Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product
Brexpiprazole (OPC-34712)

REVISED CLINICAL PROTOCOL

A Long-term, Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Flexible-Dose Brexpiprazole as Maintenance Treatment in Adolescents (13-17 Years Old) With Schizophrenia

Protocol No. 331-10-236
IND No. 101,871
EudraCT No. 2017-001459-30

CONFIDENTIAL – PROPRIETARY INFORMATION

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Immediately Reportable Event	Syneos Health Safety and Pharmacovigilance CCI [redacted]
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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 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 but not limited to replacing in-person visits with virtual visits as deemed necessary by the investigator to ensure subject safety and maintain protocol requirements.

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-10-236 IND No.: 101,871 EudraCT No.: 2017-001459-30
Protocol Title:	A Long-term, Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Flexible-Dose Brexpiprazole as Maintenance Treatment in Adolescents (13-17 Years Old) With Schizophrenia
Clinical Phase/Trial Type:	3/Long-term safety and tolerability
Treatment Indication:	Schizophrenia
Objective(s):	To further characterize the long-term safety and tolerability of brexpiprazole in adolescents with schizophrenia
Trial Design:	This is a long-term, multicenter, open-label trial designed to examine the long-term safety and tolerability of brexpiprazole in adolescent subjects, ages 13 to 17 years, with a *Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition* (DSM-5) diagnosis of schizophrenia. Subjects from Trial 331-10-234 who turned 18 years old during that trial are also permitted to enroll in this trial. Enrollment into the trial will be drawn from eligible subjects who, in the investigator's judgment, could potentially benefit from monotherapy treatment with oral brexpiprazole for schizophrenia and will include rollover subjects from the double-blind, phase 3 efficacy trial, Trial 331-10-234, and may include de novo subjects from select sites. Rollover subjects will be considered as those who are able to rollover within ≤ 7 days of the Week 6 visit of Trial 331-10-234. Subjects who are only able to rollover from Trial 331-10-234 after > 7 days from the Week 6 visit may be allowed to enter Trial 331-10-236 as de novo subjects following approval by the medical monitor. The trial will be conducted on an outpatient basis. Hospitalization for psychosocial reasons (eg, homelessness or need for shelter that is unrelated to the subject's underlying psychiatric condition) will be considered outpatient status for the purpose of enrollment in Trial 331-10-236. Subjects remaining in hospital at the Week 6 visit of Trial 331-10-234 (for other than psychosocial reasons) will be permitted to enroll in Trial 331-10-236 at the Week 6 visit of

	the double-blind trial if they are planned to be discharged from the hospital before the open-label treatment period Week 1 visit of Trial 331-10-236 and following approval by the medical monitor. De novo subjects hospitalized at the time of the Trial 331-10-236 screening visit will be permitted to be screened for the trial if they are planned to be discharged from the hospital prior to the baseline (Day 1) visit of the open-label treatment period and following approval by the medical monitor. The trial will be organized as follows: <u>Rollover Subjects from Trial 331-10-234</u> *Screening/Baseline*: Subjects will be screened for eligibility at the last visit of the double-blind trial (ie, Week 6 visit of Trial 331-10-234). Subjects or their parents/legal guardians will sign either via wet signature or electronic signature a separate informed consent form (ICF) or assent form for participation in Trial 331-10-236 before any procedures specific to the open-label trial are performed. The assessments from the last visit of the double-blind trial will serve as the baseline measures for Trial 331-10-236 for any assessment that is not unique to the open-label trial. Medical history will be updated, if necessary. Because the blind for all rollover subjects will be maintained until the last subject completes Trial 331-10-234, rollover subjects will follow a titration schedule the first week in the open-label treatment period in this trial. *Open-label Treatment*: Eligible subjects from Trial 331-10-234 will receive daily treatment with open-label brexpiprazole in the open-label treatment period of Trial 331-10-236 as described in the Investigational Medicinal Product, Dose, Formulation, Mode of Administration section. <u>De Novo Subjects</u> *Screening*: For de novo subjects who did not participate in Trial 331-10-234, the initial diagnosis of schizophrenia for this trial (as defined by DSM-5 criteria) should be made and documented by an adequately trained clinician (psychiatrist, or local medical equivalent who is experienced in treating adolescents with schizophrenia), and the diagnosis should then be confirmed utilizing the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL) performed by an adequately trained rater at the time of screening.

	Subjects will enter a pretreatment screening phase that will range from a minimum of 3 days to a maximum of 28 days to assess eligibility criteria and to washout from prohibited concomitant medications, if applicable. Screening begins on the day that the subject or legal guardian/parent signs the ICF, and the subject, if not old enough to sign the ICF, completes the assent form. Subjects will be assigned a unique screening number for each subject with a signed ICF (and assent form if required) prior to enrollment. If a de novo subject previously participated in Trial 331-10-234, they will retain their subject identification number from Trial 331-10-234. Subjects who are able to complete the required washout of prohibited medications will proceed directly to the baseline (Day 1) visit of the open-label treatment period after completion and review of screening assessments provided that all eligibility criteria are met. If the washout of prohibited medications prior to the baseline (Day 1) visit is not appropriate for subjects, in the opinion of the investigator, the subjects will participate in the conversion period. *Conversion*: If the washout of prohibited medications prior to the baseline (Day 1) of the open-label treatment period is not appropriate for subjects, in the opinion of the investigator, the subjects will undergo cross-titration to oral brexpiprazole for 1 to 4 weeks during the conversion period, as described in the Investigational Medicinal Product, Dose, Formulation, Mode of Administration section. Visits will occur at the end of each week during the conversion period. The goal of de novo subjects during the conversion period is to achieve a brexpiprazole monotherapy target starting dose of 1, 2, or 3 mg daily at any time after Week 1 per the investigator's discretion and to achieve washout of prohibited medications. The subject will proceed to the baseline (Day 1) visit of the open-label treatment period once the target starting dose has been achieved and the required washout of prohibited medications has been completed. *Baseline and Open-label Treatment*: After completing baseline assessments, eligible subjects will receive daily treatment with open-label brexpiprazole in the open-label treatment period, as described in the Investigational Medicinal Product, Dose, Formulation, Mode of Administration section. *Follow-up*: Subjects will be followed up for safety via telephone contact or clinic visit 21 (± 2) days after the last dose of IMP.

Subject Population:	The trial population will include subjects from Trial 331-10-234 and de novo subjects between 13 and 17 years of age, inclusive, at the time of informed consent/assent and at the baseline (Day 1) visit of the open-label treatment period. For de novo subjects who did not participate in Trial 331-10-234, the initial diagnosis of schizophrenia for this trial (as defined by DSM-5 criteria) must be made and documented and the diagnosis confirmed by the K-SADS-PL, at screening. Subjects from Trial 331-10-234 who turned 18 years old during that trial are also permitted to enroll in this trial. Approximately 350 subjects are anticipated to be enrolled with the expectation that at least 100 will complete a minimum of 1 year of exposure to open-label brexpiprazole.
Inclusion/Exclusion Criteria:	Rollover subjects must meet the inclusion criteria at the completion of Trial 331-10-234 for entry to Trial 331-10-236. Key inclusion criteria for both rollover and de novo subjects include the following: • Subjects with a current diagnosis of schizophrenia, as defined by DSM-5 criteria and confirmed by the K-SADS-PL completed at entry into Trial 331-10-234. For de novo subjects who did not participate in Trial 331-10-234, the initial diagnosis of schizophrenia for this trial (as defined by DSM-5 criteria) must be made and documented and the diagnosis confirmed by the K-SADS-PL, at screening. • Subjects who, in the investigator's judgment, require treatment with antipsychotic medication(s). Key exclusion criteria include the following: • Subjects with a DSM-5 diagnosis other than schizophrenia that has been the primary focus of treatment within 3 months of screening. • Subjects with a clinical presentation or history that is consistent with delirium, dementia, amnesia, or other cognitive disorders; subjects with psychotic symptoms that are better accounted for by another general medical condition(s) or direct effect of a substance (eg, medication, illicit drug use). • Any neurological disorder, with the exception of Tourette's syndrome.

	• Subjects experiencing acute depressive symptoms within the past 30 days prior to screening that, according to the investigator's judgment, require treatment with an antidepressant. • Subjects with schizophrenia who are considered treatment resistant to antipsychotic medication, including aripiprazole or brexpiprazole, at an adequate dose and duration as confirmed by medical history, investigator judgment, or subject report. Subjects with a history of relapse due to lack of medication compliance or drug abuse can be considered based on investigator judgment. • Subjects with a history of failure of clozapine treatment or response to clozapine treatment only.
Trial Site(s):	An estimated 120 sites in North America, Europe, and rest of world will enroll subjects.
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Investigational medicinal product (IMP) will be supplied to the investigators by the sponsor or designated agent and will consist of open-label brexpiprazole 0.50 mg, 1 mg, 2 mg, 3 mg and 4 mg tablets in bottles, each containing sufficient tablets for the designated visit level. Brexpiprazole will be administered orally as a once-a-day dose without regard to meals. For rollover subjects from Trial 331-10-234, the first dose of open-label brexpiprazole will be taken 1 day after the last dose of double-blind IMP is taken in Trial 331-10-234 so that treatment continues without interruption. Whenever possible, it is anticipated that the last dose of the double-blind, phase 3 efficacy trial will be taken the day of the Week 6 visit of Trial 331-10-234 (ie, the day of the screening/baseline visit for the open-label trial). Subjects should not be dosed with double-blind (331-10-234) and open-label (331-10-236) study medication on the same day. Rollover subjects from the double-blind, phase 3 efficacy trial will begin dosing with brexpiprazole in the open-label Treatment period, starting at 0.5 mg/day, increasing to 1.0 mg/day on Day 5, and an optional increase to 2 mg/day if tolerated on Day 8. If this dose is well tolerated, but the response is inadequate, weekly dose increases can be made in 1 mg increments up to a maximum dose of 4 mg/day, based on the clinical judgment of the investigator. If the dose of brexpiprazole is not well tolerated, the investigator has the option to decrease the dose of brexpiprazole in a step-wise manner (1 mg decrements) at subsequent scheduled or

unscheduled visits according to his/her clinical judgment based on the subject's response to treatment. Daily dosing for this trial includes 1, 2, 3, or 4 mg.

De novo subjects from select sites will proceed to the conversion period or the open-label treatment period after screening, depending on their current antipsychotic treatment regimen. If the washout of prohibited medications prior to the baseline (Day 1) visit of the open-label treatment period is not appropriate for subjects, in the opinion of the investigator, the subjects will undergo cross-titration to oral brexpiprazole during the conversion period. De novo subjects who enter the conversion period of 1 to 4 weeks, will receive brexpiprazole in addition to their current antipsychotic(s). The dose of brexpiprazole will be increased as clinically indicated during the conversion period. Simultaneously, the dose of other antipsychotic(s) will be decreased and eventually discontinued. Once monotherapy with brexpiprazole and the washout of prohibited medications is achieved, the subject can begin the open-label treatment period of the study. De novo subjects should be outpatient at the baseline (Day 1) visit of the open-label treatment period.

De novo subjects will begin brexpiprazole monotherapy dosing of either 0.5 mg (no conversion) or 1, 2, or 3 mg (after conversion) in the open-label treatment period. De novo subjects who do not require a conversion period will follow the same titration schedule as rollover subjects from Trial 331-10-234, ie, 0.5 mg/day on Day 1, increasing to 1 mg/day on Day 5, and an optional increase to 2 mg/day if tolerated on Day 8. If doses are well tolerated, but the response is inadequate, weekly dose increases can be made in 1 mg increments up to a maximum dose of 4 mg/day, based on the clinical judgment of the investigator. Daily dosing for this trial includes 1, 2, 3, or 4 mg.

For all subjects, the maximum dose of brexpiprazole to be used in this trial is 4 mg/day. The dose of brexpiprazole may be decreased at any time based on the investigator's judgment after the start of the open-label treatment period. Dose decreases will occur in 1 mg decrements, with the frequency of the 1 mg decreases based upon tolerability. Those unable to tolerate the minimum daily dose of brexpiprazole (1 mg/day) must be withdrawn from the trial. Rechallenge with higher doses of brexpiprazole is permitted following dose decreases, if clinically warranted based on the investigator's judgment.

	If clinically indicated, subjects may be required to return to the clinic for unscheduled visits if dose adjustments for brexpiprazole are required between scheduled visits. Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response.
Trial Assessments:	Efficacy: Positive and Negative Syndrome Scale (PANSS) and Children's Global Assessment Scale (CGAS) , Clinical Global Impression - Severity of Illness scale (CGI-S), and Clinical Global Impression - Improvement scale (CGI-I). Safety: adverse events (AEs) and concomitant medications, clinical laboratory tests, urinalysis, vital signs, 12-lead electrocardiogram (ECG), physical examination, body weight, height, body mass index (BMI), waist circumference, extrapyramidal scales (Simpson Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale [BARS]), Udvalg for Kliniske Undersogelser (UKU), New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT), Tanner Staging Scale for sexual development, and suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS). Screening/Other: demography, medical history, psychiatric history (K-SADS-PL), prior and concomitant medications, serum/urine pregnancy test, and urine drug screen.
Criteria for Evaluation:	**Primary Endpoint:** The primary endpoints of this trial are the frequency and severity of AEs, serious treatment-emergent adverse events (TEAEs) (clinical and laboratory), and discontinuation from trial due to AEs. **Secondary Endpoints** The secondary safety endpoints are as follows: • Mean change from baseline and incidence of clinically significant abnormalities in clinical laboratory tests and urinalysis results (including fasting blood lipids, glucose and insulin, serum prolactin, glycosylated hemoglobin [HbA1c] and creatine phosphokinase [CPK]), vital signs (supine and standing positions), weight, height, body mass index (BMI), waist circumference, and ECG parameters

	• Mean change from baseline on the AIMS, Simpson-Angus Scale (SAS), and Barnes Akathisia Rating Scale (BARS) • Analysis of potential suicide events recorded on the C-SSRS • Comprehensive psychotropic side effects as assessed by UKU side effect rating scale • The frequency of symptom items for the clinician-administered NY-AACENT • Baseline and postbaseline Tanner Staging Scale data • Time to discontinuation due to AE The secondary efficacy endpoints are as follows: • Change in the PANSS Total Score and the Positive and Negative Subscale Scores • Change in the CGAS Score • CGI-S scale • CGI-I scale
Statistical Methods:	Sample size was not determined by a formal computation to achieve a target power. Sample size was planned to attain at least 100 subjects completing 1 year of exposure to open-label brexpiprazole. Descriptive statistics will be provided for all efficacy and safety variables. Continuous variables will be summarized by tabulations of mean, median, range, and standard deviation. Tabulations of frequency distributions will be provided for categorical variables. A Kaplan-Meier curve will be plotted for the time to discontinuation due to AE variable. Safety tabulations will include duration on brexpiprazole, the frequency of AEs, serious TEAEs, ECGs, vital sign abnormalities, weight, BMI, waist circumference changes, laboratory abnormalities and therapy discontinuations. The efficacy variables (for subjects with schizophrenia: PANSS Total score, PANSS Positive and Negative Subscales, and CGAS) will be summarized by change from baseline over time. Tanner Staging Scale data will be summarized using shift tables. The incidence of suicidality, suicidal behavior and suicidal ideation will be summarized from the data recorded on the C-SSRS forms, and results will be summarized by visit. Other outcomes including PANSS Cognitive Subscale will be summarized for their change from baseline by visit.

	No inferential statistical analyses are planned for this open-label trial. All analyses will be exploratory and conducted only to report the long-term safety of brexpiprazole for all subjects who are administered at least 1 dose of brexpiprazole.
Trial Duration:	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 66 months, of which 40 months are allotted for recruitment of subjects. Individual participation for rollover subjects who complete the trial without early withdrawal will be approximately 25 months, consisting of a 24-month open-label treatment period, and a 21 (± 2)-day follow-up, if applicable. Individual participation for de novo subjects who complete the trial without early withdrawal will be approximately 27 months, consisting of a screening period of up to 28 days, a conversion period of 1 to 4 weeks, a 24-month open-label treatment period, and a 21 (± 2)-day follow-up, if applicable.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
ADHD	Attention-deficit/hyperactivity disorder
ADT	Antidepressant therapy
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
APO	Apomorphine
AST	Aspartate aminotransferase
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve from time 0 hours to time 24 hours
AUC_{τ}	Area under the plasma concentration-time curve to the last observable concentration
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CGAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impression - Improvement scale
CGI-S	Clinical Global Impression - Severity of Illness scale
CL/F	Apparent clearance of drug from plasma after extravascular administration
C_{max}	Maximum concentration
$C_{max,ss}$	Maximum concentration at steady state
CNS	Central nervous system
CPK	Creatine phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
D_2	Dopamine D_2
D_3	Dopamine D_3
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition*
ECG	Electrocardiogram
EPS	Extrapyramidal symptom
ET	Early termination
EudraCT	European Clinical Trial Data Base
FDA	(United States) Food and Drug Administration
GABA	Gamma-aminobutyric acid
GAS	Adult Global Assessment Scale
GCP	Good Clinical Practice

GGT	Gamma glutamyl transferase
GMR	Geometric mean ratio
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
5-HT	Serotonin type receptor
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IDDM	Insulin-dependent diabetes mellitus
IEC	Independent ethics committee
IM	Intramuscular
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional review board
IRE	Immediately reportable event
IR	Immediate-release
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version
K_i	Inhibition constant
LDH	Lactic dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MAOI	Monoamine oxidase inhibitors
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDD	Major depressive disorder
MTD	Maximum tolerated dose
NDA	New Drug Application
NY-AACENT	New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment
OC	Observed case
OPC	Otsuka Pharmaceutical Co.
PANSS	Positive and Negative Syndrome Scale
PD	Pharmacodynamic
PET	Positron emission tomography
PK	Pharmacokinetic
PQC	Product quality complaint
PTSD	Post-traumatic stress disorder
QTc	Corrected QT interval
QTcF	QT interval as corrected for heart rate by Fridericia's formula
QTcN	QT interval corrected for heart rate by the FDA Neuropharm Division formula
RBC	Red blood cell

SAE	Serious adverse event
SAS	Simpson Angus Scale
SBP	Systolic blood pressure
T_4	Thyroxine
T_x	Treatment
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum (peak) plasma concentration
TSH	Thyroid-stimulating hormone
UKU	Udvalg for Kliniske Undersogelser
ULN	Upper limit of normal
US	United States
WBC	White blood cell

1 Introduction

Schizophrenia is a severely debilitating mental illness that affects approximately 1% of the world population.[1,2] Hallucinations and delusions are the most striking characteristic positive symptoms of schizophrenia; however, more subtle negative symptoms (eg, social withdrawal, lack of emotion, energy, and motivation) may also be present. The first antipsychotics developed for the treatment of schizophrenia were dopamine D_2 (D_2) receptor antagonists. These agents were effective against positive symptoms, but showed little efficacy for negative symptoms and were also associated with a high incidence of hyperprolactinemia and extrapyramidal symptom (EPS)-related side effects.[3] Second generation antipsychotics, commonly referred to as "atypical antipsychotics," act as antagonists at serotonin 5-HT_{2A} receptors in addition to the dopamine receptor. The atypical antipsychotics are efficacious and exhibit a reduced tendency to promote EPS relative to typical antipsychotics, but they are not devoid of undesirable side effects. High incidences of weight gain, related metabolic abnormalities, and hyperprolactinemia have been observed with some of these agents.[4,5,6]

Brexpiprazole (OPC-34712, OPC 331, and Lu AF41156) is a new chemical entity discovered by Otsuka that is being co-developed by Otsuka and H. Lundbeck A/S (Lundbeck). 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. It has modulatory activity at the serotonin and dopamine systems that combines partial agonist activity at serotonergic 5-HT_{1A} and at dopaminergic D_2 receptors with antagonist activity at serotonergic 5-HT_{2A} receptors, with similar high affinities at all of these receptors (inhibition constant [K_i]: 0.1-0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic $\alpha_{1B/2C}$ with affinity in the same sub-nanomolar K_i range (K_i: 0.2-0.6 nM). The 5-HT_{1A}/D_2 receptor partial agonist activity in combination with 5-HT_{2A} and $\alpha_{1B/2C}$ receptors antagonism of brexpiprazole may correlate with antipsychotic and antidepressant efficacy.

Overall, the broad spectrum of brexpiprazole receptor binding profile shows that it has high affinity (K_i < 5 nM) for multiple monoaminergic receptors including serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, dopamine D_2, D_3, and noradrenergic α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Brexpiprazole acts as a partial agonist at the 5-HT_{1A}, D_2, and D_3 receptors

and as an antagonist at 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Dose response occupancy and brain/plasma exposure relationship were determined in vivo or ex vivo for D_2/D_3, 5-HT_{2A}, 5-HT_{1A}, 5-HT_6, and 5-HT_7 receptors as well as for the 5-HT transporter in preclinical studies. These results are consistent with the relative in vitro binding affinities and indicate that brexpiprazole may have efficient activity at several targets in the central nervous system at therapeutic plasma exposures.

Brexpiprazole 2 to 4 mg, taken orally once daily, was approved for the treatment of schizophrenia and as adjunctive treatment for major depressive disorder (MDD) in adults (ages 18 to 65) by the United States (US) Food and Drug Administration (FDA) on 10 Jul 2015. This approval for treatment of schizophrenia in adults was based on data from 2 completed short-term, fixed-dose, placebo-controlled trials. In addition, data from 2 long-term, open-label trials were included in the New Drug Application (NDA). To date, the schizophrenia program for brexpiprazole has primarily targeted adult subjects 18 to 65 years of age. In 2015, a dose-escalation pharmacokinetic (PK) trial in adolescents with schizophrenia and bipolar disorder (Trial 331-10-233) was initiated and results support dosing for the double-blind, placebo-controlled Trial 331-10-234, which was conducted to determine the safety and efficacy of brexpiprazole for the treatment of adolescents with schizophrenia. The current trial is an open-label trial using a similar dose range of brexipiprazole as maintenance treatment for adolescents with schizophrenia.

The onset of schizophrenia symptoms typically peaks in late adolescence and early adulthood; however, prodromal symptoms may be present for several years before the initial psychotic episode. In a minority of cases, the initial episode may occur during childhood or early adolescence. Patients who experience this “early-onset schizophrenia” exhibit symptoms that tend to be more severe and follow a more chronic course.[7] Whereas adults with schizophrenia typically experience exacerbations of psychotic symptoms between periods of relative normalcy, adolescents with schizophrenia may never achieve full remission of the initial episode. The prognosis for early-onset schizophrenia tends to be poor; cognitive impairment is greater compared with individuals whose onset of schizophrenia occurs later in life.[8] In addition, refinement of social interaction skills that takes place during the teen years is interrupted, leading to a reduced ability for successful function in adulthood.[9] Several antipsychotics have been investigated for the treatment of adolescent schizophrenia.[8] Management of these

subjects presents a particular challenge because developing bodies are more sensitive to side effects of antipsychotics, particularly with respect to weight gain.[10]

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Brexpiprazole decreased blood pressure (BP) 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 BP decreasing effect of brexpiprazole was suggested to result from a blockade of the α_1-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 terminal phase elimination half-life of brexpiprazole and DM-3411 was 48.3 to 80.8 hours and 48.6 to 77.5 hours, respectively. The median time to maximum (peak) plasma concentration (t_{max}) occurred at approximately 2 to 6 hours postdose for brexpiprazole and at approximately 10 to 24 hours postdose 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 95.4 and 89.3 hours, respectively; median t_{max} was 3.0 and 8.0 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.

The binding of brexpiprazole to dopamine receptors was assessed using positron emission tomography (PET). The mean D2/D3 receptor occupancies at 4 and 24 hours postdose after 0.25, 0.5, 1, 2, 4, 5, and 6 mg single-dose administration of brexpiprazole to healthy subjects were 11.4% to 17.4%, 36.5% to 46.3%, 45.6% to 60.2%, 52.7% to 68.6%, 67.9% to 79.5%, 71.9% to 88.2%, and 69.5% to 92.6%, respectively (Trial 331-07-202). Based on the single-dose D2/D3 receptor occupancy data and steady-state PK/PD modeling, it was predicted that the D2/D3 receptor occupancy after multiple daily dose administration of 1 to 2 mg and higher doses of brexpiprazole will result in at least 80% to 90% D2/D3 receptor occupancy.

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 FDA on 10 Jul 2015. Trial 331-10-233 was a phase 1, multicenter, open-label dose-escalation trial to assess the safety,

tolerability, and PK of oral brexpiprazole in adolescents with schizophrenia or other related psychiatric disorders.

In that trial, overall systemic exposure was measured by dose-normalized maximum concentration at steady state ($C_{max,ss}$) and area under the plasma concentration-time curve to the last observable concentration (AUC_{τ}), and was slightly higher (geometric mean ratio [GMR] adult/adolescent: 0.904 and 0.765, respectively), and apparent clearance of drug from plasma after extravascular administration (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 AUCs from time 0 to 24 hours (AUC_{0-24h}) (GMR adult/adolescent: 0.105), and slightly higher dose-normalized maximized concentrations (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 3 completed placebo-controlled trials (Trials 331-10-227, 331-10-228, and 331-13-214) and a long-term, open-label safety trial (Trial 331-10-238). The recently completed Trial 331-12-282 was a multicenter, randomized, double-blind, placebo and active comparator (Seroquel XR) controlled trial designed to assess the safety and efficacy of brexpiprazole (flexible dose) as adjunctive therapy to an assigned open-label antidepressant therapy (ADT) in depressed subjects. The trial was a continuous 18-week double-blind treatment period with a 30 (± 2)-day follow-up or entry into an optional open-label rollover trial.

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.

1.3 Known and Potential Risks and Benefits

Sites will routinely receive updated versions of the IB on an ongoing basis, and sites should refer to that version of the IB as needed. Please refer to the current IB for a detailed summary of available nonclinical and clinical safety data.

As of 17 Apr 2016,[11] a total of 65 clinical trials were presented in the IB: 53 clinical trials have been completed, and 12 are ongoing. Completed trials include 20 completed phase 1 clinical trials in healthy subjects or special populations (ie, hepatic and renal impaired subjects) (17 in the US, 2 in Japan, and 1 in Korea); 6 completed phase 1 trials in subjects with schizophrenia or schizoaffective disorder, MDD, or ADHD (5 in the US, 1 in Japan); 1 completed phase 1b trial in adult subjects with stable schizophrenia; 2 completed phase 2 (1 double-blind and 1 open-label), 2 completed phase 3 (both double-blind), and 1 completed phase 3b (open-label) trials in adult subjects with schizophrenia; 3 completed phase 2 (2 double-blind and 1 open-label), 4 completed phase 3 (3 double-blind and 1 open-label), and 5 completed 3b (all open-label) trials in subjects with MDD; and 1 completed phase 2 double-blind trial in subjects with ADHD. Ongoing trials include 2 phase 1 trials (1 fixed-dose PET trial in subjects with schizophrenia [US] and 1 trial in adolescents with a diagnosis of schizophrenia); 1 phase 2/3 trial in adult subjects with acute schizophrenia (Japan); 5 phase 3 and 2 phase 3b trials in subjects with schizophrenia (6 multinational, including the US, and 1 in Japan); 5 phase 3 and 1 phase 3b trials in subjects with MDD (multinational, including the US); 3 phase 3 trials in subjects with agitation associated with dementia of the Alzheimer's type (multinational, including the US); and 1 phase 3 trial in subjects with post-traumatic stress disorder (PTSD) (multinational, including the US).

Combined data from the completed phase 1 clinical trials indicate that the maximum tolerated dose (MTD) for healthy 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, or ADHD 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 ADT in subjects with MDD; up to 3 mg/day in elderly subjects (70 to 85 years of age) with MDD; and up to 4 mg/day when coadministered with marketed stimulant therapy in subjects with ADHD. Safety data are available from the 45 completed clinical trials. The total number of subjects exposed to either single or multiple doses of brexpiprazole is composed of 4488 subjects in trials conducted under US Investigational New Drug

(IND) applications and 143 subjects (collectively) in non-US IND trials conducted in Japan and Korea.

Overall, 3101/4488 subjects (69.1%) who received brexpiprazole either alone or coadministered with another marketed medication reported at least 1 treatment-emergent adverse event (TEAE). The most frequently reported TEAEs (incidence ≥ 5% of the total brexpiprazole group and more than total placebo) in all subjects who received brexpiprazole were headache (10.8%), increased weight (9.0%), insomnia (8.1%), akathisia (7.5%), dizziness (6.6%), somnolence (5.4%), and nausea (5.3%). The majority of TEAEs reported in the 45 completed brexpiprazole trials were mild or moderate in severity.

A total of 26 deaths have been reported in the brexpiprazole clinical development plan: 25 deaths in the US IND trials and 1 death in the non-US IND trials. Eight deaths occurred in schizophrenia trials, 10 deaths in MDD trials, and 8 deaths in the agitation associated with dementia of the Alzheimer's type trials. Three deaths occurred in completed trials, and the remaining 23 deaths occurred in ongoing trials. Of the 26 deaths, 15 occurred in female subjects. Serious TEAEs have been reported for 94 subjects who received brexpiprazole in the 45 completed trials, including 91 subjects in completed trials conducted under the US INDs and 3 subjects in completed non-US IND trials. Serious TEAEs had been reported for 442 subjects in ongoing trials of brexpiprazole.

A total of 312/4488 subjects (7.0%) who received brexpiprazole (either alone or coadministered with another medication) and 71/1378 subjects (5.2%) who received placebo (either alone or coadministered with another medication) discontinued from investigational medicinal product (IMP) due to TEAEs in completed brexpiprazole trials conducted under the US INDs (22 phase 1 trials, 1 phase 1b trial, 6 phase 2 trials, 12 completed phase 3 trials, and 6 phase 3b trials). A total of 2 subjects discontinued from IMP due to TEAEs in completed non-US IND trials, and 110 subjects discontinued from IMP due to TEAEs in the 2 ongoing non-US IND trials. Brexpiprazole is indicated in adult patients for use as an adjunctive therapy to antidepressants for the treatment of MDD and treatment of schizophrenia. 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 phase 2/3, phase 3, and phase 3b clinical trials (by indication): 0.5 to 2 mg/day in adult subjects with agitation associated with dementia of the Alzheimer's type and 1 to 3 mg/day in adult subjects with PTSD.

2 Trial Rationale and Objectives

2.1 Trial Rationale

The onset of schizophrenia symptoms typically peaks in late adolescence and early adulthood; however, prodromal symptoms may be present for several years before the initial psychotic episode. In a minority of cases, the initial episode may occur during childhood or early adolescence. Patients who experience this "early-onset schizophrenia" exhibit symptoms that are more severe and follow a more chronic course.[7] Whereas adults with schizophrenia typically experience exacerbations of psychotic symptoms between periods of relative normalcy, adolescents with schizophrenia may never achieve full remission of the initial episode. The prognosis for early-onset schizophrenia tends to be poor; cognitive impairment is greater compared with individuals whose onset of schizophrenia occurs later in life.[8] In addition, refinement of social interaction skills that takes place during the teen years is interrupted, leading to a reduced ability for successful function in adulthood.[9] Several antipsychotics have been investigated for the treatment of adolescent schizophrenia.[8] Management of these subjects presents a particular challenge because developing bodies are more sensitive to side effects of antipsychotics, particularly with respect to weight gain.[10]

The current phase 3 trial is part of the brexpiprazole clinical development program that has been designed to evaluate the long-term safety and tolerability of brexpiprazole in adolescents with schizophrenia. A 2 year, open-label treatment period is considered to be of adequate length to determine long-term safety and tolerability of brexpiprazole.

2.2 Dosing Rationale

Brexpiprazole has been well tolerated at multiple oral doses up to 12 mg/day in adult subjects with schizophrenia or schizoaffective disorders. A dose range of 0.25 to 6 mg/day was investigated in a phase 2 trial in adults with schizophrenia.

The safety, tolerability, and PK of brexpiprazole have been studied in healthy adult subjects and patients (18 years and older), including those with schizophrenia or schizoaffective disorder. A PK, safety, and tolerability trial in adolescent (13–17 years old) subjects with a diagnosis of schizophrenia or other related psychiatric disorders (ie, bipolar disorder) was completed (Trial 331-10-233). Subjects who were deemed eligible for Trial 331-10-233 were assigned to a dosing cohort and entered a Dose Titration Phase during which they received a starting dose of brexpiprazole (0.5 mg or 1 mg) for 2 to 10 days based on their assigned titration schedule. Following the Dose

Titration Phase, subjects entered the Fixed Dose Phase and were administered the assigned dose (0.5 mg to 4 mg) for that cohort for 14 days. For the final cohort a dose titration of 1 mg on Days 1 and 2; 2 mg on Days 3 and 4; 2.5 mg on Days 5 and 6; 3 mg on Days 7 and 8; and 3.5 mg on Days 9 and 10, followed by 4 mg daily for 14 days was followed. Brexpiprazole doses of 0.5 mg/day, 1 mg/day, 2 mg/day, 3 mg/day, and 4 mg/day were generally safe and well tolerated in adolescent subjects with schizophrenia, bipolar disorder, or other related psychiatric disorders. Overall, systemic exposure and apparent clearance did not appear to be significantly different between adolescent and adult subjects while high variability due to limited number of evaluable subjects contributed to small differences between the PK evaluable and PK populations.

Based on results of pivotal safety and efficacy adult patients with schizophrenia a dose range of 2 to 4 mg is shown to be efficacious (Rexulti Label). Based on the safety and PK data in Trial 331-10-233, no dose adjustment were deemed necessary in children and adolescent and thus a similar efficacious dose range of 1 to 4 mg is proposed for this trial. In adult patients brexpiprazole was initiated as 1 mg for 3 days followed by 2 mg for 3 days, and a similar dose initiation is proposed in adolescent patients as a similar dose initiation scheme has been evaluated in the final cohort of Trial 331-10-233 with no safety or tolerability concerns.

2.3 Trial Objectives

The objective of the trial is to characterize the long-term safety and tolerability of brexpiprazole in adolescents with schizophrenia.

3 Trial Design

3.1 Type/Design of Trial

This is a long-term, multicenter, open-label trial designed to examine the long-term safety and tolerability of brexpiprazole in adolescent subjects, ages 13 to 17 years at time of informed consent/assent and at the baseline (Day 1) visit of the open-label treatment period, with a *Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition* (DSM-5) diagnosis of schizophrenia. Subjects from Trial 331-10-234 who turned 18 years old during that trial are also permitted to enroll in this trial. For de novo subjects who did not participate in Trial 331-10-234, the initial diagnosis of schizophrenia for this trial (as defined by DSM-5 criteria) should be made and documented by an adequately trained clinician (psychiatrist, or local medical equivalent who is experienced in treating adolescents with schizophrenia), and the diagnosis should

then be confirmed utilizing the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL) performed by an adequately trained rater at the time of screening. Rollover subjects will be considered as those who are able to rollover within ≤ 7 days of the Week 6 visit of Trial 331-10-234. Subjects who are only able to rollover from Trial 331-10-234 after > 7 days from the Week 6 visit may be allowed to enter Trial 331-10-236 as de novo subjects following approval by the medical monitor.

The trial will be conducted on an outpatient basis. Hospitalization for psychosocial reasons (eg, homelessness or need for shelter that is unrelated to the subject's underlying psychiatric condition) will be considered outpatient status for the purpose of enrollment in Trial 331-10-236.

Subjects remaining in hospital at the Week 6 visit of Trial 331-10-234 (for other than psychosocial reasons) will be permitted to enroll in Trial 331-10-236 at the Week 6 visit of the double-blind trial if they are planned to be discharged from the hospital before the open-label treatment period Week 1 visit of Trial 331-10-236 and following approval by the medical monitor. De novo subjects hospitalized at the time of the Trial 331-10-236 screening visit will be permitted to be screened for the trial if they are planned to be discharged from the hospital prior to the baseline (Day 1) visit of the open-label treatment period and following approval by the medical monitor.

For rollover subjects, Trial 331-10-236 will consist of a 24-month open-label treatment period and a 21 (± 2) day follow-up period. For de novo subjects, Trial 331-10-236 will consist of a 3- to 28-day screening phase, a 1 to 4 weeks conversion phase (if necessary), a 24-month open-label treatment phase, and a 21 (± 2) day follow-up period. Visit windows of ± 3 days will be permitted during the trial; however, every effort will be made to ensure the individual open-label treatment period does not exceed 24 months.

The decision to enroll into this open-label trial from Trial 331-10-234 will be a joint decision between the investigator and subject/parent/guardian or legally acceptable representative, as applicable for local laws and will be made without knowledge of the subject's double-blind treatment assignment. The availability of the open-label trial should be discussed with these subjects and an informed consent/assent specific to Trial 331-10-236 must be completed for the Trial 331-10-234 rollover subjects before any trial-related procedures can take place. For rollover subjects, the informed consent form (ICF) for the open-label trial may be provided to potential candidates or their parent/legal guardian or legally acceptable representative, as applicable for local laws, for review and discussion toward completion of the double-blind trial, but the form must not

be signed until the day of the screening/baseline visit for Trial 331-10-236 (ie, the Week 6 visit of Trial 331-10-234). For de novo subjects, screening begins on the day that the subject or their parent/legal guardian or legally acceptable representative, as applicable for local laws, signs the ICF. If any subject should turn 18 years of age (or the age of adulthood as specified by local laws or regulations) following entry into Trial 331-10-236, the appropriate informed consent must be obtained from the subject.

A schematic of the trial design is provided in Figure 3.1-1 (rollover subjects) and Figure 3.1-2 (de novo subjects).

The trial will be organized as follows:

Rollover Subjects from Trial 331-10-234

Screening/Baseline: Subjects will be assessed for eligibility at the last visit of the double-blind trial (ie, Week 6 visit of Trial 331-10-234). Subjects or their parent/legal guardian will complete a separate ICF and subjects will provide assent as required for participation in Trial 331-10-236 before any procedures specific to the open-label trial are performed. The assessments from the last visit of the double-blind trial will serve as the baseline measures for Trial 331-10-236 for any assessment that is not unique to the open-label trial. Medical history will be updated, if necessary.

Open-label Treatment: Eligible subjects from Trial 331-10-234 will receive daily treatment with open-label brexpiprazole in the open-label treatment period of Trial 331-10-236 as described in Section 3.2.1.

Follow-up: Subjects will be followed up for safety via telephone contact or clinic visit 21 (± 2) days after the last dose of IMP.

De Novo Subjects

Screening: Subjects will enter a pretreatment screening phase that will range from a minimum of 3 days to a maximum of 28 days to assess eligibility criteria and to wash out from prohibited concomitant medications, if applicable. Screening begins on the day that the parent/legal guardian signs the ICF and provides assent (subject) as required, based on the local requirements. Subjects will be assigned a unique screening number for each subject with a signed ICF/completed assent prior to enrollment. If a de novo subject previously participated in Trial 331-10-234, they will retain their subject identification number from Trial 331-10-234. Subjects who are able to complete the required washout of prohibited medications per Table 4.1-1 will proceed directly to the baseline (Day 1) visit of the open-label treatment period after completion and review of screening

assessments provided that all eligibility criteria are met (ie, laboratory test results, electrocardiograms [ECGs]). If the washout of prohibited medications per Table 4.1-1 is not appropriate for subjects, in the opinion of the investigator, the subjects will participate in the conversion period.

Conversion: If the washout of prohibited medications prior to the baseline (Day 1) visit of the open-label treatment period is not appropriate for subjects, in the opinion of the investigator, the subjects will undergo cross-titration to oral brexpiprazole for 1 to 4 weeks, as described in Section 3.2.2. Visits will occur at the end of each week during the conversion period. The goal of de novo subjects during the conversion period is to achieve a brexpiprazole monotherapy target starting dose of 1, 2, or 3 mg daily at any time after Week 1 per the investigator's discretion and to achieve the required washout of prohibited medications as per Table 4.1-1. The subject will proceed to the baseline (Day 1) visit of the open-label treatment period once the target starting dose has been achieved and the required washout of prohibited medications has been completed.

Baseline and Open-label Treatment: After completing baseline assessments, eligible subjects will receive daily treatment with open-label brexpiprazole in the open-label treatment period, as described in Section 3.2.2.

Follow-up: Subjects will be followed up for safety via telephone contact or clinic visit 21 (± 2) days after the last dose of IMP.

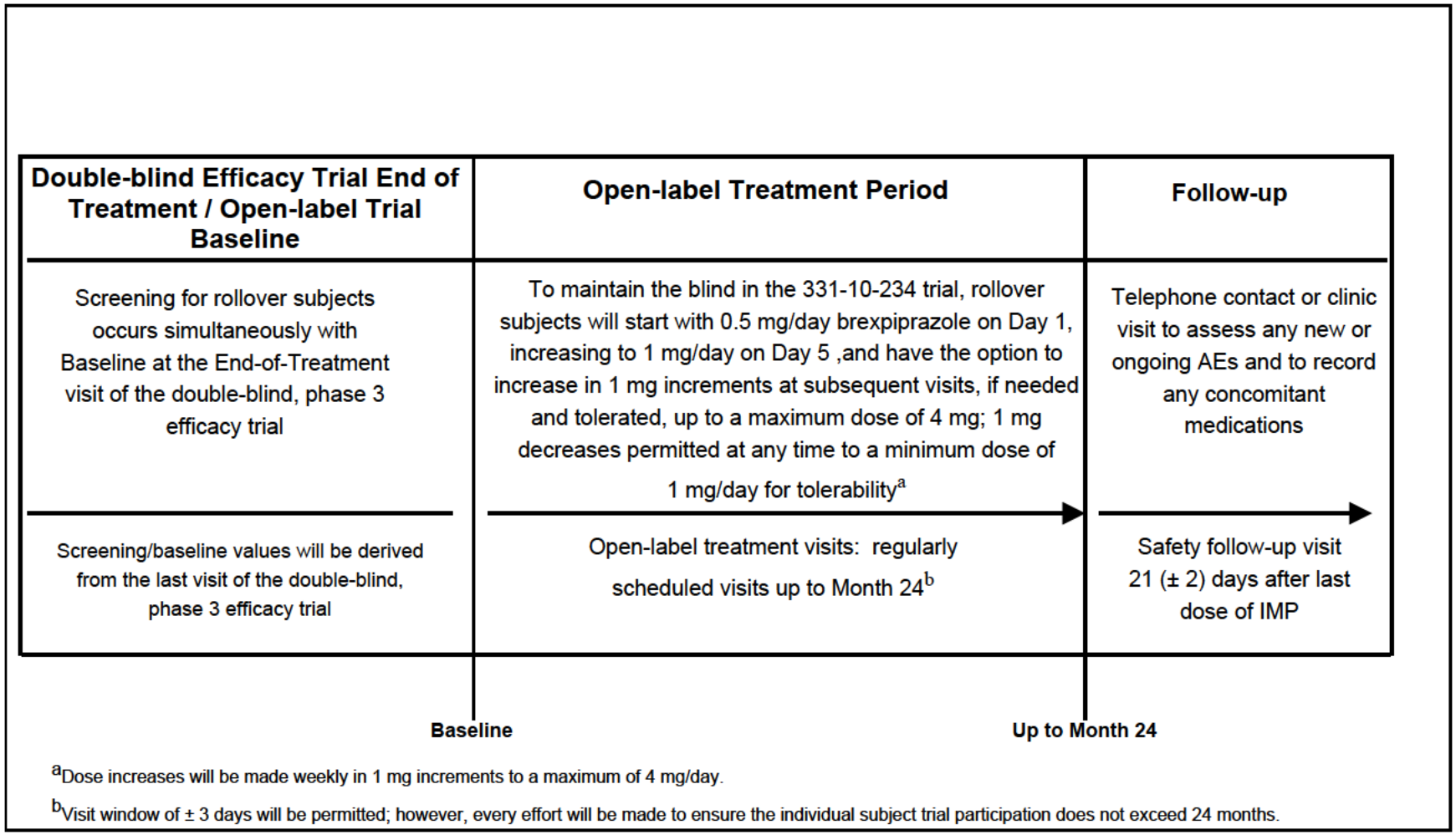
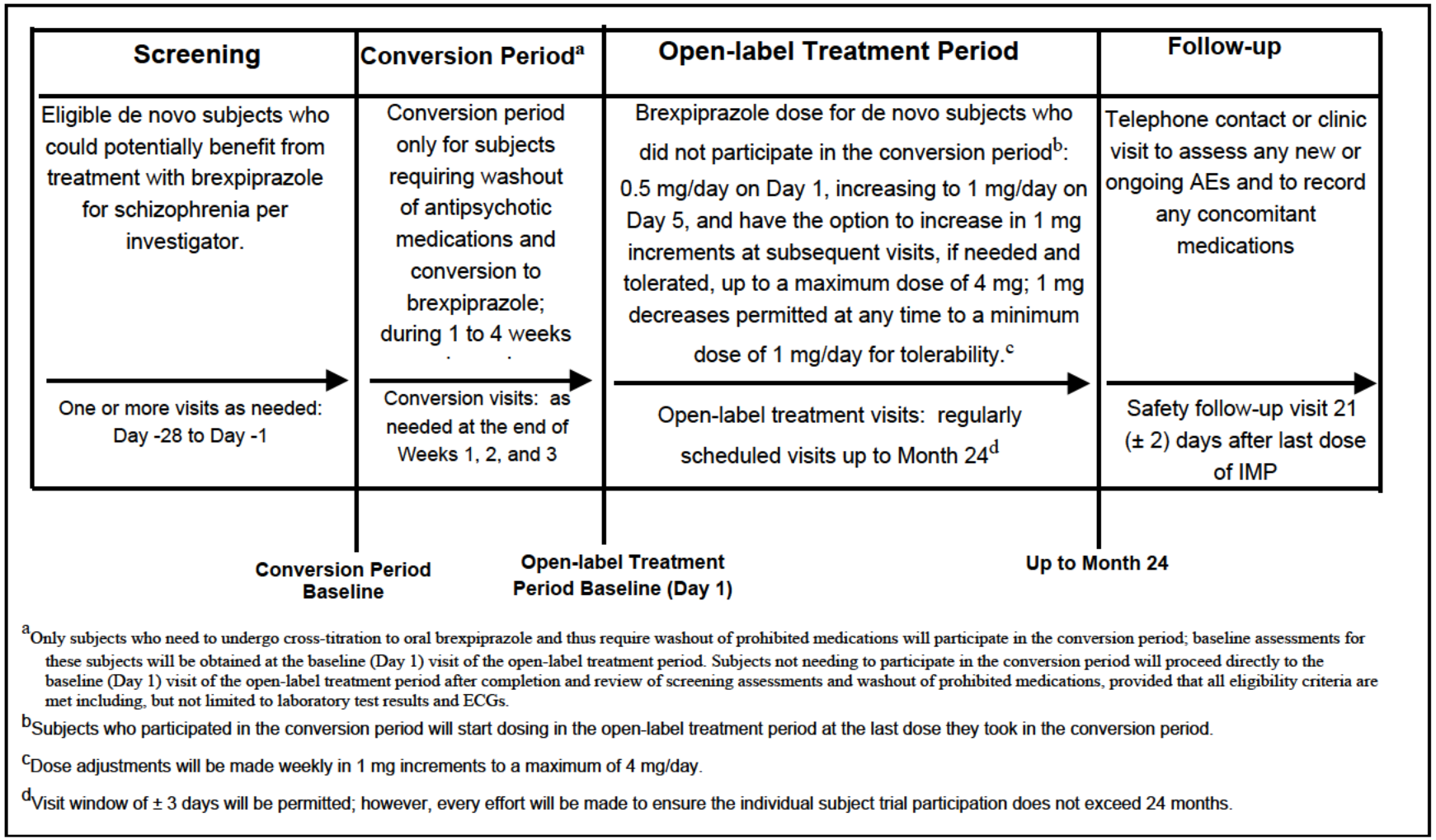


Figure 3.1-1 Trial Design Schematic - Rollover Subjects from Trial 331-10-234



[a]Only subjects who need to undergo cross-titration to oral brexpiprazole and thus require washout of prohibited medications will participate in the conversion period; baseline assessments for these subjects will be obtained at the baseline (Day 1) visit of the open-label treatment period. Subjects not needing to participate in the conversion period will proceed directly to the baseline (Day 1) visit of the open-label treatment period after completion and review of screening assessments and washout of prohibited medications, provided that all eligibility criteria are met including, but not limited to laboratory test results and ECGs.

[b]Subjects who participated in the conversion period will start dosing in the open-label treatment period at the last dose they took in the conversion period.

[c]Dose adjustments will be made weekly in 1 mg increments to a maximum of 4 mg/day.

[d]Visit window of ± 3 days will be permitted; however, every effort will be made to ensure the individual subject trial participation does not exceed 24 months.

Figure 3.1-2 Trial Design Schematic - De Novo Subjects

3.2 Trial Treatments

All doses of open-label IMP are to be taken orally once daily and can be administered without regard to meals. Every effort should be made to administer the open-label IMP at the same time every day. If the titration schedule needs to be adjusted due to clinical or subject-specific need, the site should discuss with the medical monitor.

3.2.1 Rollover Subjects from Trial 331-10-234

The first dose of open-label brexpiprazole will be taken 1 day after the last dose of double-blind IMP is taken in Trial 331-10-234 so that treatment continues without interruption. Whenever possible, it is anticipated that the last dose of the double-blind, phase 3 efficacy trial will be taken the day of the Week 6 visit of Trial 331-10-234 (ie, the day of the screening/baseline visit for the open-label trial). Subjects should not be dosed with using double-blind (331-10-234) and open-label (331-10-236) study medication on the same day.

Rollover subjects from Trial 331-10-234 will begin dosing with brexpiprazole 0.5 mg/day on Day 1, increasing to 1 mg/day on Day 5, and an optional increase to 2 mg/day if tolerated on Day 8 of the open-label treatment period. If the 2 mg dose is well tolerated, but the response is inadequate, weekly dose increases can be made in 1 mg increments to a maximum of 4 mg/day. Dose changes are allowed based on the clinical judgment of the investigator at scheduled or unscheduled visits according to his/her clinical judgment based on the subject's response to treatment. Daily dosing for this trial includes 1 mg, 2 mg, 3 mg, or 4 mg.

The dose of brexpiprazole may be decreased at any time based on the investigator's judgment after the start of the open-label treatment period. Dose decreases will occur in 1 mg decrements, with the frequency of the 1-mg decreases based upon tolerability. Those unable to tolerate the 1 mg daily dose of brexpiprazole must be withdrawn from the trial. The dosing strategy is summarized in Table 3.2.1-1. Rechallenge with higher doses of brexpiprazole (ie, in 1 mg/day increments) is permitted following dose decreases, if clinically warranted based on the investigator's judgment.

If clinically indicated, subjects may return to the clinic for unscheduled visits if dose adjustments for brexpiprazole are required between scheduled visits. Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response.

Table 3.2.1-1 Dose Adjustments for Brexpiprazole in the Open-label Treatment Period (Both Rollover Subjects from Trial 331-10-234 and Nonconversion De Novo Subjects)		
Trial Visit	**Dose Options**	**Dose Changes**
Start of the open-label treatment period, Days 1–4	0.5 mg/day (starting dose)	Not applicable
Days 5–7	1 mg/day	Not applicable
Days 8–14	1 or 2 mg/day	Maintain same dose or option to increase to 2 mg/day if tolerated
Days 15–21	1, 2, or 3 mg/day	Maintain same dose, or option to increase or decrease by 1 mg /day (minimum dose 1 mg/day)
Day 22 (Week 3) to Month 24	1, 2, 3, or 4 mg/day	Maintain same dose, or option to increase or decrease dose by 1 mg/day (minimum dose 1 mg/day and maximum dose 4 mg/day)

3.2.2 De Novo Subjects

If the washout of prohibited medications per Table 4.1-1 is not appropriate for de novo subjects, in the opinion of the investigator, the subjects must enter a conversion period to cross-titrate from their current antipsychotic treatment(s) to brexpiprazole monotherapy and to washout from prohibited medications. All other de novo subjects will enter the trial at the baseline (Day 1) visit of the open-label treatment period (see Section 3.2.2.2) after completion and review of screening assessments, provided that all eligibility criteria are met (ie, laboratory test results, ECGs), and will follow the dosing strategy for rollover subjects (Table 3.2.1-1).

3.2.2.1 Conversion

The purpose of the 1- to 4- week conversion period is to cross-titrate de novo subjects from current antipsychotic treatment(s) to monotherapy with brexpiprazole 1, 2, or 3 mg/day and achieve the required washout of prohibited medications per Table 4.1-1 to minimize the possibility of rebound (eg, cholinergic or histaminergic) from abrupt changes in antipsychotic medication. The recommended procedure for initiation of oral brexpiprazole is an ascending cross-titration scheme. The recommended procedure as it pertains to this protocol is summarized in Table 3.2.2.1-1.[12]

Table 3.2.2.1-1 Recommendation for Switching from Other Antipsychotics to Oral Brexpiprazole Monotherapy					
	Conversion Period[a]				
Trial Visit	**Conversion Baseline**	**Week 1**	**Week 2**	**Week 3**	**Baseline of Open-label Tx[b]**
Dose of brexpiprazole	0.5 mg/day	0.5 or 1 mg/day	1 or 2 mg/day	1, 2, or 3 mg/day	1, 2, or 3 mg/day
Dose of other antipsychotic(s)	No change	No change	Decrease	Discontinue	Discontinue
Dose of aripiprazole	Decrease	Decrease	Discontinue	Discontinue	Discontinue

Tx = treatment.

Note: Washout of required prohibited medications is per Table 4.1-1.

[a]Conversion period will last for 1 to 4 weeks.

[b]The baseline (Day 1) visit of the open-label treatment period will coincide with the end of the conversion period which is up to 4 weeks in duration

The scheme in Table 3.2.2.1-1 represents the optimal approach for conversion of subjects from other antipsychotic(s) to brexpiprazole and is highly recommended for use in this trial; however, the investigator may adjust the dose(s) of other antipsychotic(s) during 1- to 4-week cross-titration as deemed appropriate for individual subjects. The dose of brexpiprazole can increase up to 3 mg/day during cross-titration, but cannot decrease to less than 1 mg/day. Subjects must achieve a minimum monotherapy dose of brexpiprazole 1 mg/day at the end of the conversion period/baseline (Day 1) of the open-label treatment period in order to progress to the open-label treatment period.

3.2.2.2 Open-label Treatment Period

Timing of the first dose of brexpiprazole in the open-label treatment period for de novo subjects will be as follows:

- De novo subjects who participate in the 1- to 4- week conversion period, will receive open-label brexpiprazole in the open-label treatment period once all prohibited medications are discontinued during the conversion period per Table 4.1-1 and once all baseline evaluations are completed.
- De novo subjects who are able to complete the required washout of prohibited medications per Table 4.1-1 will receive the first dose of open-label brexpiprazole in the open-label treatment period as soon as all screening and baseline evaluations are completed.

De novo subjects who participated in the conversion period will begin dosing with brexpiprazole 1, 2, or 3 mg/day in the open-label treatment period. If this dose is well tolerated, but the response is inadequate, weekly dose increases can be made in 1 mg

increments up to a maximum dose of 4 mg/day, based on the clinical judgment of the investigator.

Daily dosing for this trial includes 1, 2, 3, or 4 mg.

The maximum dose of brexpiprazole to be used in this trial is 4 mg daily. The dose of brexpiprazole may be decreased at any time based on the investigator's judgment after the start of the open-label treatment period. Dose decreases will occur in 1 mg decrements, with the frequency of the 1 mg decreases based upon tolerability. Those unable to tolerate the minimum 1 mg daily dose of brexpiprazole must be withdrawn from the trial. The dosing strategy is summarized in Table 3.2.2.2-1. Rechallenge with higher doses of brexpiprazole (in 1 mg/day increments) is permitted following dose decreases, if clinically warranted based on the investigator's judgment.

Dose adjustments must ultimately be made based upon the clinical judgment of the investigator as it relates to tolerability and therapeutic response.

Table 3.2.2.2-1 Dose Adjustments for Brexpiprazole in the Open-label Treatment Period for De Novo Subjects after Conversion

Trial Visit	Dose Options	Dose Changes
Start of the open-label treatment period, Days 1–7	1, 2, or 3 mg/day	Maintain same dose, or option to increase or decrease dose by 1 mg/day (minimum dose 1 mg/day)
Days 8–14 and Day 15 to Month 24	1, 2, 3, or 4 mg/day	Maintain same dose, or option to increase or decrease dose by 1 mg/day (minimum dose 1 mg/day and maximum dose 4 mg/day)

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

The trial population will include subjects from Trial 331-10-234 and as needed de novo subjects between 13 and 17 years of age, inclusive, at the time of informed consent/assent and at baseline (Day 1) visit of the open-label treatment period. For de novo subjects who did not participate in Trial 331-10-234, the initial diagnosis of schizophrenia for this trial (as defined by DSM-5 criteria) must be made and documented and the diagnosis confirmed by the K-SADS-PL[13]. Subjects from Trial 331-10-234 who turned 18 years old during that trial are also permitted to enroll in this trial. Approximately 350 subjects are anticipated to be enrolled with the expectation that at least 100 will complete 1 year of exposure to open-label brexpiprazole.

3.3.2 Subject Selection and Numbering

At screening, de novo subjects will be assigned a unique subject identification number upon signing the ICF and providing assent based on sequential enrollment in the trial, as required. Subjects from Trial 331-10-234 will retain their subject identification numbers from Trial 331-10-234 and are required to sign a new ICF and assent form for this trial, as required. The clinical site will maintain a list identifying all subjects by their subject identification number and initials.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws) and documented. The ICF 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 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 will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[14] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any site-specific ICF 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 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.

At sites where the electronic ICF 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 acceptable representative) are also required to sign electronically and these signatures will be stored with the electronic ICF 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 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 if the protocol is amended, and the changes to the protocol results in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on trial participation.

If any subject should turn 18 years of age (or the age of adulthood as specified by local laws or regulations) following entry into Trial 331-10-236, the appropriate informed consent must be obtained from the subject. The subject shall be given a copy of the signed ICF and the original shall be kept on file by the investigator.

3.4.2 Inclusion Criteria

3.4.2.1 Rollover Subjects

Subjects are required to meet the inclusion criteria presented in Table 3.4.2.1-1.

Table 3.4.2.1-1	Inclusion Criteria for Rollover Subjects from Trial 331-10-234
1.	Written informed consent/assent 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.
2.	Ability, in the opinion of the principal investigator, of the subject and 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 complete subject-reported outcomes measures, and to be reliably rated on assessment scales.
3.	Male and female subjects 13 to 18 years of age, inclusive, at the time of informed consent/assent and at baseline. Subjects who turned 18 years old during Trial 331-10-234 are permitted in this trial.
4.	Subjects who complete Trial 331-10-234 and who, in the opinion of the investigator, could potentially benefit from monotherapy treatment with oral brexpiprazole for schizophrenia. The baseline visit for Trial 331-10-236 coincides with the Week 6 visit of Trial 331-10-234. If the visit cannot be done within ≤ 7 days of the Week 6 visit of Trial 331-10-234 then the subject may be able to enter Trial 331-10-236 as a de novo subject following approval by the medical monitor.
5.	Outpatient status at the last visit of Trial 331-10-234. Hospitalization for psychosocial reasons (eg, homelessness or need for shelter that is unrelated to the subject's underlying psychiatric condition) will be considered outpatient status for the purpose of enrollment in Trial 331-10-236. Subjects remaining in hospital at the Week 6 visit of Trial 331-10-234 (for other than psychosocial reasons) will be permitted to enroll in Trial 331-10-236 at the Week 6 visit of the double-blind trial if they are planned to be discharged from the hospital before the open-label treatment period Week 1 visit of Trial 331-10-236 and following approval by the medical monitor.

3.4.2.2 De Novo Subjects

Subjects are required to meet the inclusion criteria presented in Table 3.4.2.2-1.

Table 3.4.2.2-1	Inclusion Criteria for De Novo Subjects
1.	Written informed consent obtained from a legally acceptable representative (eg, guardian) 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.
2.	Ability, in the opinion of the principal investigator, of the subject and 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 complete subject-reported outcomes measures, and to be reliably rated on assessment scales.
3.	Male and female subjects 13 to 17 years of age, inclusive, at the time of informed consent/assent and at the baseline (Day 1) visit of the open-label treatment period. Subjects who turned 18 years of age since participation in Trial 331-10-234, if applicable, are permitted to enroll in this trial.

Table 3.4.2.2-1 Inclusion Criteria for De Novo Subjects	
4.	Subjects with a current primary diagnosis of schizophrenia, as defined by DSM-5 criteria and a history of the illness (diagnosis or symptoms) for at least 6 months prior to screening (as per subject, family, or healthcare provider, or by previous medical records). For subjects who did not participate in Trial 331-10-234, the initial diagnosis of schizophrenia for this trial (as defined by DSM-5 criteria) must be made and documented by an adequately trained clinician (psychiatrist, or local medical equivalent who is experienced in treating adolescents with schizophrenia), and the diagnosis should then be confirmed utilizing the K-SADS-PL performed by an adequately trained rater at the time of entry into Trial 331-10-236. (Subjects with a diagnosis of ADHD and treated with stimulants or other ADHD medications within 28 days are prohibited.)
5.	Subjects who, in the investigator's judgment, require treatment with antipsychotic medication(s).
6.	Removed with Amendment 2.
7.	Outpatient status. Hospitalization for psychosocial reasons (eg, homelessness or need for shelter that is unrelated to the subject's underlying psychiatric condition) will be considered outpatient status for the purpose of enrollment in Trial 331-10-236. Subjects hospitalized at the time of the Trial 331-10-236 screening visit will be permitted to be screened for the trial if they are planned to be discharged from the hospital prior to the baseline (Day 1) visit of the open-label treatment period and following approval by the medical monitor.
8.	Subjects willing to discontinue all prohibited psychotropic medications to meet protocol-required washouts prior to and during the trial period.
Inclusion Criteria Assessed Prior to Entry into the Conversion Period	
9.	Removed with Amendment 4.
10.	Subject is receiving antipsychotic(s) other than clozapine. These subjects must be cross-titrated to brexpiprazole monotherapy over 1 to 4 weeks during the conversion period to a minimum dose of 1 mg/day as a starting dose in the open-label treatment period (see Section 3.2.2.1).
Inclusion Criteria Assessed Prior to Entry into the Open-label Treatment Period	
11.	Adequate washout of prohibited concomitant medications (see Table 4.1-1).
12.	Subject is ready to receive oral brexpiprazole as monotherapy for treatment of schizophrenia.

3.4.3 Exclusion Criteria

3.4.3.1 Rollover Subjects

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3.1-1. Some laboratory results may not be available from the last visit at the time of entry into the open-label treatment period in this trial. Investigators will need to contact the medical monitor if there are any clinically significant laboratory results to discuss a subject's ability to continue in the trial.

Table 3.4.3.1-1 Exclusion Criteria for Rollover Subjects from Trial 331-10-234	
Sex and Reproductive Status	
1.	Sexually active males or females who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control patch, birth control depot injection, condom with spermicide, or sponge with spermicide.
2.	Females who are breast-feeding or who have a positive pregnancy test result prior to receiving IMP.
Administrative	
3.	Noncompliance, due to subject's failure to follow study procedures during the course of their participation in the double-blind phase 3 trial, Trial 331-10-234 (eg, subjects deemed to be noncompliant. with the visit schedule, trial assessments, or treatment regimen in Trial 331-10-234). The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.
Target Disease	
4.	Subjects with a clinical presentation or history that is consistent with delirium, dementia, amnesia, or other cognitive disorders; subjects with psychotic symptoms that are better accounted for by another general medical condition(s) or direct effect of a substance (eg, medication, illicit drug use).
5.	Subjects who have a significant risk of committing violent acts, serious self-harm, or suicide based on history (eg, suicide attempt in the past 1 year) or routine psychiatric status examination, or those who are homicidal or are considered to be a high risk to others, or who have an answer of "yes" on Questions 4 or 5 (current or over the past 1 month) on the suicidal ideation section of the "Since Last Visit" version of the C-SSRS.
Medical History and Concurrent Diseases	
6.	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 if, in the investigator's judgment, the subject is a suitable candidate for the trial.
7.	Subjects with IDDM are excluded. Subjects with non-IDDM may be eligible for the trial if their condition is stable as determined by satisfying **ALL** of the following criteria: • HbA1c < 7.0%, • Screening glucose (non-fasting) < 200 mg/dL. (If the non-fasting glucose is ≥ 200 mg/dL, subjects must be retested in the fasting state. Fasting glucose must be ≤ 125 mg/dL.), • Subject has been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening, • Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, **AND** • Subject's diabetes is not newly diagnosed during screening for the trial.
8.	Subjects with uncontrolled hypertension (DBP > 95 mmHg) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in SBP or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure, **OR** development of symptoms.

Table 3.4.3.1-1 Exclusion Criteria for Rollover Subjects from Trial 331-10-234	
Physical and Laboratory Results	
9.	Subjects with a positive drug screen for cocaine, alcohol, or other drugs of abuse (excluding known prescription stimulants and other prescribed medications and cannabis). Positive results for cannabis, barbiturates, or opiates in the drug screen are not exclusionary if in the investigator's documented opinion the subject does not meet DSM-5 criteria for substance use disorders and in the investigator's documented opinion the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results, and participation is agreed to by the medical monitor prior to treatment.
10.	The following laboratory test and ECG results are exclusionary: 1) Platelets $\leq 75000/mm^3$ 2) Hemoglobin ≤ 11 g/dL 3) Neutrophils, absolute $\leq 1000/mm^3$ 4) WBC count $\leq 2800/mm^3$ 5) AST > 3 × upper limit of normal 6) ALT > 3 × upper limit of normal 7) Creatinine ≥ 2 mg/dL 8) HbA1c ≥ 7.0% 9) CPK > 3 × upper limit of normal 10) Abnormal free T_4 result, unless discussed with and approved by the medical monitor. (Note: Free T_4 is measured only if result for TSH is abnormal.) 11) QTcF or QTcN ≥ 450 msec for males and ≥ 470 for females NOTE: In addition, subjects should be excluded if they have any other abnormal laboratory tests, vital sign results, or ECG findings which in the investigator's judgment is medically significant and would impact the safety of the subject or the interpretation of the trial results. Criteria are provided in Appendix 1, Appendix 2, and Appendix 3 to assist investigators in their assessments of results that may be potentially medically significant, depending on the subject's medical history and clinical presentation. Abnormal results for laboratory parameters, ECG, or vital signs should be repeated 1 time to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. Eligibility should be based on the last available measurement during Trial 331-10-234. The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.
Prohibited Therapies or Medications	
11.	Subjects who would be likely to require prohibited concomitant therapy during the trial including CYP2D6 or CYP3A4 inhibitors or CYP3A4 inducers or who are anticipated to require use of such agents during the trial.
Other	
12.	Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) or involuntarily hospitalized for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.
13.	Inability to tolerate oral medication or swallow tablets.
14.	Any subject who, in the opinion of the investigator, should not participate in the trial.
Added with Amendment 2	
15.	Subject is known to have medication compliance issues that lead to IM depot medication use.
16.	Subjects who report a true allergic response to aripiprazole or brexpiprazole.
17.	Subjects who are known poor metabolizers of CYP2D6 or CYP3A4.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; C-SSRS = Columbia-Suicide Severity Rating Scale; CPK = creatine phosphokinase; DBP = diastolic blood pressure; HbA1c = glycosylated hemoglobin; IDDM = insulin-dependent diabetes mellitus; IM = intramuscular; QTcN = QT interval as corrected for heart rate by the FDA Neuropharm Division formula; QTcF = QT interval as corrected for heart rate by Fridericia's formula; SBP = systolic blood pressure; T_4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell.

Rollover subjects who do not qualify for the open-label trial at the screening/baseline visit may not be rescreened at a later date. If results of clinical laboratory tests from the last visit of the prior double-blind trial (ie, the Week 6 visit of Trial 331-10-234) are not available to assess eligibility, the assessment for the affected criteria should be based on the last available measurement during the double-blind trial. Results from the last visit of the double-blind trial should be reviewed when they become available and action should be taken as described in Section 3.7.3.2 if there are any clinically significant and/or exclusionary values.

3.4.3.2 De Novo Subjects

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3.2-1.

Table 3.4.3.2-1 Exclusion Criteria for De Novo Subjects

Sex and Reproductive Status	
1.	Sexually active males or females who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control patch, birth control depot injection, condom with spermicide, or sponge with spermicide.
2.	Females who are breast-feeding or who have a positive pregnancy test result prior to receiving IMP.
Target Disease	
3.	Subjects with a DSM-5 diagnosis other than schizophrenia that has been the primary focus of treatment within 3 months of screening.
4.	Subjects with a clinical presentation or history that is consistent with delirium, dementia, amnesia, or other cognitive disorders; subjects with psychotic symptoms that are better accounted for by another general medical condition(s) or direct effect of a substance (eg, medication, illicit drug use).
5.	Subjects who have been hospitalized > 21 days for current exacerbation of schizophrenia at the time of the baseline (Day 1) visit of the open-label treatment period.
6.	Subjects with known intellectual disability defined as an intelligence quotient less than 70; or, either clinical evidence or known social or school history indicative of intellectual disability.
7.	Any neurological disorder, with the exception of Tourette's Syndrome.
8.	Subjects who have a significant risk of committing violent acts, serious self-harm, or suicide based on history (eg, suicide attempt in the past 1 year) or routine psychiatric status examination, or those who are homicidal or are considered to be a high risk to others, or who have an answer of "yes" on Questions 4 or 5 (current or over the past 1 month) on the suicidal ideation section of the "Baseline/Screening" version of the C-SSRS.
9.	Subjects experiencing acute depressive symptoms within the past 30 days prior to screening that, according to the investigator's judgment, require treatment with an antidepressant.

Table 3.4.3.2-1 Exclusion Criteria for De Novo Subjects	
10.	The subject is considered treatment resistant to antipsychotic medication, including aripiprazole or brexpiprazole at an adequate dose and duration as confirmed by medical history, investigator judgment, or subject report. Subjects with a history of relapse due to lack of medication compliance or drug abuse can be considered based on investigator judgment.
Medical History and Concurrent Diseases	
11.	Subjects with 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 if, in the investigator's judgment, the subject is a suitable candidate for the trial.
12.	Subjects with IDDM are excluded. Subjects with non-IDDM may be eligible for the trial if their condition is stable as determined by satisfying **ALL** of the following criteria: • HbA1c < 7.0%, • Screening glucose (non-fasting) < 200 mg/dL. (If the non-fasting glucose is ≥ 200 mg/dL, subjects must be retested in the fasting state. Fasting glucose must be ≤ 125 mg/dL.), • Subject has been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening, • Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, **AND** • Subject's diabetes is not newly diagnosed during screening for the trial.
13.	Subjects with uncontrolled hypertension (DBP > 95 mmHg) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in SBP or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure, **OR** development of symptoms.
14.	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.
15.	Subjects who have met DSM-5 criteria for substance use disorder or dependence within the past 180 days; including alcohol and benzodiazepines, but excluding caffeine and nicotine.
Physical and Laboratory Results	
16.	Subjects with a positive drug screen for cocaine, alcohol, or other drugs of abuse (excluding known prescription stimulants and other prescribed medications and cannabis). Positive results for cannabis, barbiturates, or opiates in the drug screen are not exclusionary if in the investigator's documented opinion the subject does not meet DSM-5 criteria for substance use disorders and in the investigator's documented opinion the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results, and participation is agreed to by the medical monitor prior to treatment.

Table 3.4.3.2-1 Exclusion Criteria for De Novo Subjects	
17.	The following laboratory test and ECG results are exclusionary: 1) Platelets ≤ 75000/mm^3 2) Hemoglobin ≤ 11 g/dL 3) Neutrophils, absolute ≤ 1000/mm^3 4) WBC count ≤ 2800/mm^3 5) AST > 3 × upper limit of normal 6) ALT > 3 × upper limit of normal 7) Creatinine ≥ 2 mg/dL 8) HbA1c ≥ 7.0% 9) CPK > 3 × upper limit of normal 10) Abnormal free T_4 result, unless discussed with and approved by the medical monitor. (Note: Free T_4 is measured only if result for TSH is abnormal.) 11) QTcF or QTcN ≥ 450 msec for males and ≥ 470 msec for females NOTE: In addition, subjects should be excluded if they have any other abnormal laboratory tests, vital sign results, or ECG findings which in the investigator's judgment is medically significant and would impact the safety of the subject or the interpretation of the trial results. Criteria are provided to assist investigators in their assessments of results that may be potentially medically relevant, depending on the subject's medical history and clinical presentation. Abnormal results for laboratory parameters, ECGs, or vital signs should be repeated 1 time to ensure reproducibility of the abnormality before excluding a subject based on the criteria noted above. Based on the QTcF or QTcN corrections reported by the central service, a subject will be excluded if either of the corrections equal or exceeds 450 msec for males and 470 msec for female for 2 or more of the 3 time points of the ECGs conducted. If only 1 ECG time point has a corrected QTc of equal to or greater than 450 msec for males or 470 msec for females for either correction factor and it is not reproduced at either of the other 2 time points, the subject meets the inclusion criteria.
Prohibited Therapies or Medications	
18.	Subjects with a history of failure of clozapine treatment or response to clozapine treatment only.
19.	Subjects who, according to the investigator's judgment, will not be able to comply with the washout of psychotropic medications as defined by the protocol.
20.	Subjects who would be likely to require prohibited concomitant therapy during the trial including CYP2D6 or CYP3A4 inhibitors or CYP3A4 inducers or who are anticipated to require use of such agents during the trial.
Allergies and Adverse Drug Reactions	
21.	Subjects with a history of neuroleptic malignant syndrome.
22.	Subjects with a history of true allergic response (ie, not intolerance) to more than one class of medications.
Other	
23.	Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) or involuntarily hospitalized for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.
24.	Inability to tolerate oral medication or swallow tablets.
25.	Any subject who, in the opinion of the investigator, should not participate in the trial.
Added with Amendment 2	
26.	Subject is known to have medication compliance issues that lead to IM depot medication use.
27.	Subjects who report a true allergic response to aripiprazole or brexpiprazole.
28.	Subjects who participated in any clinical trial within the last 30 days prior to screening (not applicable to participation in Trial 331-10-234).

Table 3.4.3.2-1 Exclusion Criteria for De Novo Subjects	
29.	Subjects who are known poor metabolizers of CYP2D6 or CYP3A4.
Added with Amendment 4	
30.	Subjects on IM depot therapy within 5 × half-lives of the medication prior to the baseline (Day 1) visit of the open-label treatment period.

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, de novo subjects excluded for 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 and assent must be signed and a new screening number assigned. If a de novo subject previously participated in Trial 331-10-234, they will retain their subject identification number from Trial 331-10-234.

Subjects who are discontinued from the trial during the conversion period are not eligible to be rescreened.

3.5 Endpoints

3.5.1 Primary Endpoints

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

3.5.2 Secondary Endpoints

3.5.2.1 Secondary Safety Endpoints

The secondary safety endpoints are as follows:

- Mean change from baseline and incidence of clinically significant abnormalities in clinical laboratory tests and urinalysis results (including fasting blood lipids, glucose and insulin, serum prolactin, glycosylated hemoglobin [HbA1c] and creatine phosphokinase [CPK]), vital signs (supine and standing positions), weight, height, body mass index (BMI), waist circumference, and ECG parameters
- Mean change from baseline on the Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), and Barnes Akathisia Rating Scale (BARS)
- Analysis of potential suicide events recorded on the Columbia-Suicide Severity Rating Scale (C SSRS)

- Comprehensive psychotropic side effects as assessed by Udvalg for Kliniske Undersogelser (UKU) side effect rating scale
- The frequency of symptom items for the clinician-administered New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment: (NY-AACENT)
- Baseline and postbaseline Tanner Staging Scale data
- Time to discontinuation due to AE

3.5.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

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

3.6 Measures to Minimize/Avoid Bias

Not applicable; this is an open-label trial.

3.7 Trial Procedures

Trial assessment time points are summarized in Table 3.7-1 (rollover subjects from Trial 331-10-234) and Table 3.7-2 (de novo subjects).

All visits may occur within ± 3 days of the target visit date. Follow-up contact may occur within ± 2 days of the target date.

For scheduling trial visits, a month will be considered as 31 days (± 3 days).

Although there is a ± 3-day visit window during the open-label treatment period, every attempt should be made to track each subject's monthly visits to ensure that the subject's final Month 24 visit meets the protocol's intended treatment duration of 2 calendar years.

Table 3.7-1 Schedule of Assessments - Rollover Subjects from Trial 331-10-234

Assessment	Screening/ Baseline Last visit from Trial 331-10-234/ Baseline for Trial 331-10-236	24-Month Open-label Treatment Period							End of Treatment	Follow-up (clinic visit not required)[b]
		W1, 2, 4 (± 3 days)	M2, 3, 4 (monthly) (± 3 days)	M6 (± 3 days)	M8, 10 (every 2 months) (± 3 days)	M12 (± 3 days)	M15, 18, 21 (every 3 months) (± 3 days)	M5, 7, 9, 11, 13, 14, 16, 17, 19, 20, 22, 23 (± 3 days)[a]	M24 / ET (± 3 days)	21 (± 2) days after last dose of IMP
Informed consent, update medical history, as needed	X									
Prior medications	X									
Entrance criteria	X									
PANSS	X	X W4 only	X	X	X	X	X M18 only		X	
CGI-S and CGI-I	X	X W4 only	X	X	X	X	X M18 only		X	
CGAS	X	X	X	X	X	X	X		X	
SAS, AIMS, & BARS	X	X	X	X	X	X	X		X	
C-SSRS[c]	X	X	X	X	X	X	X		X	
UKU and NY-AACENT	X	X	X	X	X	X	X		X	
Tanner Staging	X			X		X	X M18 only		X	
Physical examination	X			X		X	X M18 only		X	
Body weight and waist circumference	X	X	X	X	X	X	X		X	
Height	X			X		X	X M18 only		X	
Vital signs (supine, sitting, & standing BP, pulse, and body temperature)[d]	X	X	X	X	X	X	X		X	

Table 3.7-1 Schedule of Assessments - Rollover Subjects from Trial 331-10-234

Assessment	Screening/ Baseline Last visit from Trial 331-10-234/ Baseline for Trial 331-10-236	24-Month Open-label Treatment Period							End of Treatment	Follow-up (clinic visit not required)[b]
		W1, 2, 4 (± 3 days)	M2, 3, 4 (monthly) (± 3 days)	M6 (± 3 days)	M8, 10 (every 2 months) (± 3 days)	M12 (± 3 days)	M15, 18, 21 (every 3 months) (± 3 days)	M5, 7, 9, 11, 13, 14, 16, 17, 19, 20, 22, 23 (± 3 days)[a]	M24 / ET (± 3 days)	21 (± 2) days after last dose of IMP
ECG	X	X W4 only		X		X	X M18 only		X	
Clinical laboratory tests (hematology, serum chemistry [including prolactin, HbA1c and TSH], and urinalysis)	X	X W4 only		X		X	X M18 only		X	
Serum pregnancy test	X	X W4 only		X		X	X M18 only		X	
Urine pregnancy test	X	X[e]	X[e]	X	X[e]	X	X[e]			
Urine drug screen	X	X	X	X	X	X	X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Dispense investigational product	X	X	X	X	X	X	X			

BP = blood pressure; ET = early termination; M = month; W = week

[a]Follow-up contact may not be necessary if a subject who early terminated received the last dose of IMP > 21 (± 2) days from the ET visit.

[b]Telephone, Web, or other acceptable means of contact.

[c]"Since Last Visit" version of the C-SSRS will be completed at each visit.

[d]Vital Signs – refers to pulse and heart rate interchangeably throughout the protocol.

[e]If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test if a serum pregnancy test is not being performed during that visit. Additional urine pregnancy testing may be done at the discretion of the investigator.

Table 3.7-2 Schedule of Assessments - De Novo Subjects

Assessment	Screen	Conversion Period[a]		24-Month Open-label Treatment Period								End of Trea-tment[d]	Follow-up (clinic visit not required)[e]
		Base-line	W1, 2, 3 (± 3 days)	Baseline (D1)[b]	W1, 2, 4 (± 3 days)	M2, 3, 4 (monthly) (± 3 days)	M6 (± 3 days)	M8, 10 (every 2 months) (± 3 days)	M12 (± 3 days)	M15, 18, 21 (every 3 months) (± 3 days)	M5, 7, 9, 11, 13, 14, 16, 17, 19, 20, 22, 23 (± 3 days)[c]	M24 / ET (± 3 days)	21 (± 2) days after last dose of IMP
Informed consent, demography, medical history, psychiatric history	X												
K-SADS-PL[f]	X												
Prior medications	X			X									
Entrance criteria	X			X									
PANSS	X			X	X W4 only	X	X	X	X	X M18 only		X	
CGI-S and CGI-I	X[g]			X[g]	X W4 only	X	X	X	X	X M18 only		X	
CGAS	X			X	X	X	X	X	X	X		X	
SAS, AIMS, & BARS	X			X	X	X	X	X	X	X		X	
C-SSRS[h]	X	X	X	X	X	X	X	X	X	X		X	
UKU and NY-AACENT	X			X	X	X	X	X	X	X		X	

Table 3.7-2 Schedule of Assessments - De Novo Subjects

Assessment	Screen	Conversion Period[a]		24-Month Open-label Treatment Period								End of Trea-tment[d]	Follow-up (clinic visit not required)[e]
		Base-line	W1, 2, 3 (± 3 days)	Baseline (D1)[b]	W1, 2, 4 (± 3 days)	M2, 3, 4 (monthly) (± 3 days)	M6 (± 3 days)	M8, 10 (every 2 months) (± 3 days)	M12 (± 3 days)	M15, 18, 21 (every 3 months) (± 3 days)	M5, 7, 9, 11, 13, 14, 16, 17, 19, 20, 22, 23 (± 3 days)[c]	M24 / ET (± 3 days)	21 (± 2) days after last dose of IMP
Tanner staging	X						X		X	X M18 only		X	
Physical examination	X						X		X	X M18 only		X	
Body weight & waist circumference	X		X	X	X	X	X	X	X	X		X	
Height	X			X			X		X	X M18 only		X	
Vital signs (supine, sitting, & standing BP, pulse, and body temperature)[i]	X		X	X	X	X	X	X	X	X		X	
ECG	X			X	X W4 only		X		X	X M18 only		X	

Table 3.7-2 Schedule of Assessments - De Novo Subjects

Assessment	Screen	Conversion Period[a]		24-Month Open-label Treatment Period								End of Trea-tment[d]	Follow-up (clinic visit not required)[e]
		Base-line	W1, 2, 3 (± 3 days)	Baseline (D1)[b]	W1, 2, 4 (± 3 days)	M2, 3, 4 (monthly) (± 3 days)	M6 (± 3 days)	M8, 10 (every 2 months) (± 3 days)	M12 (± 3 days)	M15, 18, 21 (every 3 months) (± 3 days)	M5, 7, 9, 11, 13, 14, 16, 17, 19, 20, 22, 23 (± 3 days)[c]	M24 / ET (± 3 days)	21 (± 2) days after last dose of IMP
Clinical laboratory tests (hematology, serum chemistry [including prolactin, HbA1c and TSH], and urinalysis)	X			X	X W4 only		X		X	X M18 only		X	
Serum pregnancy test	X			X	X W4 only		X		X	X M18 only		X	
Urine pregnancy test	X			X	X[j]	X[j]	X	X[j]	X	X[j]			
Urine drug screen	X		X	X	X	X	X	X	X	X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense investigational product		X	X	X	X	X	X	X	X	X			

[a]The conversion period lasts up to 4 weeks with a ± 3 day window for each weekly visit.

[b]For subjects that participated in the conversion period, the baseline (Day 1) visit of the open-label treatment period will coincide with the end of the conversion period which is up to 4 weeks in duration.

[c]Telephone, Web, or other acceptable means of contact.

[d]If a subject discontinues early before Month 24, either during the conversion period or the open-label treatment period, procedures noted for Month 24 must be completed at the ET visit.

[e]All subjects (completers as well as premature withdrawals from either the conversion period or open-label treatment period) will be followed up either by telephone or other acceptable means of contact. Follow-up contact may not be necessary if a subject who early terminated received the last dose of IMP > 21 (± 2) days from the ET visit.

[f]To be completed only for de novo subjects who did not formerly participate in Trial 331-10-234.

[g]CGI-I **will not** be administered at screening or the baseline (Day 1) visit of the open-label treatment period.

[h]Baseline/Screening" version of the C-SSRS will be completed at screening and the "Since Last Visit" version will be completed at all other in-clinic visits.

[i]Vital Signs – refers to pulse and heart rate interchangeably throughout the protocol.

[j]If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test if a serum pregnancy test is not being performed during that visit. Additional urine pregnancy testing may be done at the discretion of the investigator.

3.7.1 Schedule of Assessments

3.7.1.1 Screening and Baseline

3.7.1.1.1 Rollover Subjects

Screening for rollover subjects occurs simultaneously with baseline at the end-of-treatment visit (Week 6) of Trial 331-10-234 (see Table 3.7-1). Rollover subjects entering from Trial 331-10-234 or their parent/legal guardian must sign the ICF for the open-label trial before any procedures specific to Trial 331-10-236 can be performed. Subjects will retain the same subject identification (Subject ID) number assigned in Trial 331-10-234. Screening/baseline values will be derived from the last visit of the double-blind phase 3 trial (ie, the Week 6 of Trial 331-10-234) for the following assessments: PANSS, CGI-S, CGI-I, CGAS, SAS, AIMS, BARS, C-SSRS, UKU, NY-AACENT, Tanner Staging Scale, physical examination, body weight, height, waist circumference, vital signs, ECG, clinical laboratory tests, urine drug screen, serum pregnancy test, and urine pregnancy test. The only additional procedures to be performed for rollover subjects at screening/baseline of the open-label trial are as follows:

- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- Medical history from Trial 331-10-234 will be retained, but will be updated if necessary.
- Concomitant medications will be reviewed to assure that the subject is not receiving any prohibited medications.
- AE recording will begin with the signing of the ICF for Trial 331-10-236.
- The IMP will be dispensed to the subject.

3.7.1.1.2 De Novo Subjects

De novo subjects, whether or not they participated in Trial 331-10-234 must attend separate screening and baseline visits to allow for completion of eligibility assessments and washout of prohibited concomitant medications, if applicable.

3.7.1.1.2.1 Screening

For de novo subjects, the screening period begins after written informed consent and assent have been obtained and will take place between Day −28 and Day −1 prior to enrollment. 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 the first dose. The sponsor reserves the right to utilize external quality oversight methods to ensure the validity of diagnosis, severity of illness, and other factors determining appropriateness of subject selection. After a subject has been told that a reliable informant may accompany the subject at all visits, the subject's parent/legal guardian has provided informed consent, and the subject has provided assent, a screening number will be provided. If a de novo subject previously participated in Trial 331-10-234, they will retain their subject identification number from Trial 331-10-234. 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 following approval by the medical monitor. Screening evaluations will include the following:

- Trial personnel will enter subject data into eSource to register all trial visits (initial screening visit only).
- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- Demographic data will be recorded.
- Medical and psychiatric history will be recorded, including the DSM-5 diagnosis of schizophrenia that will be made by an adequately trained clinician.
- Previous medications taken within 30 days of screening will be recorded. Lifetime antipsychotic use will be recorded. Washout from prohibited concomitant medications will begin, if applicable (see Table 4.1-1).
- Diagnosis of schizophrenia will be confirmed by the K-SADS-PL, performed by an adequately trained rater (to be completed only for de novo subjects who did not formerly participate in Trial 331-10-234).
- A qualified and certified rater will administer the PANSS.
- A qualified rater will administer the CGI-S.
- A qualified rater will administer the CGAS.
- The investigator (or qualified designee) will complete the "Baseline/Screening" C-SSRS form.
- The investigator (or qualified designee) will administer the SAS, AIMS, and BARS.
- The investigator (or qualified designee) will administer the UKU and NY-AACENT.

- The investigator (or qualified designee) will complete Tanner Staging Scale assessment.
  Note: The collection of Tanner Staging Scale data is required for this trial, and every attempt should be made to collect this information. Tanner Staging must be completed together with the physical exam in the most inconspicuous manner as possible for the subject. Tanner Staging could be completed by trial psychiatrist, trial-affiliated pediatrician, nurse-practitioner, or nurse (in case of countries or states where nurses are qualified to perform a complete physical examination). When Tanner Staging is not completed at a required visit, it should be collected at the next trial visit. A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging. Any psychiatrist who will perform the Tanner Staging evaluation will be trained and required to demonstrate inter-rater reliability before receiving certification to conduct the evaluation. A family practitioner or pediatrician who are investigators are considered trained and do not need to go through formal inter-rater reliability. Sites should make attempts to have examiners of both gender types. Attempts should be made to have examination performed by the same gender as the subject. Otherwise, a trial-affiliated personnel of the same gender (ie, nurse) as the subject should be in the same examination room as the subject.
- A physical examination will be performed.
- Body weight, height, and waist circumference will be recorded.
- Vital sign measurements (including blood pressure, pulse, and body temperature) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. See Table 3.4.3.2-1 for exclusions based on outcome of screening vital sign measurements. Vital signs are to be completed before any blood is drawn.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. Subjects with screening QT interval corrected for heart rate by Fridericia's formula (QTcF) or QT interval corrected for heart rate by the FDA Neuropharm Division formula (QTcN) $\geq$ 450 msec for males and $\geq$ 470 msec for females per the central reader's report will be excluded from the trial (see Table 3.4.3.2-1 and Section 3.7.3.4). The ECG is to be completed before any blood is drawn.
- Blood samples will be collected for clinical laboratory tests, including hematology and serum chemistry (with prolactin, glycosylated hemoglobin [HbA1c], and thyroid-stimulating hormone [TSH and free thyroxine [T_4]). Blood will be drawn after a minimum 8-hour fast, if at all possible (see Section 3.7.3.2). See Table 3.4.3.2-1 for exclusions based on outcome of screening clinical laboratory tests. Vital sign and ECG assessments should be completed before any blood samples are collected.
- A serum pregnancy test will be performed for all females. Subjects with a positive serum test result will be excluded from the trial.

- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse. See Table 3.4.3.2-1 for exclusions based on outcome of urine drug screen(s). A urine pregnancy test will be performed for all females.
- AEs and concomitant medications will be recorded beginning with the signing of the ICF.

3.7.1.1.2.2 Conversion Period

If the washout of prohibited medications prior to the baseline (Day 1) visit of the open-label treatment period is not appropriate for any de novo subject, in the opinion of the investigator, the subject must undergo cross-titration to oral brexpiprazole for 1 to 4 weeks during the conversion period, as described in Section 3.2.2.1. Visits will occur at the end of each week during the conversion period. The goal of de novo subjects during the conversion period is to achieve a brexpiprazole monotherapy target starting dose of 1, 2, or 3 mg daily at any time after Week 1 per the investigator's discretion and to achieve the required washout of prohibited medications as per Table 4.1-1. The subject will proceed to the baseline (Day 1) visit of the open-label treatment period once the target starting dose has been achieved and the required washout of prohibited medications has been completed.

All subjects will be assessed weekly at scheduled visits during the conversion period. The following evaluations will be performed at the baseline visit of the conversion period:

- The "Since Last Visit" version of the C-SSRS form will be completed.
- AEs and concomitant medications will be recorded.
- The IMP will be dispensed to the subject.

The following evaluations will be performed at each visit (ie, Week 1, 2, and 3):

- The "Since Last Visit" version of the C-SSRS form will be completed at Weeks 1, 2, and 3 visit.
- Body weight and waist circumference will be recorded.
- Vital sign measurements (including blood pressure, pulse, and body temperature) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.

- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse.
- AEs and concomitant medications will be recorded.
- The IMP will be dispensed to the subject.

If a subject discontinues prematurely before the end of the conversion period, all procedures for the Month 24/ET visit must be completed at the ET visit.

3.7.1.1.2.3 Baseline (Open-label Treatment Period)

If the subject is found to be eligible for the trial during the screening/conversion period, the subject will attend a baseline (Day 1) visit for the open-label treatment period. For subjects that participated in the conversion period, the baseline (Day 1) visit of the open-label treatment period will coincide with the end of the conversion period which is up to 4 weeks in duration. The following procedures will be completed during the baseline (Day 1) visit of the open-label treatment period, prior to the subject starting open-label IMP:

- Inclusion/exclusion criteria will be reviewed.
- Prior medications will be reviewed.
- A qualified and certified rater will administer the PANSS.
- A qualified rater will administer the CGI-S.
- A qualified rater will administer the CGAS.
- The investigator (or qualified designee) will administer the SAS, AIMS, and BARS.
- The investigator (or qualified designee) will complete the “Since Last Visit” version of the C-SSRS form.
- The investigator (or qualified designee) will administer the UKU and NY-AACENT.
- Body weight, height, and waist circumference will be recorded.
- Vital sign measurements (including blood pressure, pulse and body temperature) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.
- Blood samples will be collected for clinical laboratory tests (hematology and serum chemistry [including prolactin, HbA1c, and TSH]) after a minimum 8-hour fast. Vital sign and ECG assessments should be completed before any blood samples are collected.

- A standard 12-lead ECG will be performed predose after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.
- Urine will be collected for urinalysis and from all potential subjects for urine screen(s) for drugs of abuse.
- A urine pregnancy test will be performed predose for all females. The result must be negative prior to dosing.
- A serum pregnancy test will be collected for all females.
- AEs and concomitant medications will be recorded.
- If the subject remains eligible for the trial after completion of the baseline evaluations, trial personnel will use eSource to obtain an IMP assignment. The subject will receive the first dose of IMP from the assigned bottle, and the date and time of the first dose will be recorded in eSource.
- The IMP will be dispensed to the subject.

3.7.1.2 Open-label Treatment

All subjects will be assessed at various scheduled clinic visits as described below. A number of visits will be conducted via telephone, the Internet, or other acceptable means of contact, and are presented in Section 3.7.1.2.7.

3.7.1.2.1 Weeks 1, 2, and 4

The following evaluations will be performed at Weeks 1, 2, and 4 visits:

- A qualified rater will administer the CGAS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- The investigator (or qualified designee) will administer the SAS, AIMS, and BARS.
- The investigator (or qualified designee) will administer the UKU and NY-AACENT.
- Body weight and waist circumference will be recorded.
- Vital sign measurements (including blood pressure, pulse, and body temperature) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.
- Urine will be collected from all potential subjects for urine screen(s) for drugs of abuse. Urinalysis will be performed at Week 4.

- A urine pregnancy test will be performed for all females. The result must be negative prior to dosing. If the urine pregnancy test is positive at Weeks 1 or 2, the result should be confirmed with a serum pregnancy test if a serum pregnancy test is not being performed during that visit. Additional urine pregnancy testing may be done at the discretion of the investigator.
- AEs and concomitant medications will be recorded.
- A qualified and certified rater will administer the PANSS (Week 4 only).
- A qualified rater will administer the CGI-S and CGI-I (Week 4 only).
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn (Week 4 only).
- Blood samples will be collected for clinical laboratory tests, including hematology and serum chemistry (with prolactin, HbA1c, and TSH]). Blood will be drawn after a minimum 8-hour fast, if at all possible (see Section 3.7.3.2). See Table 3.4.3.2-1 for exclusions based on outcome of screening clinical laboratory tests (Week 4 only).
- A serum pregnancy test will be performed for all females. Subjects with a positive serum test result will be excluded from the trial (Week 4 only).
- The IMP will be dispensed to the subject.

3.7.1.2.2 Months 2, 3, and 4

The following evaluations will be performed at the Month 2, 3, and 4 visits:

- A qualified and certified rater will administer the PANSS.
- A qualified rater will administer the CGI-S and CGI-I.
- A qualified rater will administer the CGAS.
- The investigator (or qualified designee) will complete the “Since Last Visit” C-SSRS form.
- The investigator (or qualified designee) will administer the SAS, AIMS, and BARS.
- The investigator (or qualified designee) will administer the UKU and NY-AACENT.
- Body weight and waist circumference will be recorded.
- Vital sign measurements (including blood pressure, pulse, and body temperature) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.
- Urine will be collected from all potential subjects for urine screen(s) for drugs of abuse.

- A urine pregnancy test will be performed for all females. The result must be negative prior to dosing. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test, if a serum pregnancy test is not being performed during that visit. Additional urine pregnancy testing may be done at the discretion of the investigator.
- AEs and concomitant medications will be recorded.
- The IMP will be dispensed to the subject.

3.7.1.2.3 Month 6

The following evaluations will be performed at the Month 6 visit:

- A qualified and certified rater will administer the PANSS.
- A qualified rater will administer the CGI-S and CGI-I.
- A qualified rater will administer the CGAS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- The investigator (or qualified designee) will administer the SAS, AIMS, and BARS.
- The investigator (or qualified designee) will administer the UKU and NY-AACENT.
- Body weight, height, and waist circumference will be recorded.
- Vital sign measurements (including blood pressure, pulse, and body temperature) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.
- Urine will be collected from all potential subjects for urine screen(s) for drugs of abuse. Urinalysis will be performed.
- A urine pregnancy test will be performed for all females. The result must be negative prior to dosing. Additional urine pregnancy testing may be done at the discretion of the investigator.
- AEs and concomitant medications will be recorded.
- The investigator (or qualified designee) will complete the Tanner Staging Scale assessment.
- A physical examination will be performed.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.

- Blood samples will be collected for clinical laboratory tests, including hematology and serum chemistry (with prolactin, HbA1c, and TSH). Blood will be drawn after a minimum 8-hour fast, if at all possible (see Section 3.7.3.2).
- A serum pregnancy test will be performed for all females. Subjects with a positive serum test result will be discontinued from the trial.
- The IMP will be dispensed to the subject.

3.7.1.2.4 Months 8 and 10

The following evaluations will be performed at the Month 8 and 10 visits:

- A qualified and certified rater will administer the PANSS.
- A qualified rater will administer the CGI-S and CGI-I.
- A qualified rater will administer the CGAS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- The investigator (or qualified designee) will administer the SAS, AIMS, and BARS.
- The investigator (or qualified designee) will administer the UKU and NY-AACENT.
- Body weight and waist circumference will be recorded.
- Vital sign measurements (including blood pressure, pulse, and body temperature) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.
- Urine will be collected from all potential subjects for urine screen(s) for drugs of abuse.
- A urine pregnancy test will be performed for all females. The result must be negative prior to dosing. If the urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test if a serum pregnancy test is not being performed during that visit. Additional urine pregnancy testing may be done at the discretion of the investigator.
- AEs and concomitant medications will be recorded.
- The IMP will be dispensed to the subject.

3.7.1.2.5 Month 12

The following activities and assessments will occur at Month 12 visit:

- A qualified and certified rater will administer the PANSS.
- A qualified rater will administer the CGI-S and CGI-I.
- A qualified rater will administer the CGAS.

- The investigator (or qualified designee) will administer the SAS, AIMS, and BARS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- The investigator (or qualified designee) will administer the UKU and NY-AACENT.
- Body weight, height, and waist circumference will be recorded.
- The investigator (or qualified designee) will complete Tanner staging assessment.
- A physical examination will be performed.
- Vital sign measurements (including blood pressure, pulse, and body temperature) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.
- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse.
- Blood samples will be collected for clinical laboratory tests (hematology and serum chemistry [including prolactin, HbA1c, and TSH]) after a minimum 8-hour fast. Vital sign and ECG assessments should be completed before any blood samples are collected.
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.
- A serum pregnancy test will be performed for all females. Subjects with a positive serum test result will be discontinued from the trial.
- A urine pregnancy test will be performed predose for all females. The result must be negative prior to dosing. Additional urine pregnancy testing may be done at the discretion of the investigator.
- AEs and concomitant medications will be recorded.
- The IMP will be dispensed to the subject.

3.7.1.2.6 Months 15, 18, and 21

The following evaluations will be performed at the Month 15, 18, and 21 visits:

- A qualified and certified rater will administer the CGAS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- The investigator (or qualified designee) will administer the SAS, AIMS, and BARS.

- The investigator (or qualified designee) will administer the UKU and NY-AACENT.
- Body weight and waist circumference will be recorded.
- Vital sign measurements (including blood pressure, pulse, and body temperature) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.
- Urine will be collected from all potential subjects for urine screen(s) for drugs of abuse. Urinalysis will be performed at Month 18 only.
- A urine pregnancy test will be performed for all females. The result must be negative prior to dosing. If the urine pregnancy test is positive at Months 15 or 21, the result should be confirmed with a serum pregnancy test if a serum pregnancy test is not being performed during that visit. Additional urine pregnancy testing may be done at the discretion of the investigator.
- AEs and concomitant medications will be recorded.
- A qualified and certified rater will administer the PANSS (Month 18 only).
- A qualified rater will administer the CGI-S and CGI-I (Month 18 only).
- The investigator (or qualified designee) will complete Tanner Staging Scale assessment. (Month 18 only)
- A physical examination will be performed (Month 18 only).
- Height will be measured (Month 18 only).
- A standard 12-lead ECG will be performed after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn (Month 18 only).
- Blood samples will be collected for clinical laboratory tests, including hematology and serum chemistry (with prolactin, HbA1c, and TSH). Blood will be drawn after a minimum 8-hour fast, if at all possible (see Section 3.7.3.2). See Table 3.4.3.2-1 for exclusions based on outcome of screening clinical laboratory tests. Vital sign and ECG assessments should be completed before any blood samples are collected (Month 18 only).
- A serum pregnancy test will be performed for all females. Subjects with a positive serum test result will be discontinued from the trial (Month 18 only).
- The IMP will be dispensed to the subject.

3.7.1.2.7 Months 5, 7, 9, 11, 13, 14, 16, 17, 19, 20, 22, and 23

Visits for Months 5, 7, 9, 11, 13, 14, 16, 17, 19, 20, 22, and 23, will be conducted via telephone, the Internet, or other acceptable means of contact. The following activities and assessments will occur for all subjects:

- AEs and concomitant medications will be recorded.

3.7.1.2.8 Month 24/Early Termination (End of Treatment)

The treatment period for the entire trial will conclude at the Month 24 visit. If a subject discontinues early before Month 24, either during the conversion period or the open-label treatment period, procedures noted for Month 24 must be completed at the ET visit. Attempts should be made to complete all evaluations for the Month 24 visit prior to the administration of any new psychotropic medications. The following activities and assessments will occur at Month 24/ET:

- Trial personnel will register completion or discontinuation from the trial in eSource.
- A qualified and certified rater will administer the PANSS.
- A qualified rater will administer the CGI-S and CGI-I.
- A qualified rater will administer the CGAS.
- The investigator (or qualified designee) will administer the SAS, AIMS, and BARS.
- The investigator (or qualified designee) will complete the "Since Last Visit" C-SSRS form.
- The investigator (or qualified designee) will administer the UKU and NY-AACENT.
- Body weight, height, and waist circumference will be recorded.
- The investigator (or qualified designee) will complete Tanner staging assessment.
- A physical examination will be performed.
- Vital sign measurements (including blood pressure, pulse, and body temperature) will be recorded. Blood pressure and pulse are to be measured in the following order: supine, sitting, and standing after the subject has been in each position at least 3 minutes. Vital signs are to be completed before any blood is drawn.
- A standard 12-lead ECG will be performed postdose after the subject has been supine and at rest for at least 5 minutes. The ECG is to be completed before any blood is drawn.

- Blood samples will be collected for clinical laboratory tests (hematology and serum chemistry [including adrenocorticotropic hormone (ACTH), cortisol, prolactin, HbA1c, and TSH]) after a minimum 8-hour fast. Vital sign and ECG assessments should be completed before any blood samples are collected.
- A serum pregnancy test will be performed for all females.
- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse.
- AEs and concomitant medications will be recorded.

3.7.1.3 Follow-up

All subjects (rollover and de novo completers as well as premature withdrawals from either the conversion period or open-label treatment period) will be followed up either by 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 Positive and Negative Syndrome Scale

The PANSS[15] consists of 3 subscales containing a total of 30 symptom constructs. For each symptom construct, severity is rated on a 7-point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extremely severe symptoms. The symptom constructs for each subscale are as follows:

1) Positive Subscale (7 positive symptom constructs: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility),
2) Negative Subscale (7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and conversation flow, stereotyped thinking), and
3) General Psychopathology Subscale (16 symptom constructs: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance).

A copy of the PANSS is provided in Appendix 5.

3.7.2.2 Children's Global Assessment Scale

The CGAS is a 100-point rating scale measuring psychological, social and school functioning for children aged 6-17.[16] It was adapted from the Adult Global Assessment Scale (GAS). The GAS is a rating scale for evaluating the overall functioning of a subject during a specified time period on a continuum from psychological or psychiatric sickness to health. The CGAS is a valid and reliable tool for rating a child's general level of functioning on a health-illness continuum. The CGAS was developed by Schaffer and colleagues to provide a global measure of severity of disturbance in children and adolescent. Notation in the subject's trial records should substantiate the ratings. A copy of the CGAS is provided in Appendix 6.

3.7.2.3 Clinical Global Impression - Severity of Illness Scale

The severity of illness for each subject will be rated using the CGI-S.[17] To perform this assessment, the rater or investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Response choices include: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients. A sample of the CGI-S is provided in Appendix 7.

3.7.2.4 Clinical Global Impression - Improvement Scale

The efficacy of IMP will be rated for each subject using the CGI-I.[17] The rater or investigator will rate the subject's total improvement whether or not it is due entirely to drug treatment. All responses will be compared to the subject's condition at baseline prior to the first dose of double-blind IMP. Response choices include: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. A sample of the CGI-I is provided in Appendix 8.

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 (rollover subjects from Trial 331-10-234) and Table 3.7-2 (de novo subjects). 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 must be fasting for a minimum of 8 hours prior to blood draws for screening laboratory assessments, if at all possible. If fasting blood samples are not feasible at screening, nonfasting blood samples may be obtained initially for determining eligibility for the trial. 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. The central laboratory will provide laboratory results to the sponsor electronically.

Table 3.7.3.2-1 Clinical Laboratory Assessments	
Hematology: Hematocrit Hemoglobin MCHC MCV Platelets RBC count WBC count with differential Urinalysis: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high powered field pH Protein Specific gravity	Serum Chemistry: ALP ALT AST Bilirubin, total BUN Calcium Chloride Cholesterol (total, LDL and HDL) CPK Creatinine GGT Glucose LDH Potassium Protein, total Sodium Triglycerides Uric acid Additional Tests: Urine or serum pregnancy for all females TSH, with reflex to free T_4 if TSH is abnormal ACTH Cortisol HbA1c Prolactin

BUN = blood urea nitrogen; GGT = gamma glutamyl transferase; HDL = high-density lipoprotein; LDH = lactic dehydrogenase; LDL = low-density lipoprotein; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell

No more than 16.5 mL of blood will be taken at any given visit designated in Table 3.7-1 and Table 3.7-2 for the purposes of clinical laboratory assessments, analyses, or pregnancy tests.

A pregnancy test will be conducted in all females prior to trial intervention; results must be available prior to the administration of the IMP. Subjects with a positive serum test result at screening will be excluded from the trial. A urine pregnancy test will be conducted per the schedule of assessments (Table 3.7-1 for rollover subjects and Table 3.7-2 for de novo subjects). The urine pregnancy test must be negative prior to dosing on Day 1. The frequency of pregnancy tests may be modified based on local regulatory requirements. Additional urine or serum pregnancy testing may be done at the discretion of the investigator.

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 $\leq 75000/mm^3$
2) Hemoglobin ≤ 11 g/dL
3) Neutrophils, absolute $\leq 1000/mm^3$
4) WBC count $\leq 2800/mm^3$
5) Aspartate aminotransferase (AST) > 3 × the upper limit of normal (ULN)
6) Alanine aminotransferase (ALT) > 3 × the ULN
7) Creatinine ≥ 2 mg/dL
8) HbA1c ≥ 7.0%
9) CPK > 3 × ULN
10) Abnormal free T_4 unless discussed with and approved by medical monitor. (Note: Free T_4 is measured only if result for TSH is abnormal.)
11) QTcF or QTcN ≥ 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.

3.7.3.3 Physical Examination and Vital Signs

3.7.3.3.1 Physical Examination

The physical examination will consist of measurement of height and a review of the following body systems: head, ears, eyes, nose, and throat; thorax; abdomen; urogenital; extremities; neurological; and skin and mucosae. 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 FDA Form 1572. 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.

A complete physical examination is an integral part of study 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 baseline urogenital exam is required which could have been performed up to 1 calendar year prior to the date of ICF being signed, or can be performed during the screening period. Additionally, at the Trial 331-10-236 rollover screen baseline visit, the information will have been collected as part of the Trial 331-10-234 Week 6 visit. 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 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.[18]

3.7.3.3.2 Vital Signs

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

Blood pressure and heart rate measurements will be made in the supine, sitting, 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 sitting, and finally standing. Vital signs scheduled at the same visit as blood samples are to be completed before blood is drawn.

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. 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

Twelve-lead ECG recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead ECGs may be obtained per the investigator's discretion and should always be obtained in the event of an early termination. A central ECG service will be utilized for reading all ECGs in order to standardize interpretations for the safety analysis. In addition, ECG results will be evaluated at the investigational site to monitor safety during the trial. The principal investigator or qualified designee will review each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECGs should be repeated 1 time if a result is considered to be clinically significant.

A screening ECG finding of QTcF or QTcN ≥ 450 msec for males and ≥ 470 msec for females based on the results from the central reader is exclusionary (see Table 3.4.3.1-1 for rollover subjects and Table 3.4.3.2-1for de novo subjects). 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. For both rollover subjects from Trial 331-10-234 and de novo subjects, central reader results for verification of exclusion criteria at baseline visit will not be available prior to dosing; therefore, subjects will be enrolled based on screening ECG results from the central reader and baseline ECG results from the trial site. However, if the baseline ECG results from the central reader, when available, indicate a QTcF or QTcN ≥ 450 msec for males and ≥ 470 msec for females at baseline, 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), C-SSRS, UKU, NY-AACENT, and Tanner Staging Scale assessment. 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[19] (Appendix 9) 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 12 hours of scale administration (see Section 4). Investigators are encouraged to delay scale administration until 12 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[17] assessment (Appendix 10) 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 12 hours of scale administration (see Section 4). Investigators are encouraged to delay scale administration until 12 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[20] (Appendix 11) 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 12 hours of scale administration (see Section 4). Investigators are encouraged to delay scale administration until 12 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 Udvalg for Kliniske Undersogelser

The UKU scale has been included in this trial to satisfy regulatory authorities. The UKU is used to assess side effects of subjects being treated with antipsychotic drugs and to determine whether there is a causal relationship. A copy of the UKU is provided in Appendix 12.

3.7.3.5.5 New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment

The NY-AACENT is not a validated scale. It has been included in this trial to satisfy regulatory authorities. No validated scale addressing these issues is currently available.

The NY-AACENT is used to detect changes in cognitive function subsequent to pharmacological or similar treatments for neurological or psychiatric problems. It is specifically designed to be used in pediatric populations (ages 12-17 years), but can be utilized with other age groups as appropriate. The clinician-administered NY-AACENT will be completed per the schedule of assessments (Table 3.7-1 for rollover subjects and Table 3.7-2 for de novo subjects).

The clinician form is attached in Appendix 13.

3.7.3.5.6 Tanner Staging Scale

The collection of Tanner Staging data is required for this trial, and every attempt should be made to collect this information. Tanner Staging must be completed together with the physical examination by the same trial-affiliated clinician in the most inconspicuous manner for the subject as possible. Tanner Staging could be completed by trial psychiatrist, trial-affiliated pediatrician or family practitioner (additionally physician's assistant or nurse-practitioner in the US). When Tanner Staging is not completed at a required visit, it should be performed at the next trial visit.

Tanner Staging will be recorded at the visits specified in Table 3.7-1 for rollover subjects and Table 3.7-2 for de novo subjects. The Tanner Staging Scale assessment consists of 2 domains (pubic hair and breast development) for girls and 3 domains (pubic hair, penis development, and testes development) for boys. The Tanner Staging Scale assessment as a reference for the completing clinician is included in Appendix 14. A subject who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner Staging. The clinician will arrive at a single score summarizing the domains (not individual domain scores) when evaluating the subject.

Any psychiatrist who will perform the Tanner Staging Scale evaluation will be trained and required to demonstrate inter-rater reliability before receiving certification to conduct the evaluation. A family practitioner or pediatrician who are investigators are considered trained and do not need to go through formal inter-rater reliability. Sites should make attempts to have examiners of both gender types. Attempts should be made to have examination performed by the same gender as the subject. Otherwise, trial-affiliated personnel of the same gender as the subject (ie, nurse) should be in the same examination room as the subject.

3.7.3.5.7 Suicidality

Suicidality will be monitored during the trial using the Columbia-Suicide Severity Rating Scale (C-SSRS). This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events or ideation within a specified time period prior to entry into the trial, will be completed for all de novo subjects at the screening visit to determine the eligibility (prior to the first dose of open-label brexpiprazole). Any subject with active suicidal ideation within the last 30 days, 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 (see Table 3.4.3.1-1 for rollover subjects and Table 3.4.3.2-1 for de novo subjects). The "Since Last Visit" C-SSRS form will be completed at all other in-clinic visits for all subjects (rollover and de novo). Copies of the C-SSRS forms are provided in Appendix 15.

3.7.4 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 page for the last subject completing or withdrawing from the trial.

3.7.5 Independent Data Monitoring Committee

A data monitoring committee (DMC) will provide oversight for safety monitoring. The details of the DMC structure and its roles and responsibilities will be documented in a DMC charter.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

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 sponsor at the earliest possible time by telephone. The sponsor should be notified when there is a planned or inadvertent treatment interruption of 4 days or more in a 7-day period. 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. 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 starting open-label IMP, 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 TEAE
  - Clinical worsening, suicidality, and unusual changes in behavior, and the risk of increased suicidality
- Death
- Reasons unrelated to medical condition (provide detail and review AE history with subject)
- Withdrawal of informed consent
- 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.

3.8.3.4 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects' parents or legal guardians can also withdraw their consent to allow subjects to continue participation in the trial. Subjects or parents/legal guardians cannot withdraw consent 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 provides their written withdrawal of consent 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 requires a subject's refusal of ALL of the following methods of follow-up:

- 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 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. 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 may initially express their desire to interrupt or discontinue IMP administration (see Section 3.8.3.1), which is not equivalent to a complete withdrawal of consent 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 or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent 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.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not started on brexpiprazole treatment. For the purposes of this trial, treatment begins with the first dose of oral brexpiprazole during the conversion period or open-label treatment period.

Subjects who fail to qualify for the trial during screening for a reason other than a positive screen for drugs of abuse may be eligible to be rescreened one additional time at a later date. The medical monitor must be contacted before the rescreening of any de novo subject. In the event that a de novo subject is rescreened for trial participation, a

new ICF must be signed and a new screening number assigned. If a de novo subject previously participated in Trial 331-10-234, they will retain their subject identification number from Trial 331-10-234.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and 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 Month 24 will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Month 24 during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent 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 (open-label brexpiprazole) to subjects. Accountability and compliance verification should be documented in the subject's trial records. Subjects 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

This trial is intended to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent 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 (or designee) 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.

4 Restrictions

4.1 Prohibited Medications

All subjects must agree to abstain from prohibited medications during the trial. Prohibited medications for de novo subjects are listed in Table 4.1-1. Other therapies prohibited prior to enrollment and during the trial are presented in Section 4.2.

Table 4.1-1 Washout of Prohibited Medications Required Before the Trial - De Novo Subjects	
Medication	**Required Washout Prior to Open-label Treatment Period**
Antipsychotics Oral aripiprazole Oral antipsychotics (other than cariprazine and clozapine) Depot or long-acting injectable antipsychotics Cariprazine (Vraylar) and clozapine	 14 days 7 days 5 × half-lives of the medication 6 months
Antidepressants Fluoxetine or Symbyax MAOIs Citalopram and escitalopram Venlafaxine and desvenlafaxine All other antidepressants	 28 days[a] 14 days 8 days 3 days 14 days
Atomoxetine Stimulants	28 days with the diagnosis of ADHD; 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[b] Lorazepam, oxazepam, diazepam, or clonazepam Other benzodiazepines	 12 hours before scales[c] 14 days
CYP2D6 inhibitors and CYP3A4 inhibitors and inducers (see Table 4.1-4)	14 days

MAOIs = monoamine oxidase inhibitors.

[a]Extension to the screening window is needed for washout, contact the medical director.

[b]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 (see Table 4.1-3).

[c]Benzodiazepines must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety 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.

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

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 or fluoxetine d) Mood stabilizers (ie, lithium or anticonvulsants) e) Benzodiazepines, except specific benzodiazepines when used as rescue therapy[a] f) Stimulants[b] g) Other psychotropics (ie, atomoxetine)
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]Only for de novo subjects: Stimulants with the diagnosis of ADHD and treatment with stimulants within 28 days prior to screening; otherwise washout of > 5× half-life for subjects without diagnosis of ADHD.

[c]Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted 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. Non-benzodiazepine sleep aids must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety 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 on the 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.

Table 4.1-3 Oral Benzodiazepine Rescue Therapy During the Trial	
Oral Benzodiazepine	**Maximum Allowable Dose (mg/day)**
	Screening to Month 24 Visit
Lorazepam[a]	3
Oxazepam[a]	45
Diazepam[a,b]	15
Clonazepam[a,b]	1.5

[a]Benzodiazepines must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety 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 or oral clonazepam may be acceptable if prior authorization is obtained from the medical monitor.

Table 4.1-4 below provides a select list of CYP2D6 inhibitors and CYP3A4 inhibitors and inducers which are prohibited within 14 days of first dose of IMP and for the duration of the trial. Except for episodic use of ibuprofen, acetaminophen/paracetamol, naproxen, or equivalent, clinical sites must apprise the medical monitor of the use of all over-the-counter medications including supplements and vitamins. Any medication needing to be used in a chronic manner requires discussion with the medical monitor.

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

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	

4.2 Other Restrictions

4.2.1 Restricted Therapies and Precautions

Any history of electroconvulsive therapy is exclusionary.

Use of intramuscular (IM) benzodiazepines is prohibited throughout the trial. Short-term use of specific oral benzodiazepines is allowed during the trial for the control of agitation or insomnia as shown in Table 4.1-3. Short-acting benzodiazepines (ie, lorazepam or oxazepam) are to be used whenever possible. In countries or institutions where no short-acting benzodiazepines are commercially available, use of oral diazepam or oral clonazepam may be acceptable if prior authorization is obtained from the medical monitor. The investigator should contact the medical monitor to discuss any subject who requires frequent use of a benzodiazepine for agitation or insomnia beyond the first 2 weeks of the trial.

Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted 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 1 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.

Anticholinergics are permitted for the treatment of EPS up to a maximum of 4 mg/day benztropine or its equivalent and propranolol is permitted for akathisia or tremor up to a maximum of 60 mg/day. Subjects receiving a stable dose of propranolol for other conditions at entry into Trial 331-10-236 may remain on propranolol. Trial sites should only utilize medications that are approved for these indications in their respective countries.

Benzodiazepines, non-benzodiazepine sleep aids, anticholinergics, and propranolol must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying administration of efficacy and safety scales is not feasible, the scales 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 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.

4.2.2 Non-therapy Precautions and Restrictions

4.2.2.1 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.

4.2.2.2 Restrictions

With the exception of inpatient group therapy and outpatient group therapy, new-onset psychotherapy is prohibited during the trial. In other words, except for inpatient and outpatient group therapies, subjects may only receive psychotherapy (eg, individual, group, marriage, or family therapy) if they have been participating in the therapy regularly (ie, weekly) for at least 6 weeks (42 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.

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 Trial 331-10-234 End of Treatment or 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 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.

A serious adverse event (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 inpatient 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.

If a subject is experiencing an EPS, the specific EPS must be indicated on the AE page of the eSource. Examples of AEs that are considered EPS include, but are not limited to: generalized rigidity, hyperkinesia, bradykinesia, akinesia, dystonia, hypertonia, akathisia, tremor, flexed posture, involuntary muscle contractions, athetosis, and chorea. If a subject is experiencing 2 or more of these symptoms, whether or not treatment with an anticholinergic is required, this is considered as extrapyramidal syndrome and must be entered as "extrapyramidal syndrome" on the AE page of the eSource instead of the individual symptoms. Permitted treatments for EPS are described in Section 4.2.1.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity cases (any increase of AST or ALT ≥ 3 times the upper normal limit or screening value with an increase in total bilirubin ≥ 2 times the upper normal limit or screening value)
- Pregnancies are also defined as 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 CRF 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, 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 CRF. The intensity of an adverse experience 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 CRFs provided by the sponsor. Adverse event collection is to begin after a subject has signed the ICF.

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. A reported AE that undergoes a change in severity, seriousness, or toxicity should be reported as a new AE on the eSource.

Note: Normal pregnancy is not an AE and should not be recorded on the eSource; guidelines outlined in Section 5.5 should be followed for pregnancy reporting.

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 screen in 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 AST or ALT that is ≥ 3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE on the eSource.

5.5 Pregnancy

For females and for men who are sexually active, there must be a documented agreement that the subject and 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. Unless the subject is sterile (ie, females who have had a bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, birth control patch, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

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

- General information
- Informed consent 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, females must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form stating that the above-mentioned risk factors and the consequences were discussed with her.

A urine or serum pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening on all females. If a urine test is performed and is positive, the investigator will follow up with a confirmatory serum test.

During the trial, all females 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. Local regulatory requirements must be followed for follow-up and reporting on pregnancy cases and infants.

5.6 Procedure for Breaking the Blind

Not applicable; this is an open-label trial.

5.7 Follow-up of Adverse Events

For this trial, information on AEs will be followed for up to 21 (± 2) days after the last dose of IMP has been administered.

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. 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 CRF 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

Pharmacokinetics will not be assessed in this trial.

7 Statistical Analysis

7.1 Sample Size

The sample size is not based on statistical power considerations. Approximately 350 subjects are anticipated to be enrolled with the expectation that at least 100 adolescent subjects with schizophrenia will complete a minimum of 1 year of exposure to open-label brexpiprazole.

7.2 Datasets for Analysis

The following analysis samples are defined for this trial:

Enrolled Sample: All subjects who sign an informed consent form for the trial.

Safety Sample: All subjects who receive at least 1 dose of brexpiprazole.

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

7.3 Primary and Secondary Endpoint Analyses

7.3.1 Primary Endpoint Analysis

The primary objective of this trial is to evaluate safety and tolerability. The primary endpoints are the frequency and severity of AEs, serious TEAEs (clinical and laboratory), and discontinuation from trial due to AEs. As there is no primary efficacy objective, there is no defined efficacy endpoint.

7.3.2 Secondary Endpoint Analysis

Descriptive statistics will be provided for mean change from baseline in PANSS Total Score, PANSS Positive and Negative Subscales, and CGAS scores for subjects with schizophrenia. The analysis will be carried out on the Efficacy Sample. Descriptive statistics will be summarized at each trial visit using the observed cases (OC) data set and at the last visit using the last observation carried forward (LOCF) data set.

7.4 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).

7.5 Safety Analysis

7.5.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA [most current version]) preferred term. The incidence of the following events will be summarized for the Safety Sample:

- 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

In addition, a Kaplan-Meier curve will be plotted for the time to discontinuation due to AEs.

7.5.2 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.

7.5.3 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 ≥ 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.

7.5.4 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.

7.5.5 Other Safety Data

7.5.5.1 Special Pediatric Safety Assessments

Some special pediatric safety assessments will be performed in this trial. They include comprehensive psychotropic side effects as assessed by the UKU side effect rating scale, and cognitive adverse effects as assessed by NY-AACENT.

Descriptive statistics will be provided for the frequency of symptom items recorded in the Safety Sample. In addition, for symptoms recorded in NY-AACENT, a total score at any level of present, attribution, severity or impairment may be calculated. The total score and its change from baseline at each visit will be summarized using descriptive statistics for the Safety Sample by disease under study.

7.5.5.2 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.

7.5.5.3 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.

7.5.5.4 Tanner Staging

Shift tables will be provided for the Tanner Staging scores.

8 Management of Investigational Medicinal Product

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

8.1 Packaging and Labeling

The IMP will be provided to the investigator(s) by the sponsor or designated agent. The IMP (open-label brexpiprazole) will be supplied in child resistant high density polyethylene bottles, containing 18 tablets for 0.5 mg strength and 34 tablets for the 1, 2, 3, and 4 mg strengths. Each bottle used in the dosing period will be labeled to clearly disclose the subject identification (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.

Brexpiprazole tablets 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.

8.3 Accountability

The investigator or designee must maintain an inventory record of IMP received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all used IMP containers, unused IMP, and partially used IMP must be returned to the sponsor or a designated agent, or destroyed at the trial site(s). The IMP may only be destroyed by the trial site(s). The IMP may only be destroyed by the trial sites if approved by the sponsor and if the IMP destruction meets all local regulations. All IMP returned to the sponsor must be accompanied by the appropriate documentation and be clearly identified by protocol number with trial site number on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits). The assigned trial monitor will facilitate the return or destruction of used IMP containers, unused IMP, and partially used IMP.

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 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 IMP-PQC@otsuka-us.com.

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

8.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, subject, investigator, site)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number 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 compliant 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.

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. 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, ~~wrong data~~ 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 (or designee'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 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 (CIOMS) 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 using screens in eSource, the investigator, subinvestigator, 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 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 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, or the sponsor conclude that the protocol amendment substantially alters the trial design or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB/IEC, repeat written informed consent 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 to such acknowledgement in any publications resulting from its conduct.

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Appendix 1 Criteria for Identifying Vital Signs of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate[b]	> 120 bpm < 50 bpm	≥ 15 bpm increase ≥ 15 bpm decrease
Systolic Blood Pressure[b]	> 180 mmHg < 90 mmHg	≥ 20 mmHg increase ≥ 20 mmHg decrease
Diastolic Blood Pressure[b]	> 105 mmHg < 50 mmHg	≥ 15 mmHg increase ≥ 15 mmHg decrease
Orthostatic Hypotension	≥ 20 mmHg decrease in systolic blood pressure and a ≥ 25 bpm increase in heart rate from supine to sitting/standing	Not Applicable (baseline status not considered)
Weight	-	≥ 7% increase ≥ 7% decrease

[a]In order to be identified as potentially clinically relevant, an 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.

[b]As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST (SGOT)	≥ 3 x upper limit of normal (ULN)
ALT (SGPT)	≥ 3 x ULN
Alkaline phosphatase	≥ 3 x ULN
LDH	≥ 3 x ULN
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric Acid	
Men	≥ 10.5 mg/dL
Women	≥ 8.5 mg/dL
Bilirubin (total)	≥ 2.0 mg/dL
CPK	≥ 3 x ULN
Prolactin	> ULN
Hematology	
Hematocrit	
Men	≤ 37 % and decrease of ≥ 3 percentage points from Baseline
Women	≤ 32 % and decrease of ≥ 3 percentage points from Baseline
Hemoglobin	
Men	≤ 11.5 g/dL
Women	≤ 9.5 g/dL
White blood count	≤ 2,800/ mm^3 or ≥ 16,000/ mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Absolute neutrophil count	≤ 1,000/ mm^3
Platelet count	≤ 75,000/ mm^3 or ≥ 700,000/ mm^3
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤ 90 mEq/L or ≥ 118 mEq/L
Potassium	≤ 2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤ 126 mEq/L or ≥ 156 mEq/L
Calcium	≤ 8.2 mg/dL or ≥ 12 mg/dL
Glucose	
Fasting	≥ 100 mg/dL
Non-Fasting	≥ 200 mg/dL
Total Cholesterol, Fasting	≥ 240 mg/dL
LDL Cholesterol, Fasting	≥ 160 mg/dL
HDL Cholesterol, Fasting	
Men	< 40 mg/dL
Women	< 50 mg/dL
Triglycerides, Fasting	≥ 150 mg/dL

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Rate		
Tachycardia	≥ 120 bpm	increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm	decrease of ≥ 15 bpm
Rhythm		
Sinus tachycardia[b]	≥ 120 bpm	increase of ≥ 15 bpm
Sinus bradycardia[c]	≤ 50 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	

[a]In order to be identified as potentially clinically relevant, an 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.

[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.

Appendix 4 Handling and Shipment of Bioanalytical Samples

Handling of Specimens

Labels should be secured to each storage tube. Labels should contain the following information: Protocol number; subject number; time point of sample collection (eg, Day 1 predose); and aliquot/matrix (eg, Plasma Aliquot 1 or Plasma Aliquot 2). All tubes must be labeled such that the protocol number, date of collections, and protocol time can be verified. It is important to note the exact time of the blood collection in eSource, not the scheduled time for the drawing.

Pharmacokinetic Plasma Samples

None collected for this trial.

Pharmacogenomics Sample

None collected for this trial.

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