laboratory will be retained electronically within the lab vendor's online portal and assessed by the investigator or qualified designee for clinical significance within eSource.

Protocol 331-201-00148

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology: Hematocrit Hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelets RBC count WBC count with differential MCH RDW RBC morphology Urinalysis: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high powered field pH Protein Specific gravity Urine drug screen: Amphetamines Barbiturates Opiates Benzodiazepines Cannabinoids Cocaine Marijuana Methadone Phencyclidine Propoxyphene	Serum Chemistry: Albumin Alkaline phosphatase ALT AST Bicarbonate Bilirubin, total BUN Calcium Chloride Cholesterol (total, HDL, LDL) CPK Creatinine GGT Glucose Insulin LDH Potassium Protein, total Sodium Triglycerides Uric acid Additional Tests: Blood alcohol test Urine or serum pregnancy for all FOCBP Serum TSH, with reflex to free T_4 if TSH is abnormal ACTH Cortisol HbA1c Serum prolactin (blinded) Coagulation Parameters: PT aPTT INR

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; HDL = high density lipoprotein; INR = international normalized ratio; LDH = lactic dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; PT = prothrombin time; RBC = red blood cell; RDW = red cell distribution width; WBC = white blood cell

The total volume of blood to be collected during the trial will be documented in the ICF/IAF.

A urine pregnancy test will be conducted in all females of childbearing potential (FOCBP) prior to trial intervention; results must be available prior to the administration

of the IMP. A confirmatory serum pregnancy test will be done for subjects with a positive urine test. Subjects with a positive serum test result at screening will be excluded from the trial. The frequency of pregnancy tests may be modified based on local regulatory requirements and pregnancy tests can be performed at any point during trial if pregnancy is suspected.

A urine drug screen and blood alcohol test will occur in children ≥ 13 years of age that engage in social activities with peers without adult supervision.

Any value outside the normal range will be flagged for the attention of the investigator, who must indicate whether or not a flagged value is of clinical significance. If 1 or more values are questionable, the test(s) may be repeated. If the result of any test (or repeat test, if done) is indicated as clinically significant in the samples taken during the screening period, the subject will NOT be enrolled into the trial without the permission of the medical monitor. In addition, follow-up unscheduled laboratory tests should be performed on clinically significant abnormalities. Unscheduled laboratory tests may be repeated at any time at the discretion of the investigator for appropriate medical care.

The following laboratory test results are exclusionary:

1) Platelets ≤ 130 × 10^3/uL for ≤ 12 years of age, ≤ 140 × 10^3/uL for ≥ 13 years of age
2) Hemoglobin ≤ 11.2 g/dL for ≤ 12 years of age, ≤ 11.6 g/dL for ≥ 13 years of age
3) Neutrophils, absolute ≤ 1.00 × 10^3/uL for ≤ 12 years of age, ≤ 1.35 × 10^3/uL for ≥ 13 years of age
4) Aspartate aminotransferase (AST) ≥ 2 × the upper limit of normal (ULN)
5) Alanine aminotransferase (ALT) ≥ 2 × the ULN
6) Creatinine ≥ 0.7 mg/dL for ≤ 12 years of age, ≥ 1.1 mg/dL for ≥ 13 years of age
7) HbA1c ≥ 6.5%
8) CPK ≥ 2 × ULN
9) QTcF ≥ 450 msec for males and ≥ 470 msec for females

In addition, subjects should be excluded if they have any other abnormal laboratory test result at screening that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results. However, any abnormal screening laboratory result(s) considered to be clinically significant should be repeated as soon as possible to confirm the finding(s) before excluding the subject from the trial. Appendix 2 is included to assist investigators in their assessments of

results that may be potentially medically significant, depending on the subject's medical history and clinical presentation.

Clinical laboratory samples at Week 8 should be taken as part of the predose PK blood draw.

3.7.3.3 Physical Examination and Vital Signs

3.7.3.3.1 Physical Examination

The physical examination (PE) will consist of measurement of weight, height, and a review of the following body systems: head, ears, eyes, nose, and throat; thorax; abdomen; urogenital; extremities; neurological; and skin and mucosae. A complete PE is an integral part of trial safety assessments and includes a urogenital assessment. A urogenital assessment should be performed on all trial subjects according to local medical standards as applied to other body systems. For the purposes of this trial, at a minimum, a screening urogenital exam is required, which could have been performed up to one calendar year prior to the date of the ICF being signed, or can be performed during the screening period. The urogenital examination may be performed by the subject's primary care provider or pediatrician as long as the source records are obtained, and the findings documented. Post-baseline, medically relevant questions about the urogenital body system must be asked of the subject at all protocol-required physical exams, with answers documented accordingly in the source. The extent and scope of any part of the physical examination is to be left to the discretion of the investigator as deemed appropriate for each subject. The following guidelines will aid in the standardization of body weight measurements:

- The same scale should be used to weigh a given subject each time, if possible.
- Scales should be calibrated and reliable; scales should be at zero just prior to each subject's weigh-in session.
- A subject should void prior to being weighed and be minimally clothed (ie, no shoes or heavy overgarments).
- Weight should be recorded before a subject's meal and at approximately the same time at each visit (screening, baseline/Day 1, and Week 8).

Height will be measured with a stadiometer, measuring stick or tape. The principal investigator or his/her appointed designee is primarily responsible to perform the physical examination. If the appointed designee is to perform the physical examination, he/she must be permitted by local regulations and his/her name must be included on the

Delegation of Authority Log. Whenever possible, the same individual should perform all physical examinations. Any condition present at the post-treatment physical examination that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

The following procedures will aid in the standardization of waist circumference measurements:

- The subject should be minimally clothed (ie, lightweight clothing; no heavy overgarments).
- Waist circumference should be recorded before a subject's meal and at approximately the same time at each visit.
- Measurement will be accomplished by locating the upper hip bone and the top of the right iliac crest and placing a weighted measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should assure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation.[20]

3.7.3.3.2 Vital Signs

Vital sign measurements will include body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate.

Blood pressure and heart rate measurements will be made in the supine and standing positions after the subject has been in each position for at least 3 minutes. The supine measurements will be performed first, followed by standing. Every attempt should be made for the subject need to remain in supine and standing position for 3 minutes to obtain vital signs. If the subject experiences changes in behavior (eg, restlessness, crying) due to the procedure these should be noted in the chart next to the vital sign reading and will not be considered a protocol deviation. For the clinic visits, equipment at the site will be used for measurements. For the virtual visits, equipment will be provided to the caregiver with instructions for home use. The results of these tests must be reviewed by the investigator in order to determine if any results are considered to be clinically significant.

Subjects should be excluded if they have any vital sign measurement at screening that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results (refer to Section 3.4.2). However, any abnormal screening vital sign result(s) considered to be clinically significant may be

repeated once to confirm the finding(s) before excluding the subject from the trial. Appendix 1 is included to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation.

3.7.3.4 Electrocardiogram Assessments

All ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Every attempt should be made for the subject to remain supine for 5 minutes to obtain the ECG reading. If the subject experiences changes in behavior (eg, restlessness, crying) due to the procedure these should be noted in the chart next to the ECG reading and will not be considered a protocol deviation. Additional ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an ET. Electrocardiogram results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator or qualified designee will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECGs will be repeated if any results are considered to be clinically significant.

If, according to the investigator's judgment, any abnormal ECG finding is deemed medically significant (impacting the safety of the subject and/or the interpretation of the trial results) or meets an exclusion criterion, the subject should be excluded from the trial. Abnormal results for ECGs should be repeated once at screening with 3 consecutive ECG recordings to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. Each ECG recording should be taken approximately 5 minutes apart (the ECG result reported will be evaluated at each time point). The central ECG service will provide the corrections for the 3 ECGs performed.

A screening ECG finding of QTcF ≥ 450 msec for males and ≥ 470 msec for females based on the results from the central reader is exclusionary. In addition, subjects should be excluded if they have any other abnormal ECG finding at screening that, in the investigator's judgment, is medically significant in that it would impact the safety of the subject or the interpretation of the trial results. However, any screening ECG with abnormal result(s) considered to be clinically significant should be repeated as soon as possible to confirm the finding(s) before excluding the subject from the trial. Appendix 3 is provided as a guide for determining potentially clinically relevant ECG abnormalities. If ECG was conducted at screening with results within normal range and obtained less than 28 days prior to baseline, then ECG does not need to be repeated at the baseline visit. However, if the ECG results repeated at baseline indicate a QTcF ≥ 450 msec for

males and ≥ 470 msec for females, the investigator must contact the medical monitor to discuss the subject's continued participation in the trial.

3.7.3.5 Other Safety Assessments

It is required that a trained and experienced clinician administer the safety assessments, including the EPS scales (SAS, AIMS, and BARS), and C-SSRS (child version). The number of raters within each trial site should be kept to a minimum. All efforts will be made to ensure that the same clinician administers the scales for a given subject. Notations in the subject's trial records should substantiate the ratings. Training and materials for rating will be provided by Otsuka or designee.

3.7.3.5.1 Simpson Angus Scale

The SAS[21] consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms, and a score of 4 representing a severe condition. The SAS Total Score is the sum of the scores for all 10 items. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 8 hours of scale administration (see Section 4). Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the SAS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

3.7.3.5.2 Abnormal Involuntary Movement Scale

The AIMS[18] assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) will be observed unobtrusively while the subject is at rest (eg, in the waiting room), and the investigator will also make global judgments on the subject's dyskinesias (items 8 through 10). Each item will be rated on a 5-point scale, with a score of zero representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness, severe distress). For this scale, the subject is to be sitting on a hard, firm chair. In addition, the AIMS includes two yes/no questions that address the subject's dental status. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 8 hours of scale administration (see Section 4). Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying

administration of the scale is not feasible, the AIMS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

The AIMS Movement Rating Score is defined as the sum of items 1 through 7 (ie, items 1 through 4, facial and oral movements; items 5 and 6, extremity movements; and item 7, trunk movements).

3.7.3.5.3 Barnes Akathisia Rating Scale

The BARS[22] consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items will be rated on a 4-point scale, with a score of zero representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation will be made on a 6-point scale, with zero representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, subjects will be observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (eg, while engaged in neutral conversation or engaged in activity on the ward) may also be rated. Subjective phenomena are to be elicited by direct questioning. Anticholinergics, propranolol, benzodiazepines, and non-benzodiazepine sleep aids are not permitted within 8 hours of scale administration (see Section 4). Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of the scale is not feasible, the BARS should still be administered and the use of the medication documented, including a notation of the drug name, dose, and time of administration on the eSource.

The BARS Global Score is defined as the global clinical assessment of akathisia.

3.7.3.5.4 Columbia-Suicide Severity Rating Scale

Suicidality will be monitored during the trial using the C-SSRS (child version). Any subject with active suicidal ideation within the last 3 months, suicidal behaviors within the last year, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial. The C-SSRS "Baseline/screening" version is administered at screening to assess lifetime and recent history of suicidal ideation and behavior, and the "Since Last Visit" C-SSRS form will be completed at all other timepoints. In some circumstances, it may be necessary for caregivers to assist the subject with completion of the C-SSRS (eg, if the subject is unable to respond to questions

reliably according to investigator judgment). Investigators should use their discretion as to whether caregiver assistance is needed.

3.7.3.6 Other Assessments

3.7.3.6.1 Autism Diagnostic Interview - Revised

The ADI-R is a semi-structured caregiver interview used for diagnosis of autism, planning treatment, and distinguishing autism from other developmental disorders. The interview focuses on behaviors in three domains: language/communication, reciprocal social interactions, and restricted/repetitive/stereotyped behaviors and interests. It is suitable for individuals with a mental age of 2 years or older. The ADI-R must be administered by a qualified clinician trained in the use of the assessment.

An ADI-R assessment completed within the past 3 years is considered acceptable for use by the investigator in making a current diagnosis. Assessment with the Autism Diagnostic Observation Schedule (ADOS) can also serve as documentation in place of the ADI-R, provided that it was completed within the last 3 years. Subjects with a well-established and ADI-R/ADOS supported DSM-IV-TR diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given a DSM-5 diagnosis of ASD.

3.7.3.6.2 Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version

The Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version (K-SADS-PL) is a semi-structured interview aimed at early diagnosis of affective disorders such as depression, bipolar disorder, and anxiety disorder. The majority of items in the K-SADS-PL are scored using a 0 to 3 point rating scale. Scores of 0 indicate no information is available; scores of 1 suggest the symptom is not present; scores of 2 indicate sub-threshold presentation and scores of 3 indicate threshold presentation of symptoms. The K-SADS-PL ratings are made based on clinician summary of available sources of information, including interview with child and parent, if available.

If a subject is rescreened for participation in the trial, the K-SADS-PL does not need to be repeated at the screening visit.

3.7.4 Prior and Concomitant Medications

The investigator will record all medications and therapies taken by the subject from 30 days prior to signing of informed consent/assent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or

secondary objectives) in the eSource. The investigator will record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in the eSource.

3.7.5 Pharmacokinetic/Pharmacogenomic Assessments

A total of 3 blood samples (4 mL each) from each subject will be collected in vacutainers containing sodium heparin and processed into plasma for PK analysis. One PK sample will be collected 1 to 4 hours postdose on Day 1 and two PK samples will be collected at the Week 8 visit (predose and 1-4 hours postdose). The longest time possible within the 1 to 4 hour range is preferred but should be no less than 1 hour. At Day 1 visit, the time of IMP administration and the time of the PK blood draw should be recorded. At Week 8 visit, the time of IMP administration for that day as well as the 3 previous days and the time of both the predose and postdose PK blood draws should be recorded. The postdose blood draw is collected between 1 to 4 hours postdose. Blood samples will be analyzed for brexpiprazole (OPC-34712). Metabolites of brexpiprazole may also be analyzed, if needed. In addition, PK samples may be used to investigate issues that may arise during sample analysis, if needed. All plasma samples will be shipped to the central laboratory. Additional information will be provided in the operations or laboratory manual.

A blood sample (4 mL) for pharmacogenomic (PGx) analysis will be collected at the time point presented in the Schedule of Assessments, (Table 3.7-1). The PGx blood sample will be taken in order to extract DNA and determine the CYP2D6 genotype and predicted phenotype. Genotypes for other genes related to absorption, distribution, metabolism, and excretion will also be determined. Phenotyping of these additional genes is not currently planned but may be considered in future. If so, the genotyping data may be included as part of covariate analysis in a population PK analysis to be reported separately.

Additional information will be provided in the operations or laboratory manual.

CCI [redacted]

Protocol 331-201-00148

CCI [redacted]

3.7.7 End of Trial

The end of trial date is defined as the last date of contact or the date of final contact attempt from the post-treatment follow-up eSource for the last subject completing or withdrawing from the trial.

3.7.8 Independent Data Monitoring Committee

This trial will be monitored by an independent Data Monitoring Committee (DMC). The DMC will monitor safety based on a predetermined schedule as outlined in the DMC charter. The DMC meetings will occur as outlined in the DMC charter, but can be convened at any time at the discretion of the DMC chair or the trial medical monitor. The details of the DMC structure and its role and responsibilities will be documented in the DMC charter.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial or Treatment Arm(s)

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, IRBs/IECs, and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB/IEC if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP. A particular trial site may be terminated from the trial at the discretion of the investigator, sponsor, or IRB/IEC, eg, for non-enrollment of subjects or noncompliance with GCP or with the protocol. The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Interruption

All attempts should be made to avoid treatment interruption during the trial. For subjects who have an interruption of treatment, the investigator or designee will contact the medical monitor as soon as possible. The investigator and medical monitor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and medical monitor. The treatment interruption will be recorded in the eSource and also recorded as a protocol deviation (Section 3.13).

3.8.3.2 Treatment Discontinuation

After randomization, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.5.

If a subject discontinues from the trial prematurely, the reason must be fully evaluated and recorded appropriately in source documents and in eSource. If the subject is being withdrawn because of an AE, that AE should be indicated as the reason for withdrawal. All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary.

3.8.3.3 Documenting Reasons for Treatment Discontinuation

A subject may discontinue IMP for a number of reasons including those listed below:

- Reasons related to AE:
  - Subject decides to discontinue because of annoyance or discomfort due to a non-serious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - Serious adverse event (SAE)
    - Other potentially IMP-related safety concerns or AEs
- Death

- Reasons unrelated to medical condition (provide detail and review AE history with subject)
- Withdrawal of informed consent/assent (complete written withdrawal of consent/assent form)
- Lost to follow-up
- Pregnancy (see Section 5.5)
- Termination of all or part of the trial by the sponsor

If the subject discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow up procedures in Section 5.7 must be followed.

3.8.3.4 Withdrawal of Consent/Assent

All subjects have the right to withdraw their consent/assent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent/assent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject (or their legal guardian) provides their written withdrawal of consent/assent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent/assent requires a subject's refusal of ALL of the following methods of follow up (these methods of follow up will also be noted in the trial ICF/IAF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent/assent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent/assent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject (or their legal guardian) may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent/assent for further participation (see Section 3.8.3.2). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects (or their legal guardian) who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent/assent to participate in the trial.

3.8.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be given instructions to meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent/assent.

3.9 Screen Failures

A screen failure subject is one from whom informed consent/assent is obtained and is documented in writing (ie, subject signs an ICF/IAF), but who is not started on treatment, whether through randomization or open assignment.

Screen failures may be rescreened at any time if the exclusion characteristic has changed. Subjects who sign an ICF/IAF but who are not started on treatment are permitted to be rescreened. In the event that the subject is rescreened for trial participation, a new ICF/IAF must be signed and new ID assigned.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this

trial, subjects who complete Week 8 visit will be defined as trial completers. Protocol specified post-treatment follow-up contacts will not qualify as the "last scheduled visit."

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the Week 8 visit during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent/assent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

3.12 Subject Compliance

Responsible trial personnel will dispense the IMP according to the visits outlined in the Schedule of Assessments (Table 3.7-1). Accountability and compliance verification should be documented in the subject's trial records. Subjects and their guardians must be counseled on the importance of taking the IMP as directed at all trial visits. If poor compliance continues (eg, multiple missed doses resulting in less than 80% overall compliance), discontinuation of the subject from the trial should be considered.

3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent/assent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the site monitor.

Protocol 331-201-00148

4 Restrictions

4.1 Prohibited Medications

All subjects must agree to discontinue all prohibited medications during the screening period, after signing the ICF/IAF, in order to meet the protocol-specified washout periods. Table 4.1-1 provides the required duration of washout for selected prohibited medications. All other prohibited medications must be discontinued at least 24 hours before the first dose of IMP. Select CYP 2D6 inhibitors and CYP 3A4 inhibitors and inducers are listed in Table 4.1-4. The oral benzodiazepine therapy permitted during the trial is summarized in Table 4.1-3.

Protocol 331-201-00148

Table 4.1-1 List of Washout of Prohibited Medications	
Medication	**Required Washout Prior to Dosing**
Antipsychotics Oral aripiprazole Oral antipsychotics (other than cariprazine and clozapine) Depot or long-acting injectable antipsychotics or clozapine	 14 days 7 days EXCLUDED
Antidepressants Fluoxetine or Symbyax MAOIs Citalopram and escitalopram Venlafaxine and desvenlafaxine All other antidepressants	 28 days 14 days 14 days 14 days 14 days
Other psychotropics Atomoxetine	For subjects without ADHD diagnosis - 7 days
Stimulants	Minimum 5× half- life for subjects without diagnosis of ADHD
Mood stabilizers (ie, lithium or anticonvulsants)	7 days
Varenicline	5 days
Oral benzodiazepines used as rescue therapy during washout[a] Lorazepam, oxazepam, diazepam, alprazolam, or clonazepam Other benzodiazepines	 8 hours before scales[b] 14 days
CYP2D6 inhibitors and CYP3A4 inhibitors and inducers (see Table 4.1-3).	14 days

[a]Use of IM benzodiazepines and continual use of oral benzodiazepines are prohibited throughout the trial. However, limited use of specific oral benzodiazepines is permitted during screening to treat agitation or insomnia as shown in Table 4.1-3.

[b]Benzodiazepines must not be administered within 8 hours prior to scheduled efficacy assessments, and EPS scales. Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of efficacy and EPS scales is not feasible, the scales should still be administered and the use of benzodiazepine documented, including a notation of the drug name, dose, and time of administration in eSource.

Table 4.1-2 lists all medications prohibited during the trial, including exceptions, where appropriate.

Protocol 331-201-00148

Table 4.1-2	**List of Medications Prohibited During the Trial**
1.	All psychotropic agents including, but not limited to, the following: a) Antipsychotics, including IR IM and depot or long-acting injectable formulations b) Antidepressants (including MAOIs) c) Symbyax d) Mood stabilizers (ie, lithium or anticonvulsants) e) Benzodiazepines, except specific benzodiazepines when used as rescue therapy[a] f) Stimulants, except when being used for treatment of ADHD[b] g) Other psychotropics
2.	Ramelteon and other non-benzodiazepine sleep aids, except for limited use of specific medications for the treatment of insomnia[c]
3.	Antihistamines (except for loratadine and cetirizine)
4.	Varenicline
5.	Other nutritional supplements and nonprescription herbal preparations with central nervous system effects (eg, St. John's Wort, omega-3 fatty acids, kava extracts, GABA supplements) unless approved in advance by the medical monitor
6.	CYP2D6 inhibitors and CYP3A4 inhibitors and inducers (see Table 4.1-4)
7.	Investigational agents

GABA = gamma-aminobutyric acid; IR = immediate-release.

[a]Use of IM benzodiazepines and continual use of oral benzodiazepines are prohibited throughout the trial. However, limited use of specific oral benzodiazepines is allowed for the control of agitation or insomnia as shown in Table 4.1-3.

[b]Must be on a stable dose for ≥ 30 days. Stimulant dose at entry must not be changed during trial participation.

[c]Non-benzodiazepine sleep aids (ie, clonidine, melatonin, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted in the trial for the treatment of insomnia, but not on the same day as administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, sites should only utilize one of the listed medications that are approved for this indication in their respective countries and the country specific prescribing information is to be used to determine the maximum allowable daily dose for the treatment of insomnia (exceptions: clonidine, which is commonly prescribed off label as a sleep aid, and melatonin, which is available over the counter [OTC]). Non-benzodiazepine sleep aids must not be administered within 8 hours prior to scheduled efficacy assessments, and EPS scales. Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of efficacy and EPS scales is not feasible, the scales should still be administered and the use of the sleep aid documented, including a notation of the drug name, dose, and time of administration in eSource.

During the course of the trial, oral benzodiazepine rescue medication can be used for symptomatic relief based on the investigator's judgment with the exceptions and restrictions outlined in Table 4.1-3. All concomitant medications should be prescribed according to the respective drug labels. Subjects who are started on therapy should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, and the risk of increased suicidality must be balanced with the clinical need.

Protocol 331-201-00148

Table 4.1-3 Oral Benzodiazepine Rescue Therapy During the Trial	
Oral Benzodiazepine	**Maximum Allowable Dose (mg/day)[c]**
	Screening to Week 8 Visit
Lorazepam[a]	3
Oxazepam[a]	45
Diazepam[a,b]	15
Clonazepam[a,b]	1.5
Alprazolam[a,b]	1.0

[a]Benzodiazepines must not be administered within 8 hours prior to scheduled efficacy and EPS scales. Investigators are encouraged to delay scale administration until 8 hours have elapsed, if at all possible. However, if delaying administration of efficacy and EPS scales is not feasible, the scales should still be administered and the use of benzodiazepine documented, including a notation of the drug name, dose, and time of administration on the eSource.

[b]In countries or institutions where no short-acting benzodiazepines are commercially available, use of oral diazepam, alprazolam, or clonazepam may be acceptable if prior authorization is obtained from the medical monitor.

[c]Body weight of the subject should be considered when dosing decisions are made by the investigator. Daily doses should not exceed the maximum.

Table 4.1-4 provides a select list of CYP2D6 inhibitors and CYP3A4 inhibitors and inducers which are prohibited within 14 days of first dose of IMP, unless otherwise noted in Table 4.1-1, and for the duration of the trial.

Table 4.1-4 Selected CYP2D6 Inhibitors and CYP3A4 Inhibitors and Inducers Prohibited During the Trial	
Selected CYP2D6 Inhibitors	
Celecoxib	Hydroxyzine
Chloroquine	Methadone
Chlorpheniramine	Moclobemide
Clemastine	Paroxetine
Clomipramine	Pyrilamine
Diphenhydramine	Quinidine
Fluoxetine	Terbinafine
Halofantrine	Tripelennamine
Selected CYP3A4 Inhibitors	
Amiodarone	Fluvoxamine
Amprenavir	Indinavir
Aprepitant	Itraconazole
Chloramphenicol	Ketoconazole
Cimetidine	Nefazodone
Clarithromycin	Nelfinavir
Clotrimazole (if used orally)	Quinupristin/Dalfopristin
Delavirdine	Ritonavir
Diltiazem	Saquinavir
Erythromycin	Troleandomycin

Protocol 331-201-00148

Table 4.1-4 Selected CYP2D6 Inhibitors and CYP3A4 Inhibitors and Inducers Prohibited During the Trial	
Selected CYP2D6 Inhibitors	
Fluconazole	Verapamil
Selected CYP3A4 Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Efavirenz	Rifampin
Nevirapine	St. John's Wort
Oxcarbazepine	Troglitazone
Phenobarbital	

4.1.1 Restricted Therapies and Precautions

Anticholinergics are permitted for the treatment of EPS up to a maximum of 4 mg/day benztropine, or its equivalent, and propranolol is permitted as needed, but subject age and body weight should be considered for dose selection. Subjects receiving a stable dose of propranolol for other conditions at entry into Trial 331-201-00191 may remain on propranolol. Trial sites should only utilize medications that are approved for these indications in their respective countries.

The subject's best medical interests should guide the investigator in the management of conditions that are pre-existing or that develop during the trial (intercurrent illness or AEs). The investigator should examine the acceptability of all concomitant medications not explicitly prohibited. In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medications (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) without prior consultation with the investigator. All trial personnel should be familiar with the content of the IB for brexpiprazole in order to manage the subject's condition adequately and select appropriate concomitant medications, if needed.

4.2 Other Restrictions

Any history of electroconvulsive therapy is exclusionary.

4.2.1 Non-therapy Precautions and Restrictions

4.2.1.1 Precautions

Subjects should not undergo any elective medical procedure without prior consultation with the investigator. An elective procedure (minor surgery, dental surgery, orthopedic

surgery, etc) that might require hospitalization or general anesthesia should be deferred until after the trial whenever clinically appropriate.

4.2.1.2 Restrictions

With the exception of group therapy, new-onset psychotherapy is prohibited during the trial. In other words, except for outpatient group therapies, subjects may only receive psychotherapy (eg, individual, group, or family therapy) if they have been participating in the therapy regularly (ie, weekly) for 30 days prior to screening/baseline and commit to maintain their participation during the course of the trial at the current frequency or unless permission is obtained from the medical monitor.

Consumption of grapefruit, grapefruit products, Seville oranges, or Seville orange products within 72 hours prior to dosing and during the trial is prohibited. Subjects will be instructed to refrain from drinking alcoholic beverages or using illicit drugs during participation in the trial. The investigator may request a blood or urine drug screen at any time during the trial if there is a suspicion of illicit drug use in children ≥ 13 years of age that engage in social activities with peers without adult supervision.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs would not include information recorded as medical history at screening for pre planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the IMP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

An SAE includes any event that results in any of the following outcomes:

- Death

- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious adverse events are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event:

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity case (see Section 5.4).
- Pregnancies are also defined as immediately reportable events (IREs). Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eSource if there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is

considered medically relevant by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the eSource. The intensity of an AE is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related: There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.

Not Related: There is no temporal or causal relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eSource provided by the sponsor. Collection of AEs is to begin after a subject has signed the ICF/IAF.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events

The investigator must immediately report after either the investigator or site personnel become aware of any SAE, potential serious hepatotoxicity, or confirmed pregnancy, by telephone, fax, or e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE eSource.)

Subjects experiencing SAEs should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 2 times the upper limit of normal (ULN), a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 1.6 times the ULN, complete an IRE form with all values listed and also report as an AE on the eSource.

5.5 Pregnancy

FOCBP are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months).

For FOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide. The contraceptive method will be documented at each trial visit.

Before enrolling FOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all FOCBP. The topics should generally include:

- General information
- Informed consent/assent form
- Pregnancy prevention information

- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject and the subject's legally acceptable representative (eg, guardian) must sign an ICF/IAF stating that the above-mentioned risk factors and the consequences were discussed with them.

A urine pregnancy test for human chorionic gonadotropin will be performed at screening on all FOCBP and female subjects ≥12 years of age and all female subjects < 12 years of age, if menstruation has started. If a urine test is performed and is positive, the investigator will follow up with a confirmatory serum test.

During the trial, all FOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the Clinical Safety and Pharmacovigilance department (see the cover page of this protocol for contact information).

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator must report to the sponsor, on appropriate Pregnancy Surveillance Form(s),

follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

5.6 Procedure for Breaking the Blind

The investigator is encouraged to contact the sponsor/ clinical research organization (CRO) medical monitor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical monitor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical monitor). The investigator must contact the sponsor/CRO medical monitor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Clinical Safety and Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eSource with the current status noted. If a subject has an AE or has not recovered from an AE at the last scheduled contact, follow-up contacts will be scheduled at least every 4 weeks until resolution of the AE is confirmed, or the condition is considered clinically stable. All nonserious events that are ongoing at the last scheduled contact will be recorded as ongoing on the eSource. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

5.7.2 Follow-up of Serious Adverse Events

This trial requires that subjects be actively monitored for SAEs up to 21 (± 2) days after the last dose of IMP is administered.

Serious AEs that are **identified or ongoing at the last scheduled contact** must be recorded on the AE eSource page and reported to the sponsor according to the reporting procedures outlined in Section 5.3. This may include **unresolved previously reported SAEs, or new SAEs.** The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has been resolved.

5.7.3 Follow-up and Reporting of Serious Adverse Events Occurring after Last Scheduled Contact

Any new SAEs reported by the subject to the investigator that occur **after the last scheduled contact**, and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined trial period (ie, up to last scheduled contact). The investigator should follow SAEs identified after the last scheduled contact until the events are resolved, stabilized, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor up to the point the event has been resolved or stabilized.

6 Pharmacokinetic Analysis

Pharmacokinetic data collected in this trial will be examined in a population PK analysis which will be reported separately from the clinical study report. Pharmacogenomics data collected will be used to determine each subject's CYP2D6 metabolizer status which will be utilized in the population PK analysis.

7 Statistical Analysis

7.1 Sample Size

Approximately 102 subjects will be randomized (51 per treatment arm). A sample size of 51 subjects per arm will provide at least 85% power at a nominal 2-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) = 10.

7.2 Datasets for Analysis

The following analysis samples are defined for this trial:

Randomized Sample: All subjects who were randomized into the trial. Subjects are considered randomized when they are assigned a treatment number by IRT at the end of the screening period. A subject receiving trial treatment outside of the IRT will not be considered randomized, but safety will be reported.

Safety Sample: All subjects who received at least 1 dose of IMP. Subjects will be excluded from this population only if there is documented evidence (ie, drug dispensed = drug returned or no trial drug dispensed) that the subject did not take IMP. If a subject is dispensed trial medication and is lost to follow up, he/she will be considered exposed.

Efficacy Sample: All subjects who receive at least 1 dose of brexpiprazole and have a baseline and at least 1 post baseline efficacy evaluation for the primary efficacy endpoint.

Datasets for PK and PD analyses are described in Section 6.

7.3 Handling of Missing Data

In general, missing data will be handled by analysis of mixed model repeated measures (MMRM) methodology based on all observed cases(OC) data from protocol-specified visits under the assumption of missing at random (MAR), which is a reasonable assumption in longitudinal clinical trials with psychiatric drugs.[23] However, the possibility of "missing not at random" (MNAR) data cannot be ruled out. As sensitivity analyses for the MAR assumption, pattern mixture models based on multiple imputation with mixed missing data mechanism will be used to investigate the response profile of dropout patients by last dropout reason under the MNAR mechanism.

The OC dataset consists of actual observations recorded at each visit during the double-blind treatment period, and no missing data will be imputed.

7.4 Primary and Secondary Endpoint Analyses

7.4.1 Primary Endpoint Analysis

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

The primary estimand defining the treatment effect of interest in the protocol uses the hypothetical strategy specified in the International Council for Harmonisation (ICH) E9 Addendum. The objective of the primary analysis is to compare the efficacy of brexpiprazole versus placebo in reducing irritability in children and adolescents ages 5 to 17 years with a diagnosis of ASD. The estimand, or target of estimation, following the hypothetical strategy is the treatment effect seen, assuming no withdrawals occurred. Subjects who withdraw from IMP treatment either could have lost their treatment effect, had the subjects not taken any other treatment after withdrawal, or could have their treatment effect been masked, had the subjects taken other treatment after withdrawal. This means that any observations made after subjects stop IMP will most likely not contribute relevant information about the treatment effect of the drug. Due to this strategy, the last efficacy assessment after premature trial discontinuation will be done only once at the ET Visit. Every effort will be made to complete all of the ET evaluations prior to administering any additional medications for the treatment of ASD or other prohibited medications. In the case of terminal or lost to follow-up events, no ET evaluations would be expected, and only scheduled assessments would be performed before such an event occurred.

The primary estimand for this trial is defined by the following components:

- Target Population: Children and adolescent subjects 5 to 17 years of age with irritability associated with ASD who met the protocol-defined inclusion/exclusion criteria and were qualified for the Efficacy Sample
- Endpoint: Change from Baseline to Week 8 in the ABC-I subscale score
- Intercurrent Events: Intercurrent events refer to premature treatment discontinuation (ie, early dropout) prior to Week 8 attributable to adverse events, lack of efficacy, withdrawal of consent/assent, or any other causes
- Measure of Intervention Effect: Difference in endpoint means between the brexpiprazole arm and the placebo arm.

In this hypothetical strategy, the event of withdrawing IMP is considered MAR, and the primary endpoint of the trial could be considered to be a combination of the responses of on treatment completers at Week 8 and the imputation of the endpoint to Week 8 following the trend in each treatment group, using the MMRM method to impute missing data for subjects who withdraw IMP during the trial. All data collected during the trial treatment period will be used for statistical analysis. For the primary efficacy analysis, the treatment effect will be estimated using the MMRM method described below. Under the MAR assumption, MMRM provides an unbiased estimate of treatment effect for the

treatment period. Analyses with missing values imputed by multiple imputation (MI) under MNAR and other methods will be performed as sensitivity analyses.

The primary statistical comparison of interest is the difference between brexpiprazole and placebo at Week 8, analyzed using a MMRM analysis with an unstructured (UN) variance-covariance matrix for within-subject variation, and with the change from baseline in ABC-I subscale score during the double-blind treatment period as the dependent variable based on the Efficacy Sample OC dataset. The model will include fixed-class effect terms of treatment, trial center, visit week, and an interaction term of treatment-by-visit week, and includes the interaction term of baseline values of ABC-I subscale score by visit week as a covariate. The primary comparison between brexpiprazole and the placebo arm at Week 8 will be estimated as the difference between least squares means. The comparison will be tested at a significance level of 0.05 (2-sided).

If there is a convergence problem with the MMRM model based on the UN variance covariance matrix, the following structures other than the UN will be used in order of: 1) heterogeneous toeplitz (TOEPH), 2) heterogeneous autoregressive of order 1 (ARH1), and 3) heterogeneous compound symmetry (CSH), and the first (co)variance structure converging to the best fit will be used as the primary analysis. If a structured covariance has to be used, the empirical “sandwich” estimator of the standard error of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix.

Small centers will be defined as centers that do not have at least one evaluable subject (evaluable with respect to the primary efficacy variable) in each treatment arm in the double-blind treatment period. All small centers will be pooled to form “pseudo centers” for the purpose of analysis according to the following algorithm. Small centers will be ordered from the largest to the smallest based on the number of evaluable subjects (ie, subjects who have baseline and at least one post-baseline value for the primary endpoint in the double-blind treatment period). The process will start by pooling the largest of the small centers with the smallest of the small centers until a non-small center is formed. This process will be repeated using the centers left out of the previous pass. In case of ties in center size, the center with the smallest center code will be selected. If any centers are left out at the end of this process, they will be pooled with the smallest pseudo centers, or if no pseudo centers exist, they will be pooled with the smallest non-small center.

Protocol 331-201-00148

7.4.2 Secondary Endpoint Analysis

The key secondary efficacy endpoint is change from baseline to Week 8 in CGI-S score. This secondary endpoint will be analyzed using the same MMRM model as described in the primary endpoint analysis. Additionally, by-treatment descriptive statistics for CGI-S score will be provided for each trial visit.

Further details will be provided in the statistical analysis plan (SAP).

CCI

7.4.4 Interim Analysis

To ensure that trial is adequately powered, the estimate of the trial variability will be obtained in a blinded fashion upon approximately 75% of the subjects having completed or discontinued from the trial. The variability will be estimated based on a blinded and pooled analysis of all treatment arms and sample size could be further increased. For full details please refer to the SAP.

7.5 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height, and BMI will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable).

7.6 Safety Analysis

7.6.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized by treatment group:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

7.6.2 Clinical Laboratory Data

The incidence of potentially clinically significant values for routine laboratory tests and of prolactin concentrations above the upper limit of normal will be calculated for the Safety Sample.

In addition to the evaluation of potentially clinically significant values, mean change from baseline in clinical laboratory values will be calculated. Results will be summarized by visit.

7.6.3 Physical Examination and Vital Signs Data

The incidence of potentially clinically significant vital sign abnormalities will be calculated. Body weight changes will be evaluated by calculating the mean change from baseline and by tabulating the incidence of clinically significant changes in body weight, defined as $\geq$ 7% increase or decrease from baseline. Mean changes in BMI, waist circumference and z-scores for height and body weight from baseline will also be summarized by visit. Physical examination findings will be listed by subject.

To account for normal growth in a pediatric population, percentiles and z-scores for height, weight and BMI will be derived. A BMI z-score change < 0.5 is considered not clinically significant.[10]

7.6.4 Electrocardiogram Data

Mean change from baseline and the incidence of clinically significant changes will be calculated for ECG parameters for the Safety Sample.

For the analysis of QT and QTc, data from 3 consecutive complexes (representing 3 consecutive heart beats) will be measured to determine average values. The following QT corrections will be used for reporting purposes in the clinical study report:

1) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: $QTcF = QT/(RR)^{0.33}$
2) QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN = QT/(RR)^{0.37}$

Results will be summarized by visit.

7.6.5 Other Safety Data

7.6.5.1 Extrapyramidal Symptoms

Descriptive statistics will be provided for the mean change from baseline to end of period in SAS, AIMS, and BARS scores for the Safety Sample. Results will be summarized by visit.

7.6.5.2 Suicidality

The incidence of suicidality, suicidal behavior and suicidal ideation will be calculated from the potential suicide events recorded on the C-SSRS. Results will be summarized by visit and presented for all subjects in the Safety Sample.

8 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the brexpiprazole IB.[11]

8.1 Packaging and Labeling

Trial medication will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. The IMP (brexpiprazole and placebo) will be supplied as child-resistant blister cards, containing sufficient tablets for the window visit. Each blister card used in the dosing period will be labeled to clearly disclose the subject ID, compound ID, trial number, sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements and other information required by local regulatory authorities.

8.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither investigators nor any designees may provide IMP to any subject not participating in this protocol.

The blister packs should be stored according to the storage conditions indicated on the IMP label. The clinical site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day. When applicable, containers for shipping to subjects will include appropriate temperature monitoring.

8.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational, active control, or placebo) received, dispensed, administered, and returned.

8.4 Returns and Destruction

The IMP will be destroyed by the clinical trial site. The IMP may only be destroyed by the trial site(s), if approved by the sponsor and if the IMP destruction meets all local regulations. The IMP accountability must be completed and verified by the assigned trial monitor prior to destruction. The trial site(s) may utilize qualified third party vendors for IMP destruction.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects

- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Online – Send information required for reporting purposes (listed below) to OAPI-EQCProductComplaints@Otsuka-us.com
- Phone - Rocky Mountain Call Center at 1-800-438-6055.

Identification of a PQC by the subject should be reported to the site investigator, who should then follow one of the reporting mechanisms above.

8.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return it in the product retrieval package, which will be provided by the sponsor.

It must be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

Protocol 331-201-00148

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF/IAF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

Source document and source data will be captured electronically in this trial, and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected into a system that is fully validated. Changes to the data will be captured by an automatic audit trail.

The trial site will be given a tablet to directly record subject data and clinical observations on electronic forms. Designated trial site staff will not be given access to the system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol-required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the site for data collected directly into the application - rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified by the trial clinical research associate, and the location of the source data (ie, eSource, paper, or a local

electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Another exception will be safety laboratory data, where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source record will take place, however on-site monitoring inspections will continue to take place in order to review data entry source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

9.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following 3 periods:

- A period of at least 2 years after the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor’s Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent/assent process, and comparison of eSource with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB or IEC according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling eSource, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject numbers in eSource. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent/assent and subsequent approval/favorable opinion by the IRB/IEC. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the

sponsor. Each amendment will be submitted to the IRB/IEC, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB/IEC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB/IEC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF/IAF will require similar modification. In such cases, after approval/favorable opinion of the new ICF/IAF by the IRB/IEC, repeat written informed consent/assent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent/assent to such acknowledgement in any publications resulting from its conduct.

15 References

1 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association, 2013.

2 Christensen DL, Baio J, Braun KVN, Bilder, D, Charles J, Constantino JN, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. MMWR Surveill Summ. 2016;65(No. SS-3):1-23.

3 Lecavalier L. Behavioral and emotional problems in young people with pervasive developmental disorders: relative prevalence, effects of subject characteristics, and empirical classification. J Autism Dev Disord. 2006;36(8):1101–1114.

4 Samson AC, Phillips JM, Parker KJ, Shah S, Gross JJ, Hardan AY. Emotion dysregulation and the core features of autism spectrum disorder. J Autism Dev Disord. 2014;44(7):1766–1772.

5 Autism and Developmental Disabilities Monitoring Network Surveillance Year 2000 Principal Investigators; Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, six sites, United States, 2000. MMWR Surveill Summ. 2007;56(1):1–11.

6 Lavelle TA, Weinstein MC, Newhouse JP, Munir K, Kuhlthau KA, Prosser LA. Economic burden of childhood autism spectrum disorders. Pediatrics. 2014;133(3):e520-e529.

7 Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J Am Acad Child Adolesc Psychiatry. 2006;45(7):771-791.

8 Varley CK, McClellan J. Implications of marked weight gain associated with atypical antipsychotic medications in children and adolescents. JAMA. 2009;302:1811-1812.

9 Fung LK, Mahajan R, Nozzolillo A, Bernal P, Krasner A, Jo B, et al. Pharmacologic treatment of severe irritability and problem behaviors in autism: a systematic review and meta-analysis. Pediatrics. 2016;137(s2):S124-S135.

10 Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA. 2009;302(16):1765-1773.

11 Otsuka Pharmaceutical Development & Commercialisation, Inc. Brexpiprazole (OPC-34712) Investigator's Brochure, Edition 17. Otsuka Report, issued 27 Sep 2021.

12 Autism and Developmental Disabilities Monitoring Network Surveillance Year 2000 Principal Investigators. Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, six sites, United States, 2000. MMWR Surveill Summ. 2007;56(No. SS-1):1–11.

13 Elbe D, Lalani Z. Review of the Pharmacotherapy of Irritability of Autism. J Can Acad Child Adolesc Psychiatry. 2012;21(2):130-146.

14 CCI [redacted]

15 Aman MG, Singh NN. Aberrant Behavior Checklist-Community. East Aurora, NY: Slosson; 1994.

16 Kaat AJ, Lecavalier L, Aman MG. Validity of the aberrant behavior checklist in children with autism spectrum disorder. Journal of Autism and Developmental Disorders. 2014;44:1103-1116.

17 International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guideline For Good Clinical Practice: E6(R1). Geneva, Switzerland: International Conference on Harmonisation; 1996.

18 Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976.

19 CCI [redacted]

20 The Practical Guide: Identification, evaluation, and treatment of overweight and obesity in adults. Developed by National Institutes of Health National Heart, Lung and Blood Institute. North American Association for the Study of Obesity. NIH Publication Number 00-4084, October 2000.

21 Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970;212(Suppl 44):S11-19.

22 Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-676.

23 Little RJA. Modeling the drop-out mechanism in repeated measures studies. J Am Stat Assoc. 1995;90(431):1112-1121.

24 Hughes HK, Kahl LK. The Johns Hopkins Hospital: The Harriet Lane Handbook. 21st edition. 2015.

25 Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3).

26 Soghier L, Pham K, Rooney S. Reference range values for pediatric care. The American Academy of Pediatrics. 2014.

27 Covance. Central laboratory services manual; Protocol 331-201-00148. Created 28 Sep 2019, revised 11 Dec 2019.

[28] American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S13-S28.

Protocol 331-201-00148

Appendix 1 Criteria for Identifying Vital Signs Outside of Normal Range Values and of Potential Clinical Relevance[a]

Variable	Criterion Value	Change Relative to Baseline
Heart Rate[24]	< 60 bpm or > 110 bpm	Increase or decrease of ≥ 15 bpm
Systolic Blood Pressure[25]		
Preschooler (5 y)	< 80 mmHg or > 115 mmHg	Increase or decrease of ≥ 20 mmHg
School-age (6-9 y)	< 85 mmHg or > 115 mmHg	Increase or decrease of ≥ 20 mmHg
Preadolescent (10-12 y)	< 90 mmHg or > 120 mmHg	Increase or decrease of ≥ 15 mmHg
Adolescent (13-17 y)	< 90 mmHg or > 120 mmHg	Increase or decrease of ≥ 15 mmHg
Diastolic Blood Pressure[25]		
Preschooler (5 y)	< 45 mmHg or > 80 mmHg	Increase or decrease of ≥ 15 mmHg
School-age (6-9 y)	< 50 mmHg or > 80 mmHg	Increase or decrease of ≥ 15 mmHg
Preadolescent (10-12 y)	< 60 mmHg or > 80 mmHg	Increase or decrease of ≥ 15 mmHg
Adolescent ≥ 13 y	< 60 mmHg or > 85 mmHg	Increase or decrease of ≥ 15 mmHg

[a]The criterion value and change relative to baseline represented in this table are intended to identify on-treatment values outside of normal changes and that could potentially be clinically relevant. In order to be identified as potentially clinically relevant, the on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column. When evaluating these values the emotional state of the subject must be taken into consideration (eg, crying, screaming) and documented as applicable.

Adapted information.[24,25]

Protocol 331-201-00148

Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance[24,26,27,28]

Laboratory Tests	Criteria (Normal Ranges) for Subjects 5 to 17 Years of Age
Chemistry	
AST	≥ 2 × ULN
ALT	≥ 2 × ULN
ALP	≥ 2 × ULN
Bicarbonate	
< 6 y	< 17.0 or > 26.0 mEq/L (17.0–26.0 mEq/L)
6 y to 12 y	< 19.0 or > 27.0 mEq/L (19.0–27.0 mEq/L)
≥ 12 y	< 19.3 or > 29.3 mEq/L (19.3–29.3 mEq/L)
BUN	≥ 24 mg/dL (≤ 4 mg/dL or ≥ 24 mg/dL)
Creatinine ≤ 12 y	≥ 0.7 mg/dL (≤ 0.2 mg/dL or ≥ 0.7 mg/dL)
≥13 y	≥ 1.1 mg/dL (≤ 0.3 mg/dL or ≥ 1.1 mg/dL)
Uric Acid	
≤ 12 y	≥ 6.7 mg/dL (≤ 1.6 mg/dL or ≥ 6.7 mg/dL)
≥ 13 y	≥ 8.2 mg/dL (≤ 2.2 mg/dL or ≥ 8.2 mg/dL)
Bilirubin (total)	≥ 1.6 mg/dL (≤ 0.2 mg/dL or ≥ 1.6 mg/dL)
CPK	≥ 2 × ULN
Prolactin	
≤ 12 y	≥ 21.00 ng/dL (≤ 2.63 ng/dL or ≥ 21.00 ng/dL)
≥ 13 y	≥ 39.00 ng/dL (≤ 2.52 ng/dL or ≥ 39.00 ng/dL)
Hematology	
Hematocrit	
≤ 12 y	≤ 33 % (≤ 33 % or ≥ 44%)
≥ 13 y	≤ 34 % (≤ 34 % or ≥ 54%)
Hemoglobin	
≤ 12 y	≤11.2 g/dL (≤ 11.2 g/dL or ≥ 15.5 g/dL)
≥ 13 y	≤ 11.6 g/dL (≤ 11.6 g/dL or ≥ 18.1 g/dL)
White blood count	≤ 4.35 × 10^3/uL (≤ 4.35 × 10^3/uL or ≥ 13.65 × 10^3/uL)
Eosinophils	
≤ 12 y	≥ 4.8%
≥ 13 y	≥ 4.1%
Neutrophils	≤ 40.5% (≤ 40.5% or ≥ 75.0 %)
Absolute neutrophil count	
≤ 12 y	≤ 1.00 × 10^3/uL or ≥ 9.00 × 10^3/uL
≥ 13 y	≤ 1.35 × 10^3/uL or ≥ 8.15 × 10^3/uL
Platelet count	
≤ 12 y	≤ 130 × 10^3/uL (≤ 130 × 10^3/uL or ≥ 570 × 10^3/uL)
≥ 13 y	≤ 140 × 10^3/uL (≤ 140 × 10^3/uL or ≥ 400 × 10^3/uL)
Urinalysis	
Protein	Change from baseline
Glucose	Presence
Additional Criteria	
Chloride	≤ 94 mEq/L or ≥ 112 mEq/L
HbA1c	≥ 5.7%
ACTH	< 7.2 pg/mL - > 63.3 pg/mL
Cortisol	AM: 6.7 ug/dL - 22.60 ug/dL PM: < 10 ug/dL
Potassium	≤ 3.3 mEq/L or ≥ 5.2 mEq/L

Protocol 331-201-00148

Laboratory Tests	Criteria (Normal Ranges) for Subjects 5 to 17 Years of Age
Sodium	≤ 132 mEq/L or ≥ 148 mEq/L
Calcium	≤ 8.3 mg/dL or ≥ 10.9 mg/dL
Glucose	
Fasting	≥ 100 mg/dL (≥ 70 mg/dL and ≤ 100 mg/dL)
Nonfasting	≥ 139 mg/dL (≥ 70 mg/dL and ≤ 139 mg/dL)
Total Cholesterol, Fasting	
≤ 12 y	≥ 217 mg/dL (≤ 97 mg/dL or ≥ 217 mg/dL)
≥ 13 y	≥ 217 mg/dL (≤ 124 mg/dL or ≥ 217 mg/dL)
LDL Cholesterol, Fasting	≥ 130 mg/dL
HDL Cholesterol, Fasting	
≤ 12 y	≤ 34 mg/dL (≤ 34 mg/dL or ≥ 75 mg/dL)
≥ 13 y	≤ 30 mg/dL (≤ 30 mg/dL or ≥ 74 mg/dL)
Triglycerides, Fasting	
≤ 12 y	≥ 131 mg/dL (≤ 30 mg/dL or ≥ 131 mg/dL)
≥ 13 y	≥ 148 mg/dL (≤ 32 mg/dL or ≥ 148 mg/dL)
TSH	
≤ 12 y	≤ 0.34 mIU/mL or ≥ 5.40 mIU/mL
≥ 13 y	≤ 0.34 mIU/mL or ≥ 5.60 mIU/mL
Free T4	
≤ 12 y	≤ 9 pmol/L or ≥ 30 pmol/L
≥ 13 y	≤ 10 pmol/L or ≥ 24 pmol/L
PT	≥ 12.3 sec (≤ 9.7 sec or ≥ 12.3 sec)
aPTT	≥ 29.4 sec (≤ 21.9 sec or ≥ 29.4 sec)
INR Not taking anticoagulants Taking anticoagulants	 ≥ 1.2 (≤ 0.8 or ≥ 1.2) ≥ 3.0 (≤ 2.0 or ≥ 3.0)

The recommended criteria represented in this table are intended to identify on-treatment outside of normal values that could potentially be clinically relevant. Variations based on local laboratory ranges may need to be considered.

Adapted information.[24,26,27,28]

Protocol 331-201-00148

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rhythm		
Sinus tachycardia[b]	≥ 110 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 60 bpm	decrease of ≥ 15 bpm
Supraventricular premature beat	all	not present → present
Ventricular premature beat	all	not present → present
Supraventricular tachycardia	all	not present → present
Ventricular tachycardia	all	not present → present
Atrial fibrillation	all	not present → present
Atrial flutter	all	not present → present
Conduction		
1° atrioventricular block	PR ≥ 200 msec	increase of ≥ 50 msec
2° atrioventricular block	all	not present → present
3° atrioventricular block	all	not present → present
Left bundle-branch block	all	not present → present
Right bundle-branch block	all	not present → present
Pre-excitation syndrome	all	not present → present
Other intraventricular conduction block[d]	QRS ≥ 120 msec	increase of ≥ 20 msec
Infarction		
Acute or subacute	all	not present → present
Old	all	not present → present ≥ 12 weeks post-trial entry
ST/T Morphological		
Myocardial Ischemia	all	not present → present
Symmetrical T-wave inversion	all	not present → present
Increase in QTc	QTcF ≥ 450 msec for males, ≥ 470 msec for females	increase of 60 msec from baseline

[a]The criterion value and change relative to baseline represented in this table are intended to identify on-treatment values outside of normal changes and that could potentially be clinically relevant. In order to be identified as potentially clinically relevant, the on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column. When evaluating these values the emotional state of the subject must be taken into consideration (eg, crying, screaming) and documented as applicable.

[b]No current diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, or other rhythm abnormality.

[c]No current diagnosis of atrial fibrillation, atrial flutter, or other rhythm abnormality.

[d]No current diagnosis of left bundle branch block or right bundle branch block.

ccl

ccl

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

Protocol 331-201-00148

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, brexpiprazole (OPC-34712), the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where brexpiprazole (OPC-34712) will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB- or IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB/IEC approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent/assent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and sub-investigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

Document Name: Protocol 331-201-00148 Amendment 5

Document Number: CCI [redacted]

Document Version: 10.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Clinical Approval	07-Jul-2022 17:50:55
PPD	Clinical Approval	07-Jul-2022 18:16:08
PPD	Biostatistics Approval	07-Jul-2022 22:08:38

Otsuka Pharmaceutical Development & Commercialization, Inc

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

ADDENDUM FOR CLINICAL PROTOCOL FOR TRIAL 331-201-00148

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Brexpiprazole in Treatment of Children and Adolescents With Irritability Associated With Autism Spectrum Disorder

Protocol No. 331-201-00148
IND No. 141257
EudraCT No. 2019-000723-40

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	CCI [redacted]
Issue Date:	06 Jul 2020
Version No.:	1.0

Protocol 331-201-00148

Trial Conduct for COVID-19

All procedures and assessments in the protocol are to be followed to the fullest extent possible. The sponsor, in coordination with the sites, investigators, and medical monitor, will continuously monitor and evaluate the benefits and risks to subject participation in the clinical trial as it relates to COVID-19. If any protocol-specified activities were not able to be performed, or cannot be performed due to COVID-19 considerations, the appropriate measures to be followed will be provided in this document.

Protocol 331-201-00148

Table of Contents

Trial Conduct for COVID-19 2
Table of Contents 3
List of In-text Tables 4
List of In-text Figures 5
List of Abbreviations and Definitions of Terms 6
1 Trial 331-201-00148 COVID-19 Protocol Summary 7
1.1 Trial Design Schematic 7
1.2 Schedule of Assessments 8
2 General Considerations 12
2.1 Telemedicine Virtual Visits 12
2.2 Reconsent 12
2.3 Protocol Deviations 12
2.4 Guidance to Record Adverse Events and Discontinuations Due to COVID-19 12
2.5 Statistical Analyses 13
2.6 Clinical Outcomes 13
3 Trial Population 14
3.1 Inclusion Criteria 14
3.2 Exclusion Criteria 14
4 Trial Procedures 14
4.1 Safety Assessments 14
4.1.1 Weight and Waist Circumference 14
4.1.2 Pregnancy 15
4.1.3 Extrapyramidal Symptom Scales 15
4.2 Efficacy Assessments 15
4.2.1 Pediatric Quality of Life 15
5 Investigational Medicinal Product 16

Protocol 331-201-00148

List of In-text Tables

Table 1.2-1 COVID-19 Impact Schedule of Assessments 8

Protocol 331-201-00148

List of In-text Figures

Figure 1.1-1 COVID-19 Impact Trial Design Schematic..... 7

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ABC	Aberrant Behavior checklist
ACTH	Adrenocorticotropic hormone
ADI-R	Autism Diagnostic Interview – Revised
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ASD	Autism Spectrum Disorder
BARS	Barnes Akathisia Rating Scale
CGI-S	Clinical Global Impression - Severity
CRO	Clinical research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EPS	Extrapyramidal symptoms
ET	Early termination
CCI	[redacted]
FOBCP	Females of child bearing potential
HbA1c	Glycosylated hemoglobin
IMP	Investigational medicinal product
K-SADS-PL	Kiddie-Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version
CCI	[redacted]
CCI	[redacted]
SAE	Serious adverse event
SAS	Simpson Angus Scale
TSH	Thyroid-stimulating hormone

1 Trial 331-201-00148 COVID-19 Protocol Summary

1.1 Trial Design Schematic

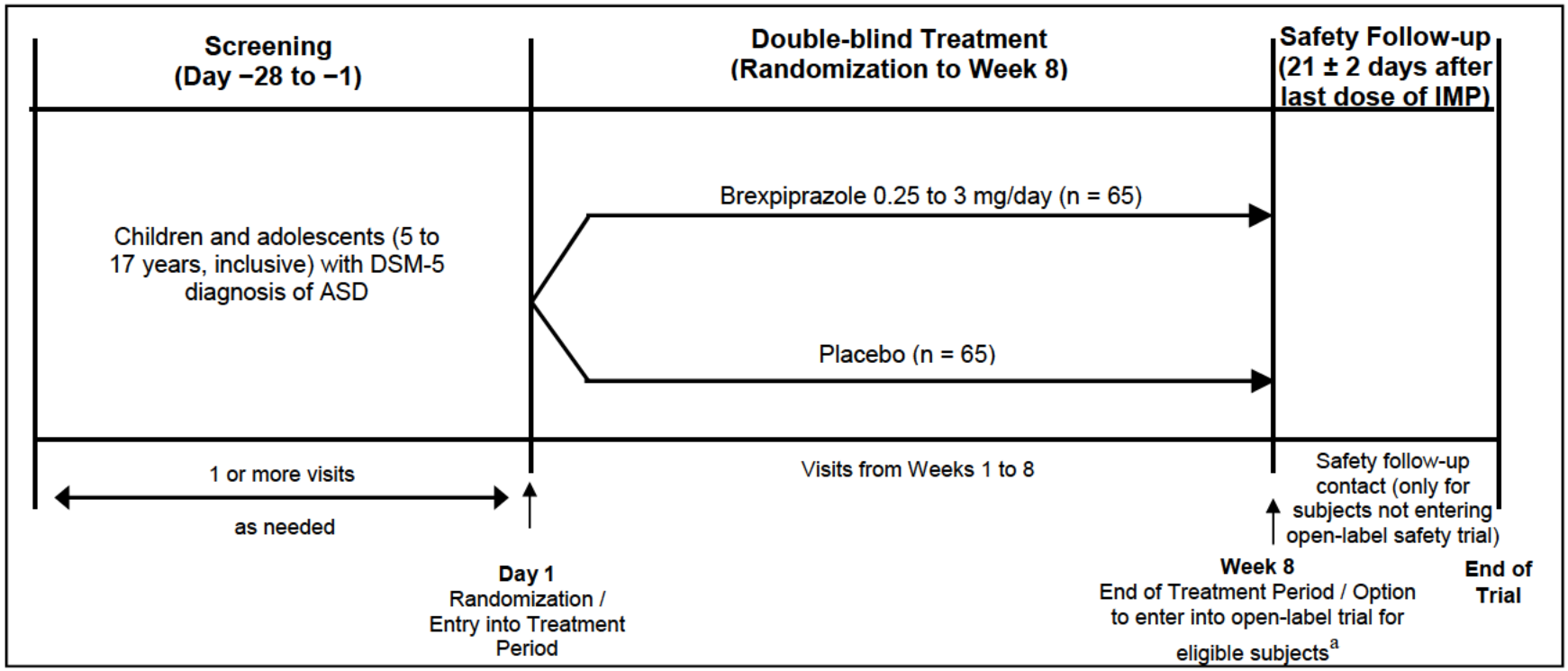

Figure 1.1-1 COVID-19 Impact Trial Design Schematic

ASD = Autism Spectrum Disorder; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*; IMP = investigational medicinal product.
Note: If an in office screening and baseline visit cannot be performed, then the subject cannot be enrolled in the trial. All other visits are virtual visits.

[a]In order to enter the open-label trial, the Week 8 visit must be in office per the protocol. Subjects who complete this trial and are not able to directly rollover into the open-label trial or are terminated early as a direct result of the COVID-19 pandemic will have an opportunity to enter the open-label trial as delayed rollover subjects upon completion of an in office screening visit.

.

1.2 Schedule of Assessments

Table 1.2-1 COVID-19 Impact Schedule of Assessments

	Screening	Double-blind Treatment							Follow-up	
Assessment	**Day -28 to -1**	**Baseline (Day 1)**	**Week 1 (Day 7 ± 2 days)**	**Week 2 (Day 14 ± 2 days)**	**Week 3 (Day 21 ± 2 days)**	**Week 4 (Day 28 ± 2 days)**	**Week 6 (Day 42 ± 2 days)**	**Week 8/ET (Day 56 ± 2 days)**	**21 ± 2 days) after last dose of IMP**	**Notes**
	In office	**In office**	**Virtual**	**Virtual**	**Virtual**	**Virtual**	**Virtual**	**Virtual[a]**	**By Tele-phone**	
Trial Entrance and History										
Informed consent/assent	X									
Inclusion/exclusion criteria	X	X								
Demography	X									
Medical history	X									
Psychiatric history	X									
ADI-R[b]	X									
Prior medications and washout, if applicable	X									
K-SADS-PL[c]	X									
Randomization		X								
Efficacy Assessments										
ABC	X	X	X	X	X	X	X	X		
CGI-S	X	X	X	X	X	X	X	X		
CCI [redacted]										
Safety Assessments										
Physical examination	X									
Vital signs	X	X	X	X	X	X	X	X		
Height	X							X		

Table 1.2-1 COVID-19 Impact Schedule of Assessments

	Screening	Double-blind Treatment							Follow-up	
Assessment	**Day -28 to -1** **In office**	**Baseline (Day 1)** **In office**	**Week 1 (Day 7 ± 2 days)** **Virtual**	**Week 2 (Day 14 ± 2 days)** **Virtual**	**Week 3 (Day 21 ± 2 days)** **Virtual**	**Week 4 (Day 28 ± 2 days)** **Virtual**	**Week 6 (Day 42 ± 2 days)** **Virtual**	**Week 8/ET (Day 56 ± 2 days)** **Virtual[a]**	**21 ± 2 days) after last dose of IMP** **By Tele-phone**	**Notes**
Body weight and waist circumference	X	X						X		Section 4.1.1
Clinical laboratory tests (hematology, serum chemistry, and urinalysis)	X[d]	X[e]								
Prolactin (blinded)	X									
Pregnancy test	X							X		Section 4.1.2
ECG	X[d]	X[e]								
C-SSRS (child version)	X	X	X	X	X	X	X	X	X	
Extrapyramidal symptoms scales (SAS, AIMS, and BARS)		X		X (AIMS and BARS only)				X (AIMS and BARS only)		Section 4.1.3
Urine drug screen	X									
Blood alcohol test	X									
ACTH	X									
Cortisol	X									
HbA1c	X									
TSH with reflex to free T_4 if abnormal	X									
Coagulation parameters	X									

Table 1.2-1 COVID-19 Impact Schedule of Assessments

	Screening	Double-blind Treatment							Follow-up	
Assessment	**Day -28 to -1**	**Baseline (Day 1)**	**Week 1 (Day 7 ± 2 days)**	**Week 2 (Day 14 ± 2 days)**	**Week 3 (Day 21 ± 2 days)**	**Week 4 (Day 28 ± 2 days)**	**Week 6 (Day 42 ± 2 days)**	**Week 8/ET (Day 56 ± 2 days)**	**21 ± 2 days) after last dose of IMP**	**Notes**
	In office	**In office**	**Virtual**	**Virtual**	**Virtual**	**Virtual**	**Virtual**	**Virtual[a]**	**By Tele-phone**	
Adverse events	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	
Pharmacokinetic and Pharmacogenomic Assessments										
Pharmacokinetic sampling[f]		X								
Pharmacogenomic sampling[g]		X								
CCI [redacted]										
Other Procedures										
IMP dispensing		X	X	X	X	X	X			
IMP accountability			X	X	X	X	X	X		

ABC = Aberrant Behavior checklist; ACTH = adrenocorticotropic hormone; ADI-R = Autism Diagnostic Interview – Revised; AIMS = Abnormal Involuntary Movement Scale; CGI-S = Clinical Global Impressions – Severity; BARS = Barnes Akathisia Rating Scale; CRO = clinical research organization; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EPS = extrapyramidal symptoms; ET = early termination; CCI [redacted]; HbA1c = glycosylated hemoglobin; K-SADS-PL = Kiddie-Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version; CCI [redacted]; CCI [redacted]; SAS = Simpson Angus Scale; TSH = thyroid-stimulating hormone.

Note: If efficacy or safety assessments cannot be obtained at consecutive virtual visits, the investigator should discuss possible discontinuation of the subject with the medical monitor.

[a]In order to enter the open-label trial, the Week 8 visit must be in office per the protocol. Subjects who complete this trial and are not able to directly rollover into the open-label trial or are terminated early as a direct result of the COVID-19 pandemic will have an opportunity to enter the open-label trial as delayed rollover subjects upon completion of an in office screening visit.

[b]Assessment must be done unless previously completed within the last 3 years. Assessment with the Autism Diagnostic Observation Schedule (ADOS) can also serve as documentation for ADI-R rating provided that it was completed within the last 3 years.

[c]If a subject is rescreened for participation in the trial, the K-SADS-PL does not need to be repeated at the screening visit.

[d]The screening period may be extended in order to repeat clinical laboratory tests and ECGs; if an extension is required, the site should contact the medical monitor.

[e]Baseline clinical laboratory tests (hematology, serum chemistry, and urinalysis) and ECGs are not collected if screening clinical laboratory tests/ECGs were obtained within 28 days prior to the baseline visit and within normal ranges.

[f]One PK sample will be collected 1 to 4 hours postdose on Day 1. Two PK samples will be collected at the Week 8 visit (predose and 1-4 hours postdose). The actual time of the PK sample will be recorded as well as the dosing time prior to the PK sample collection. The longest time possible within the 1 to 4 hour range is preferred but should be no less than 1 hour.

[g]Pharmacogenomic CCI [redacted] (if done), are to be taken with the postdose PK draw to avoid additional blood draws.

Protocol 331-201-00148

2 General Considerations

2.1 Telemedicine Virtual Visits

Telemedicine virtual visits will be completed using the existing trial equipment and systems for virtual visits.

2.2 Reconsent

If there is an immediate need to reconsent subjects during the period of COVID-19 restrictions, a paper reconsent process will be followed and sites are encouraged to contact the contract research organization (CRO) and sponsor with questions.

2.3 Protocol Deviations

Protocol deviations that occur as a direct result of the COVID-19 pandemic must be recorded in eSource separately from other protocol deviations as soon as they are identified and will be recorded as "Major" in eSource for data capture purposes. Examples of the types of COVID-19 related deviations to be reported may include: missed visits, missed assessments, assessments performed remotely (completed outside of protocol procedure), missed investigational medicinal product (IMP) dose, IMP dispensed/returned via courier, IMP not returned to site/site unable to verify medication compliance, out of window visits, changes in rater, and prohibited concomitant medication. A "direct result" is defined as being due to actual illness of the subject or caregiver, or as a result of quarantine, social distancing, or site closures. All other deviations will follow the normal deviation process described in the protocol and should not be entered proactively by sites.

2.4 Guidance to Record Adverse Events and Discontinuations Due to COVID-19

If a subject tests positive OR is presumed positive with COVID-19, the subject may continue in the trial with virtual visits only at the discretion of the investigator as long as they remain asymptomatic for COVID-19, but an adverse event (AE) of "Coronavirus Infection" OR "Coronavirus Positive Test Result" must be recorded on the AE page of the electronic case report form (eCRF). All subjects who have mild symptoms of COVID-19 must be reviewed with the medical monitor and approval must be received for the subject to continue in the trial. A positive test result or a presumed positive subject is not automatically a serious adverse event (SAE), unless an SAE criterion is met (eg, hospitalization). If the event meets the criterion for an SAE, then the subject will be discontinued from the trial.

If a subject discontinues due to COVID-19 either because the subject tests positive OR is presumed positive with COVID-19, then the primary reason for discontinuation should be reported as "Adverse Event" and indicate the AE number in the "Specify the reason for discontinuation" space that corresponds with the AE of "Coronavirus Infection" OR "Coronavirus Positive Test Result." Be sure to remember to enter an AE in the AE form for the "Coronavirus Infection" OR "Coronavirus Positive Test Result."

If a subject discontinues due to COVID-19 other than the subject testing positive OR being presumed positive with COVID-19, then the primary reason for discontinuation should be reported as "Other." Be sure to specify the reason as "COVID-19" followed by the reason ensuring that the prefix of the description includes "COVID-19." Do note that the reason "Other" should be selected even if the subject decides to withdraw consent or if the investigator decides to withdraw the subject due to COVID-19 concerns.

In the case that a caregiver is COVID-19 positive and another caregiver is available to continue the trial, the situation should be discussed with the medical monitor to determine continuation in the trial on a case-by-case basis. If there is no other caregiver, the subject needs to be early terminated from the trial.

2.5 Statistical Analyses

Any impact of COVID-19 on the planned statistical analyses for the trial will be described in the final statistical analysis plan.

2.6 Clinical Outcomes

The administration of scales at virtual visits should be performed as described in the protocol, CCI [redacted]

To decrease variability, sites should attempt to standardize the method of administration for a scale for an individual subject and across all subjects in the trial. Assessments should be administered by the same qualified/trained rater who rated the subject previously; if this is not possible due to staff availability and/or technological limitations, discuss relevant information with previous raters to obtain clinical context (note that per protocol raters must be trained/qualified to conduct assessments in all cases). Raters should conduct all assessments for that visit during the same remote session, where possible.

Please refer to the Study Operations Manual for modification of administration methods for virtual visits.

3 Trial Population

3.1 Inclusion Criteria

There are no changes to the inclusion criteria due to COVID-19 for purposes of this addendum. Inclusion criteria can be found in Section 3.4.2 of the protocol.

3.2 Exclusion Criteria

There are no changes to the exclusion criteria due to COVID-19 for purposes of this addendum. Exclusion criteria can be found in Section 3.4.3 of the protocol.

The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.

4 Trial Procedures

4.1 Safety Assessments

Safety assessments at virtual visits will be performed as described in the protocol. Assessments which are not currently described for virtual visits will be completed as described below.

4.1.1 Weight and Waist Circumference

Weight and waist circumference will be measured as described in the protocol at the virtual visits defined in this COVID-19 Addendum Schedule of Assessments (Table 1.2-1) with the following changes:

- Caregivers will be asked to use any weight collection device they currently own, regardless of calibration or validation, for weight measurements. (If there is no home weight collection device, the site will provide or reimburse for equipment.);
- Weight and waist circumference measurement does not need to be videotaped. The caregiver will be instructed to provide the weight and waist circumference measurement result to site staff during the virtual visit. Subjects will be instructed to be as consistent as possible regarding the time of day the measurements are taken, and to notify the site staff of the measurement results via telephone, or other means, on the appropriate visits.
- Site staff will be instructed to record the weight and waist circumference measurement in eSource, and if there are believed to be any errors, inconsistencies, or safety concerns with the reported home measurement, the medical monitor should be notified.

4.1.2 Pregnancy

A pregnancy test will be performed as described in the protocol at the virtual visits defined in this COVID-19 Addendum Schedule of Assessments (Table 1.2-1) with the following changes:

- For the pregnancy test for females of childbearing potential (FOCBP), the site will provide the necessary tests and instructions so the test may be performed at home;
- Applicable subjects will perform a pregnancy test prior to dosing with IMP, ensuring a date and time-stamped picture or video of the result is taken. The caregiver is to provide/show the result during the virtual visit.
  - If negative, site to inform the subject to proceed with dosing.
  - If positive, the site must instruct the subject to immediately stop taking IMP, and the site will refer to the Pregnancy section of the protocol for appropriate immediately reportable event reporting.

4.1.3 Extrapyramidal Symptom Scales

The Abnormal Involuntary Movement Scale (AIMS) and Barnes Akathisia Rating Scale (BARS) will be assessed at the virtual visits defined in this COVID-19 Addendum Schedule of Assessments (Table 1.2-1) by providing the subject and caregiver verbal instructions and observing their movements over video. The Simpson Angus Scale (SAS) will not be assessed remotely.

4.2 Efficacy Assessments

Efficacy assessments at virtual visits will be performed as described in the protocol. CCI [redacted]

CCI [redacted]

CCI [redacted]

Protocol 331-201-00148

CCI

5 Investigational Medicinal Product

Investigational medicinal product will be shipped directly to caregivers and subjects as per existing procedures for this trial.

Otsuka

This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

Document Name: Protocol 331-201-00148 Addendum

Document Number: CCI [redacted]

Document Version: 2.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Clinical Approval	07-Jul-2020 12:35:13
PPD	Biostatistics Approval	06-Jul-2020 16:36:31
PPD	Approved for Clinical Pharmacology and Nonclinical	07-Jul-2020 14:18:34

PPD

PPD , MD, MS
PPD GCD-CNS

Physician/MD Approval 07-Jul-2020