Table of Contents

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product
Brexpiprazole (OPC-34712)

REVISED CLINICAL PROTOCOL

A Multicenter, Randomized, Double-blind, Placebo- and Active-controlled Trial to Evaluate the Efficacy of Brexpiprazole Monotherapy for the Treatment in Adolescents (13-17 years old) With Schizophrenia

Protocol No. 331-10-234
IND No. 101,871
EudraCT No. 2017-001447-12

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Immediately Reportable Event	Syneos Health Safety and Pharmacovigilance
Issue Date:	10 Mar 2017
Date of Amendment 1	24 Aug 2018
Administrative Change 1	31 May 2019
Date of Amendment 2	16 Jun 2020
Date of Amendment 3	05 Jul 2022
Version No.:	5.0

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

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.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)	Protocol No.: 331-10-234 IND No.: 101,871 EudraCT No.: 2017-001447-12
Protocol Title:	A Multicenter, Randomized, Double-blind, Placebo- and Active-controlled Trial to Evaluate the Efficacy of Brexpiprazole Monotherapy for the Treatment in Adolescents (13-17 years old) With Schizophrenia
Clinical Phase/Trial Type:	3/Therapeutic confirmatory
Treatment Indication:	Schizophrenia
Objective(s):	To evaluate the short-term efficacy and safety of brexpiprazole monotherapy in the treatment of adolescents with schizophrenia
Trial Design:	This is a multicenter, randomized, double-blind, placebo- and active-controlled trial designed to assess the effect of brexpiprazole compared to placebo in adolescent subjects, ages 13 to 17 years, with a *Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition* (DSM-5) diagnosis of schizophrenia. The initial diagnosis of schizophrenia should be made by an adequately trained clinician (psychiatrist or local medical equivalent who is experienced in treating adolescents with schizophrenia). The diagnosis should then be confirmed by 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. The trial is planned to be conducted on an outpatient basis. This trial has a 6-week double-blind treatment period. After a minimum 3-day washout period, subjects who continue to meet all entrance criteria (including Positive and Negative Syndrome Scale [PANSS] Total Score ≥ 80) at the baseline visit (Day 1) will be randomized 1:1:1 to 1 of 3 double-blind treatment arms: • brexpiprazole • aripiprazole • Placebo

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

	Brexpiprazole will be titrated to a minimum dose of 2 mg in 8 days and aripiprazole will be titrated to a minimum dose of 10 mg, the therapeutic dose as per the United States (US) package insert. Subjects who are unable to tolerate the minimum dose will be discontinued. At the end of the titration period, investigators will be able to adjust the dose of double-blind investigational medicinal product (IMP) not to exceed brexpiprazole 4 mg/day or aripiprazole 20 mg depending upon treatment arm. Following the first dose increase, if the dose adjustment is not well tolerated, the dose may be reduced back to the minimum dose allowed by protocol (ie, brexpiprazole 2 mg and aripiprazole 10 mg). Subjects not able to tolerate the decreased dose will be discontinued from the trial. Mandatory evaluations will take place at Day 1 (baseline), Day 4 (telephone call), and Weeks 1, 2, 3, 4, 5, and 6. However, at the discretion of the treating physician, more frequent evaluations are permitted. Eligible subjects who complete the 6-week double-blind efficacy phase may have the option to enroll into an open-label safety trial of brexpiprazole (Protocol 331-10-236). All subjects who do not enroll in the open-label rollover trial (Protocol 331-10-236) will be assessed by a telephone assessment 21 (± 2) days after the last dose of IMP to assess adverse events (AEs).
Subject Population:	The trial population will include male and female subjects between 13 and 17 years of age, inclusive, at the time of informed consent/assent and at baseline (Day 1) who continue to have a confirmed DSM-5 diagnosis of schizophrenia and a PANSS Total Score ≥ 80 at screening and at baseline (Day 1). Approximately 645 subjects are anticipated to be screened with the expectation that 315 subjects will be randomized.
Inclusion/Exclusion Criteria:	Subjects must meet the inclusion criteria at both screening and baseline. Key inclusion criteria include the following: • Subjects ages 13-17 inclusive at time of consent/assent and at baseline (Day 1) with a current primary diagnosis of schizophrenia, as defined by DSM-5 criteria and confirmed by the K-SADS-PL, and a history of the illness (diagnosis or symptoms) for at least 6 months prior to screening.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

- PANSS Total Score of ≥ 80.

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).
- Subjects who have been hospitalized > 21 days for a current exacerbation of schizophrenia at the time of the baseline visit.
- Subjects 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 who have a significant risk of committing violent acts, serious self-harm, or attempting 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 Columbia-Suicide Severity Rating Scale (C-SSRS).
- 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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

	infarction or ischemic heart disease, arrhythmia, congestive heart failure, or cancer); subjects with a comorbid serious systemic illness that requires pharmacotherapy; subjects with any history of electroconvulsive therapy. • Subjects who test positive for drugs of abuse at screening. A positive test for amphetamines, barbiturates, opiates, benzodiazepines may not result in exclusion of the subjects if the investigator determines that the positive test is a result of prescription medicine(s). When a subject tests positive for cannabinoids (tetrahydrocannabinol) at screening, the investigator is required to evaluate the subject's ability to abstain from using this substance during the trial and to discuss his/her evaluation with the Medical Advisor prior to randomization.
Trial Sites:	An estimated 120 sites in North America, Europe, and the rest of the world (ROW) will enroll subjects.
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Brexpiprazole, aripiprazole, and placebo oral tablets will be supplied to the investigators by the sponsor or designated agent as child-resistant blister cards each containing sufficient tablets for the window visit. When accessed by the site, an interactive web response system will assign a specific blister card to be dispensed to a subject. For the 6-week double-blind treatment period, subjects will be randomized 1:1:1 to 1 of 3 double-blind treatment arms: • 2–4 mg brexpiprazole daily • 10–20 mg aripiprazole daily (subjects will start at 2 mg and titrate per label for adolescents diagnosed with schizophrenia) • Placebo For all subjects, the number of tablets taken during the titration period will be identical to ensure the double-blind nature of the trial. Titration with brexpiprazole will start at 0.5 mg/day, increase to 1 mg/day, and increase again to 2 mg/day, which is the minimum dose. Titration with aripiprazole will start at 2 mg/day, increase to 5 mg/day, and increase again to 10 mg/day, which is the minimum dose. At the end of the titration period, investigators may either keep the subject at a maintenance dose or up-titrate by 1 mg (brexpiprazole) or 5 mg (aripiprazole) to a maximum dose of 4 mg/day (brexpiprazole) or 20 mg/day (aripiprazole).

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

	Subjects who cannot tolerate the minimum dose of 2 mg brexpiprazole or 10 mg aripiprazole will be discontinued from the trial.
Trial Assessments:	Efficacy: PANSS, Children's Global Assessment Scale (CGAS), Clinical Global Impression - Severity of Illness scale (CGI-S), and Clinical Global Impression - Improvement scale (CGI-I). Pharmacokinetic: blood sampling for brexpiprazole and metabolite plasma concentrations. Safety: AEs and concomitant medications, clinical laboratory tests, 12-lead electrocardiogram (ECG), vital signs, physical examination, 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), and suicidality (C-SSRS). Screening/Other: demography, medical history, psychiatric history (K-SADS-PL), CCI [redacted] prior and concomitant medications, Tanner Staging, serum/urine pregnancy test, and urine drug screen.
Criteria for Evaluation	**Primary Endpoint:** • Change from baseline to Week 6 in PANSS Total Score **Secondary Endpoints:** The secondary efficacy endpoints are as follows: • Change in the PANSS Positive and Negative Subscale Scores • Percentage of subjects achieving response. Response is defined as at least 30% improvement from baseline in PANSS Total Score or CGI-I score of 1 or 2. • Percentage of subjects achieving remission. Remission is defined as a score of ≤ 3 on each of the following specific PANSS items: delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), passive/apathetic social withdrawal (N4), and lack of spontaneity and conversation flow (N6). • Change in the CGAS Score

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

	• Change in the Clinical Global Impression Severity (CGI-S) scale • Clinical Global Impression Improvement (CGI-I) scale Safety will be assessed by the following: • The frequency and severity of AEs, serious AEs (clinical and laboratory), and discontinuation from the trial due to AEs • Weight, height, body mass index, and waist circumference • Analysis of potential suicide events recorded on the C-SSRS • Clinical laboratory tests and urinalysis results (including serum prolactin), vital signs, and ECG parameters • Changes on the SAS, AIMS, and BARS • Comprehensive psychotropic side effects as assessed by the UKU side effect rating scale • Cognitive adverse effects as assessed by the NY-AACENT
Statistical Methods:	Based on the results of the aripiprazole trial conducted in adolescent subjects with schizophrenia (Protocol 31-03-239), aripiprazole 30 mg and 10 mg had a reduction in PANSS Total Score of 7.40 and 5.46, respectively, compared to placebo. The standard deviation (SD) at Week 6 was 19. Assuming that brexpiprazole 2–4 mg has comparable treatment effects to aripiprazole 30 mg, as well as the same SD, a sample size of 105 subjects per arm will provide at least 80% power at a nominal 2-sided alpha level of 0.05 to detect a −7.4 point reduction in PANSS Total score change from baseline to Week 6 for brexpiprazole vs placebo assuming an SD = 19. With 1:1:1 allocation ratio, the overall sample size of this trial is planned to be 315 subjects. The primary efficacy variable in this trial is the change from baseline to Week 6 in PANSS Total Score. The primary statistical comparison of interest is brexpiprazole 2–4 mg vs. placebo. With the assumption of missing at random (MAR), a mixed model repeated measures (MMRM) analysis with fixed effect factors of treatment, trial site, visit, treatment visit interaction, and fixed effect covariates baseline and baseline visit interaction will be applied to the change from baseline from Week 1 to Week 6 based on all available data (observed case dataset). The data will be modeled using an unstructured variance covariance matrix for the within subject variation. A

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

	statistical test of the least squares (LS) mean differences at Week 6 of the MMRM analysis will serve as the analysis of the primary endpoint. In case there is a convergence problem with the MMRM model with the unstructured variance covariance matrix, the following structures other than unstructured will be used in order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry, and the first (co)variance structure converging to the best fit will be used as the primary analysis. If a structured covariance has to be used, the "sandwich" estimator of the standard error of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix. In order to explore the robustness of the primary analysis based on the MAR assumption, sensitivity analysis of the primary efficacy endpoint under a "missing not at random" assumption will be conducted, using a pattern-mixture model.
Trial Duration:	Individual participation for subjects who complete the trial without early withdrawal will be approximately 13 weeks, consisting of a screening period of up to 28 days, a 6-week double-blind treatment period, and a 21 (± 2)-day follow-up, if applicable. Subjects may have the option to enter an open-label rollover trial after completion of treatment. Only subjects who do not participate in the open-label trial will be followed up via telephone contact 21 (± 2) days after the last dose of IMP.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Table of Contents

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

List of In-text Tables

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

List of In-text Figures

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

List of Appendices

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADHD	Attention-deficit/hyperactivity disorder
ADT	Antidepressant therapy
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APO	Apomorphine
AST	Aspartate aminotransferase
$AUC_{0\text{-}24h}$	Area under the concentration-time curve from time zero to 24 hours
AUC_{τ}	Area under the plasma concentration-time curve to the last observable concentration
BARS	Barnes Akathisia Rating Scale
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
$C_{max,ss}$	Maximum concentration at steady state
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CPK	Creatine phosphokinase
CRO	Clinical Research Organization
CIOMS	Council for International Organizations of Medical Science
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
D2	Dopamine D_2
D3	Dopamine D_3
DBP	Diastolic blood pressure
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition*
e-signature	Electronic signature
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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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-HT1A	Serotonin type 1A receptor
5-HT2A	Serotonin type 2A receptor
IAF	Informed assent form
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
ITT	Intent-to-treat
IWRS	Interactive web response system
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
LS	Least squares
MAOIs	Monoamine oxidase inhibitors
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MDD	Major depressive disorder
MI	Multiple imputation
MMRM	Mixed model repeated measures
MNAR	Missing not at random
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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

PD	Pharmacodynamic
PET	Positron emission tomography
PGx	Pharmacogenomic
PK	Pharmacokinetic
PQC	Product quality complaint
P-Q-LES-Q	Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire
PTSD	Post-traumatic stress disorder
QD	Once daily
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
ROW	Rest of world
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Simpson Angus Scale
SBP	Systolic blood pressure
SD	Standard deviation
T_4	Thyroxine
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 or USA	United States or United States of America
WBC	White blood cell

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

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 (D2) 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} (5-HT2A) 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 $5HT_{2A}$ 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}, $5HT_7$, 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}, $5HT_7$, α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Dose

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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 this trial. Protocol 331-10-234 is being conducted to determine the safety and efficacy of brexpiprazole for the acute treatment of 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" tend to 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]

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

CCI

[redacted]

1.1.1 Efficacy Pharmacology

Brexpiprazole functions as a partial agonist at the D_2 receptor. In in vitro assay systems based on forskolin-induced cyclic adenosine monophosphate accumulation and calcium mobilization in human dopamine D_{2L} receptor-expressing cells, its intrinsic activity at the D2 receptor was slightly lower than that of aripiprazole, another D_2 receptor partial agonist. Brexpiprazole inhibited apomorphine (APO)-induced hyperlocomotion, APO-induced stereotyped behavior, and conditioned avoidance response in rats, which are predictive animal models for antipsychotic-like efficacy. The inhibitory effects of brexpiprazole were more potent than those of aripiprazole. Moreover, in contrast to the D_2 receptor antagonist risperidone, brexpiprazole did not increase plasma prolactin levels in reserpine-treated rats, thus demonstrating a D_2 receptor partial agonistic profile in vivo. Despite its lower intrinsic activity at the D_2 receptor, the in vivo catalepsy liability of brexpiprazole, an index of EPS, was similar to that of aripiprazole, but still lower than that of the typical antipsychotic haloperidol. Furthermore, brexpiprazole showed high binding affinity for the 5-HT_{2A} receptor and dose-dependently inhibited (±)-2,5-dimethoxy-4-iodoamphetamine-induced head twitch response in rats, indicating that the compound has 5-HT_{2A} receptor antagonistic activity; the effect of brexpiprazole was more potent than that of aripiprazole. In addition, brexpiprazole exhibited high binding affinities for the D_3 and 5-HT_{1A} receptors, acting as a partial agonist at these receptors.

1.1.2 Safety Pharmacology

In safety pharmacology studies in rats at an oral dose of 30 mg/kg or higher, brexpiprazole induced pharmacologically mediated clinical signs considered to be due to depression of the central nervous system (CNS) and dose-dependent decreases in body temperature. When orally administered at up to 30 mg/kg in conscious male beagle dogs, brexpiprazole showed no effect on respiratory parameters or heart rate at any dose tested. Brexpiprazole decreased blood pressure at doses of 3 mg/kg or higher and prolonged both

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

QT interval and corrected QT interval (QTc, by Van de Water's formula) at 30 mg/kg. Brexpiprazole inhibited human *ether-a-go-go* related gene current in Chinese hamster ovary cells at concentrations of 10^{-8} mol/L or higher, with a 50% inhibitory concentration of 1.17×10^{-7} mol/L. The mechanism for the blood pressure decreasing effect of brexpiprazole was suggested to result from a blockade of the 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.[12]

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 post dose for brexpiprazole and at approximately 10 to 24 hours post dose for DM-3411. In healthy subjects, administration of single-dose brexpiprazole with a high-fat meal did not affect its rate and extent of absorption.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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 post dose 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,

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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: 0.765 and0.904, 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 area under the concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24h}$) (GMR adult/adolescent: 1.05), and slightly higher dose-normalized C_{max} (GMR adult/adolescent: 0.904) were observed in adolescents when compared to adults. The difference in the results for the two populations may be due to potential noncompliance, especially in the lower dose groups (0.5 and 1.0 mg), when dosing was not under medical supervision.

1.2.3 Major Depressive Disorder

The efficacy of brexpiprazole as adjunctive therapy for the treatment of MDD has been studied in 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.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

(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.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

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" tend to 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 demonstrate the efficacy and safety of brexpiprazole for the treatment of adolescents with schizophrenia. A 6-week double-blind treatment period is considered to be of adequate length to determine whether an antipsychotic effect has been demonstrated. Criteria for early termination (ET) from double-blind treatment will be determined by the investigator and corroborated with quantitative assessments. The aripriprazole arm proposed in this trial provides assay sensitivity.

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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 at doses of 0.5 mg/day, 1 mg/day, 2 mg/day, 3 mg/day, and 4 mg/day was 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 in 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 is deemed necessary in children and adolescents and thus a similar efficacious dose range of 2 to 4 mg is proposed for this trial. In adult patients, brexpiprazole is 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 was 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 evaluate the short-term efficacy and safety of brexpiprazole monotherapy in the treatment of adolescents with schizophrenia.

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, randomized, double-blind, placebo- and active-controlled trial designed to assess the effect of brexpiprazole compared to placebo in adolescent subjects, ages 13 to 17 years at the time of informed consent/assent and at baseline (Day 1), with a *Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition* (DSM-5) diagnosis of schizophrenia. The initial diagnosis of schizophrenia should be made by an adequately trained clinician (psychiatrist or local medical equivalent who is experienced in treating adolescents with schizophrenia). The diagnosis should then be confirmed by utilizing the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Lifetime version (K-SADS-PL), performed by an adequately trained rater at the time of screening. The trial is planned to be conducted on an outpatient basis. Any hospitalization needed for prospective subjects, such as hospitalization needed to allow subjects to change medications in preparation for this trial requires discussion with the Medical Advisor.

This trial has a 6-week treatment double-blind period.

After a minimum 3-day washout period, subjects who continue to meet all entrance criteria (including Positive and Negative Syndrome Scale [PANSS] Total Score ≥ 80) at the baseline visit (Day 1) will be randomized 1:1:1 to 1 of 3 double-blind treatment arms:

- 2–4 mg brexpiprazole daily
- 10–20 mg aripiprazole daily
- Placebo

Brexpiprazole will be titrated to the minimum target dose of 2 mg in 8 days and aripiprazole will be titrated to the appropriate therapeutic dose consistent with the US package insert (minimum dose of 10 mg). Subjects who are unable to tolerate the minimum target dose will be discontinued. At the end of the titration period, investigators will be able to adjust the dose of double-blind IMP not to exceed 4 mg/day in the brexpiprazole treatment arm or 20 mg/day in the aripiprazole treatment arm. If subjects are not able to tolerate the minimum dose, they will be discontinued from the trial.

During the double-blind treatment phase, mandatory evaluations will take place at Day 1 (baseline), Day 4 (telephone call), and Weeks 1, 2, 3, 4, 5, and 6. However, at the discretion of the treating physician, more frequent evaluations are permitted. Data collected from subjects undergoing ad hoc evaluations may be excluded from efficacy analysis.

Eligible subjects who complete the trial may have the option to enroll into an open-label safety trial of brexpiprazole (Protocol 331-10-236). All subjects who do not enroll in the open label rollover trial (Protocol 331-10-236) will be assessed either via site visit or telephone assessment 21 (± 2) days after the last dose of IMP to assess adverse events (AEs).

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

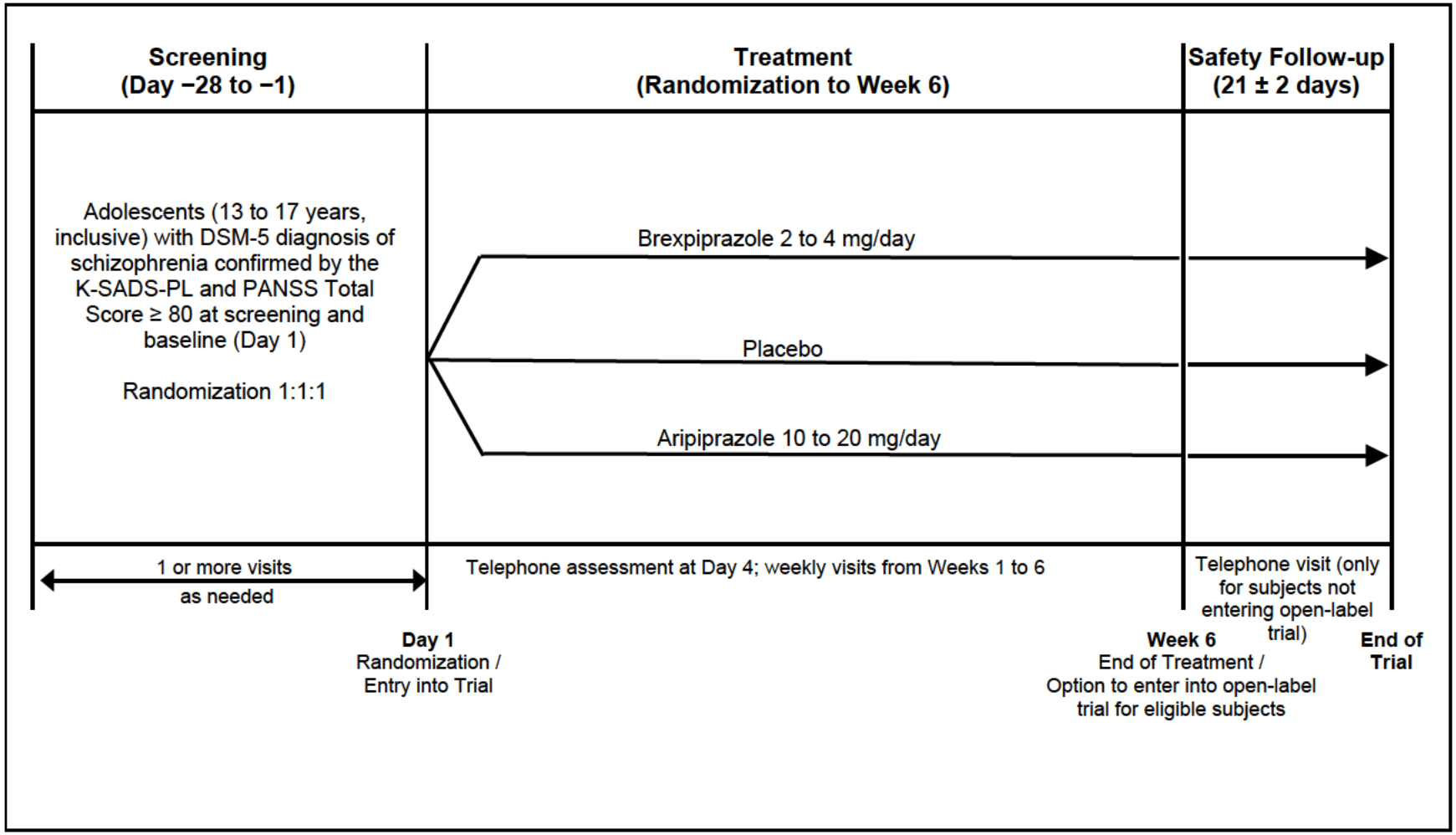

Figure 3.1-1 Trial Design Schematic

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

3.2 Trial Treatments

During the first week of the titration phase, brexpiprazole, aripiprazole, and placebo tablets will be dispensed via titration cards, 1 for Days 1 to 7. After Day 8, IMP will be supplied as weekly child-resistant blister cards, each containing sufficient tablets for 7 (+ 2) days. When requested by the site, an interactive web response system (IWRS) will assign a specific blister card to be dispensed to a subject.

Subjects will be randomized 1:1:1 to 1 of 3 double-blind treatment arms in the 6-week treatment double-blind period:

- 2 mg brexpiprazole daily by Day 8; 2–3 mg daily by Day 15; dose may increase to 4 mg after Day 21
- 10 mg aripiprazole daily by Day 8; dose may increase in 5 mg increments weekly to a maximum of 20 mg after Day 21
- Placebo

The dosing schedule during the treatment phase is presented in Table 3.2-1. For all subjects, the number of tablets taken during the titration period (Day 1 to Day 7) will be identical to ensure the double-blind nature of the trial. Subjects randomized to brexpiprazole will take 0.5 mg the first 4 days as a titration, then take 1 mg per day from Days 5 to 7. From Days 8 to 14, subjects will take the minimum dose of 2 mg. From Days 15 to 21, the dose may be changed from 2 mg to 3 mg, or it may remain at 2 mg. After this titration period, investigators may keep the subject at a maintenance dose, increase the dose by 1 mg to a maximum of 4 mg/day, or decrease the dose by 1 mg.

Subjects randomized to aripiprazole will take 2 mg the first 4 days as a titration, then take 5 mg per day from Days 5 to 7, and 10 mg from Days 8 to 14. Beginning on Day 15, the dose may be changed from 10 mg to 15 mg, or it may remain at 10 mg. After Day 21, investigators may keep the subject at a maintenance dose, increase the dose by 5 mg to a maximum of 20 mg, or down-titrate the subject's dose if tolerability is an issue. Subjects who cannot tolerate the minimum dose of 2 mg brexpiprazole or 10 mg aripiprazole will be discontinued from the trial.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Table 3.2-1 Dosing Schedule During the Treatment Period			
Trial Day/Week	**Brexpiprazole 2–4 mg/day**	**Aripiprazole 10–20 mg/day**	**Placebo**
Days 1-4	0.5 mg	2 mg	placebo tablets QD
Days 5-7	1 mg	5 mg	placebo tablets QD
Days 8-14	2 mg	10 mg	placebo tablets QD
Days 15–21	2–3 mg with option to maintain 2 mg or increase[a] to 3 mg	10 mg or 15 mg with option to maintain 10 mg or increase[a] to 15 mg	placebo tablets QD
Day 22+ (Weeks 4-6[b])	2, 3, or 4 mg with option to remain at the same dose, or increase or decrease dose by 1 mg	10, 15, or 20 mg with option to remain at the same dose, or increase or decrease dose by 5 mg	placebo tablets QD

QD = once daily.

[a]Dose increases are allowed only at weekly intervals. Dose decreases are allowed at any time for tolerability as long as the minimum required dose is maintained.

[b]Beginning at Day 22, the dose may be increased or decreased if needed for tolerability or efficacy. Subjects who cannot tolerate the minimum dose of 2 mg brexpiprazole or 10 mg aripiprazole will be discontinued from the trial.

All doses of double-blind IMP are to be taken orally once daily and can be administered without regard to meals.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

The trial population will include male and female subjects between 13 and 17 years of age, inclusive, at the time of informed consent/assent and at baseline (Day 1) who continue to have a confirmed DSM-5 diagnosis of schizophrenia and a PANSS Total Score ≥ 80 at screening and at baseline (Day 1). Approximately 645 subjects are anticipated to be screened with the expectation that 315 subjects will be randomized.

3.3.2 Subject Selection and Numbering

At screening, subjects will be assigned a unique subject identification number upon signing the informed consent form (ICF) based on sequential enrollment in the trial. Subjects will be assigned a unique subject number upon enrollment, prior to dosing on Day 1. The clinical site will maintain a list identifying all subjects by their subject identification number and initials.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

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 FDA regulations in 21 Code of Federal Regulations (CFR) Part 50, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[13] and local regulatory requirements. The investigator will ensure the sponsor reviews and authorizes any site-specific ICF used in this 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 and assent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

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

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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 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.

In addition to the English version of the ICFs, the documents may also be translated by the central translation vendor into local languages for use in this trial.

3.4.2 Inclusion Criteria

Subjects are required at screening and baseline to meet the inclusion criteria presented in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1.	Written informed consent, assent, or both obtained from a legally acceptable representative (eg, guardian) or subject prior to the initiation of any protocol-required procedures. In addition, the subject must provide informed assent at screening and must be able to understand that he or she can withdraw from the trial at any time. All informed consent/assent procedures must be in accordance with the trial site's IRB/IEC and local regulatory requirements.
2.	Male and female subjects 13 to 17 years of age, inclusive, at the time of informed consent/assent and at baseline (Day 1).
3.	Subjects with a current primary diagnosis of schizophrenia, as defined by DSM-5 criteria and confirmed by the K-SADS-PL, and a history of the illness (diagnosis or symptoms) for at least 6 months prior to screening (as per subject, family, or healthcare provider, or by previous medical records). The initial diagnosis of schizophrenia must be made and documented initially by an adequately trained clinician (psychiatrist or local medical equivalent who is experienced in treating adolescents with schizophrenia), and the diagnosis should be confirmed afterwards by utilizing the K-SADS-PL performed by an adequately trained rater. (Subjects with a diagnosis of ADHD and treated with stimulants or other ADHD medications within 28 days are prohibited.)
4.	Subjects who, in the investigator's judgment, require treatment with antipsychotic medication(s).
5.	Subjects with a PANSS Total Score $\geq$ 80 at screening and at baseline (Day 1).
6.	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.

3.4.3 Exclusion Criteria

Subjects will be excluded if at screening and baseline, they meet any of the exclusion criteria in Table 3.4.3-1.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Table 3.4.3-1 Exclusion Criteria	
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 a current exacerbation of schizophrenia at the time of the baseline visit.
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.	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.
9.	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.
10.	Subject is known to have medication compliance issues that lead to IM depot medication use.
Medical History and Concurrent Diseases	
11.	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 Advisor prior to randomization.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Table 3.4.3-1 Exclusion Criteria	
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 fasting glucose must be ≤ 125 mg/dL or non-fasting glucose < 200 mg/dL. If the non-fasting glucose is ≥ 200 mg/dL, subjects must be retested in the fasting state. At retest, fasting glucose must be ≤ 125 mg/dL • Subject has been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to screening or diabetes has been well-controlled by diet for at least 28 days prior to screening, • Subject has not had any hospitalizations within the 12 months prior to screening due to diabetes or complications related to diabetes, **AND** • Subject's diabetes is not newly diagnosed during screening for the trial.
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 test positive for drugs of abuse at screening are excluded. A positive test for amphetamines, barbiturates, opiates, benzodiazepines may not result in exclusion of the subjects if the investigator determines that the positive test is a result of prescription medicine(s). When a subject tests positive for cannabinoids (tetrahydrocannabinol) at screening, the Investigator is required to evaluate the subject's ability to abstain from using this substance during the trial and to discuss his/her evaluation with the Medical Advisor prior to randomization.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Table 3.4.3-1 Exclusion Criteria	
Physical and Laboratory Results	
16.	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, unless discussed with and approved by the Medical Advisor. (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 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	
17.	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.
18.	Subjects who would be likely to require prohibited concomitant therapy during the trial, including subjects receiving CYP2D6 or CYP3A4 inhibitors or CYP3A4 inducers at screening or who are anticipated to require use of such agents during the trial.
19.	Subjects on IM depot therapy within 5 × half-life of the medication prior to screening.
Allergies and Adverse Drug Reactions	
20.	Subjects with a history of neuroleptic malignant syndrome.
21.	Subjects with a history of true allergic response (ie, not intolerance) to more than one class of medications.
22.	Subjects who report a true allergic response to aripiprazole or brexpiprazole.
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.	Subjects who participated in any clinical trial within the last 30 days prior to screening.
26.	Any subject who, in the opinion of the investigator, should not participate in the trial.
27.	Subjects who are known poor metabolizers of CYP2D6 or CYP3A4.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

ALT = alanine aminotransferase; AST = aspartate aminotransferase; C-SSRS = Columbia-Suicide Severity Rating Scale; CPK = creatine phosphokinase; CYP = cytochrome P450; DBP = diastolic blood pressure; ECG = electrocardiogram; HbA1c = glycosylated hemoglobin; IDDM = insulin-dependent diabetes mellitus; IM = intramuscular; QTcF = QT interval as corrected for heart rate by Fridericia's formula; QTcN = QT intervalcorrected for heart rate by the FDA Neuropharm Division formula; SBP = systolic blood pressure; T_4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell.

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

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

3.5 Endpoints

3.5.1 Primary Endpoint

The primary endpoint is as follows:

- Change from baseline to Week 6 in PANSS Total Score

The estimand of the primary efficacy endpoint is described in Section 7.4.

3.5.2 Secondary Endpoints

3.5.2.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

3.5.2.2 Secondary Safety Endpoints

Safety will be assessed by the following:

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

CCI

[redacted]

3.6 Measures to Minimize/Avoid Bias

Subjects will be randomly assigned through an IWRS to receive brexpiprazole, aripiprazole, or placebo. The randomized treatments will be administered in a double-blind fashion. Treatment assignments will be based on a computer-generated randomization code provided by the Otsuka Pharmaceutical Development & Commercialization, Inc. Biometrics Department.

Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, operating the IWRS, and reporting serious adverse events (SAEs) to regulatory agencies.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

3.7 Trial Procedures

Individual participation for subjects who complete the trial without early withdrawal will be approximately 13 weeks, consisting of a screening period of up to 28 days, a 6-week double-blind treatment period, and a 21 (±2)-day follow up, if applicable. Subjects may have the option to enter an open-label rollover trial after completion of treatment. Only subjects who do not participate in the open-label trial will be followed up at a clinic visit 21 (± 2) days after the last dose of IMP. The Day 4 visit may occur within ± 1 days of the target visit date. All visits after Day 4 may occur within ± 2 days of the target visit date. Follow-up contact may occur within ± 2 days of the target date.

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Table 3.7-1 Schedule of Assessments

Assessment	Screening	6-Week Double-blind Treatment Period								Follow-up Visit
		Day 1	Day 4[a] (± 1 day)	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 5 (± 2 days)	Week 6/ET (± 2 days)	21 (± 2) days after last dose of IMP
Informed consent, demography, medical history, psychiatric history	X									
Entrance criteria	X	X								
Prior medications	X	X								
K-SADS-PL	X									
PANSS	X	X		X	X	X	X	X	X	
CGAS	X	X		X	X	X	X	X	X	
CGI-S		X		X	X	X	X	X	X	
CGI-I				X	X	X	X	X	X	
P-Q-LES-Q		X							X	
C-SSRS		X		X	X	X	X	X	X	
SAS, AIMS, BARS	X	X		X	X	X	X	X	X	
UKU	X	X		X	X	X	X	X	X	
NY-AACENT	X	X		X	X	X	X	X	X	
Tanner Staging[b]	X								X	
Physical examination	X								X	
Body weight and waist circumference	X	X		X	X	X	X	X	X	
Height	X								X	
Dispense Investigational Product		X		X	X	X	X	X		
Clinical laboratory tests (hematology, serum chemistry [including blinded prolactin], and urinalysis)	X	X					X		X	
HbA1c and TSH	X	X							X	

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Table 3.7-1 Schedule of Assessments

Assessment	Screening	6-Week Double-blind Treatment Period								Follow-up Visit
		Day 1	Day 4[a] (± 1 day)	Week 1 (± 2 days)	Week 2 (± 2 days)	Week 3 (± 2 days)	Week 4 (± 2 days)	Week 5 (± 2 days)	Week 6/ET (± 2 days)	21 (± 2) days after last dose of IMP
Vital signs (supine, sitting, and standing blood pressure, body temperature and pulse)[c]	X	X		X	X	X	X	X	X	
ECG	X	X[d]							X[d]	
Serum pregnancy test	X	X					X		X	
Urine pregnancy test[e]	X	X							X	
Urine drug screen	X[f]						X[f]		X[f]	
Pharmacokinetic samples		X[g]					X[g]		X[g]	
Pharmacogenomic sample		X								
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X

ET = early termination.

[a]The Day 4 assessments will be conducted via telephone contact.

[b]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 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 the 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.

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

[d]An ECG will be obtained predose on Day 1 and postdose on Week 6.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

[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.

[f]A urine drug screen, including a urine alcohol test, is required at the designated times, but either or both can be conducted at any time during the phase at the discretion of the investigator.

[g]A plasma PK sample will be obtained 1–6 hours postdose on Day 1, Week 4, and Week 6. The time of the IMP dose will be recorded. At the Week 4 and 6 visits, the time of the last 3 doses of IMP will also be recorded.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

3.7.1 Schedule of Assessments

3.7.1.1 Screening

The screening period begins after written informed consent has 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 randomization. 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 and signed the ICF or provided assent, a screening number will be provided via eSource. Completion of screening activities may require more than 1 visit; however, only the initial visit will be registered. The screening period maximum of 28 days may be extended after discussion with the medical monitor. Screening evaluations will include the following:

- Trial personnel will enter subject data into eSource to register all trial visits.
- An assessment of all inclusion and exclusion criteria will be made to determine the subject's eligibility for the trial.
- 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.
- A qualified and certified rater will administer the PANSS.
- 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 administer the UKU and NY-AACENT.
- The investigator (or qualified designee) will complete Tanner Staging assessment.

  Note: The collection of Tanner Staging data is required for this study, and every attempt should be made to collect this information. Tanner Staging must be completed together with the physical examination in the most inconspicuous manner as possible for the subject. Tanner Staging could be completed by study psychiatrist, study affiliated pediatrician, nurse-practitioner, or nurse (in case of countries or states where nurses are qualified to perform a complete physical examination). When

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Tanner Staging is not completed at a required visit, it should be collected at the next study 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, body temperature, and pulse) 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 3.4.3-1 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 3.4.3-1 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 blinded 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 fasting is at all possible (see Section 3.7.3.2). See Table 3.4.3-1 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 3.4.3-1 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.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

3.7.1.2 Baseline/Day 1 (Randomization)

If the subject is found to be eligible for the trial during the screening period, the subject will attend a baseline visit during which the following procedures will be completed prior to randomization:

- Inclusion/exclusion criteria will be verified. Review of inclusion/exclusion criteria at the baseline visit will be based on assessments performed during screening.
- Prior medications will be reviewed.
- A qualified and certified rater will administer the PANSS.
- A qualified rater will administer the CGAS.
- A qualified and certified rater will administer the CGI-S.
- The P-Q-LES-Q assessment will be completed by the subject.
- 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.
- Body weight and waist circumference will be recorded.
    - Vital sign measurements (including blood pressure, body temperature, and pulse) 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 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.
- Blood samples will be collected for clinical laboratory tests (hematology and serum chemistry [including blinded prolactin, HbA1c, and TSH]) after a minimum 8-hour fast, if fasting is possible. Vital sign and ECG assessments should be completed before any blood samples are collected.
- 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.
- Blood will be drawn for a plasma PK sample, which will be obtained 1–6 hours postdose, and the sampling time will be recorded.
- A pharmacogenomics (PGx) sample will be collected to determine the CYP2D6 metabolizer status.
- AEs and concomitant medications will be recorded.
- If the subject remains eligible for the trial after completion of the baseline evaluations, trial personnel will capture trial data within the eSource and randomize the subject to obtain an IMP assignment. The subject will receive the first dose of

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

IMP from the assigned double-blind titration card and the date and time of the first dose will be recorded in eSource.

3.7.1.3 Day 4

All subjects will be contacted by telephone on Day 4 to record AEs and concomitant medications.

3.7.1.4 Weeks 1, 2, 3, 4, and 5

All subjects will be assessed weekly at scheduled visits during double-blind treatment in the acute treatment phase. The following evaluations will be performed at *each* visit (ie, Weeks 1, 2, 3, 4, and 5):

- A qualified rater will administer the PANSS.
- A qualified rater will administer the CGAS.
- A qualified rater will administer the CGI-I.
- A qualified rater will administer the CGI-S.
- 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, body temperature, and pulse) 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, if applicable at the specific visit.
- Drug accountability.
- AEs and concomitant medications will be recorded.
- The IMP will be dispensed to the subject.

The following additional evaluations will be performed at *Week 4 only*:

- Blood samples will be collected for clinical laboratory tests (hematology and serum chemistry [including blinded prolactin]) after a minimum 8-hour fast, if fasting is possible. Vital sign assessments should be completed before any blood samples are collected.
- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

- A plasma PK sample will be obtained within 1-6 hours postdose when possible. The time of each PK sample as well as the time of the last 3 doses of IMP will be recorded.
- A serum pregnancy test will be performed for all females.

3.7.1.5 Week 6 (End of Treatment)

The treatment period will conclude at the Week 6 visit. Subjects will take the last dose of IMP either prior to the Week 6 visit on the same calendar day or during the Week 6 visit whenever possible, depending on the time of day when the subject typically takes the IMP relative to the scheduled time for the visit. The following activities and assessments will occur at Week 6/end of treatment:

- 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 CGAS.
- A qualified and certified rater will administer the CGI-S.
- A qualified and certified rater will administer the CGI-I.
- The P-Q-LES-Q assessment will be completed by the subject.
- 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.
- The investigator (or qualified designee) will complete Tanner Staging assessment.
- A physical examination will be performed.
- Body weight, height, and waist circumference will be recorded.
    - Vital sign measurements (including blood pressure, body temperature, and pulse) 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 blinded prolactin, HbA1c, and TSH]) after a minimum 8-hour fast, if fasting is possible. Vital sign and ECG assessments should be completed before any blood samples are collected.
- A urine pregnancy test will be performed predose for all females.
- A serum pregnancy test will be performed for all females.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

- Urine will be collected from all potential subjects for urinalysis and urine screen(s) for drugs of abuse.
- A plasma PK sample will be obtained within 1-6 hours postdose when possible. The time of each PK sample as well as the time of the last 3 doses of IMP will be recorded.
- Drug accountability.
- AEs and concomitant medications will be recorded.

Eligible subjects who complete this 6-week trial will have the option to enroll into an open-label safety trial of brexpiprazole (Protocol 331-10-236). If subjects are not able to tolerate the assigned dose or the decreased dose, or have no improvement in schizophrenia symptoms, they will be discontinued from the trial.

3.7.1.6 Early Termination

If a subject discontinues early before Week 6, procedures noted for Week 6 must be completed at the ET visit. Attempts should be made to complete all evaluations, particularly efficacy assessments (ie, PANSS, CGAS, CGI-S, and CGI-I), prior to the administration of any new psychotropic medications. However, if the subject receives a new antipsychotic prior to ET procedures, no efficacy assessments should be done. Any prohibited medications started before the end of the trial assessments should be documented as a protocol deviation.

3.7.1.7 Follow-Up

All subjects who do not enroll in the open-label rollover trial (Protocol 331-10-236) will be followed up by a telephone assessment 21 (± 2) days after the last dose of IMP to assess any new or ongoing AEs and to record any concomitant medications.

3.7.2 Efficacy Assessments

It is required that a qualified and experienced clinician administer the efficacy assessments (ie, PANSS, CGAS, CGI-S, and CGI-I). Raters will be trained on the administration of these scales and, in addition, must be certified for this trial to administer the PANSS. 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, certification, and materials for rating will be provided. The P-Q-LES-Q (a subject-rated scale) will be collected as specified in the protocol. Instructions on how to complete the form are contained at the top of the scale (Appendix 9).

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

3.7.2.1 Positive and Negative Syndrome Scale

The PANSS consists of 3 subscales containing a total of 30 symptom constructs.[14] 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.[15] 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.[16] 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.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

3.7.2.4 Clinical Global Impression - Improvement Scale

The efficacy of IMP will be rated for each subject using the CGI-I.[16] 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

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology: Hematocrit Hemoglobin Mean Corpuscular Hemoglobin Concentration Mean Corpuscular Volume Platelets Red Blood Cell (RBC) count White Blood Cell (WBC) count with differential Urinalysis: Appearance Color Blood Glucose Microscopic analysis, WBC/RBC counts per high powered field pH Protein Specific gravity	Serum Chemistry: Alkaline Phosphatase (ALP) Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Bilirubin, total Blood Urea Nitrogen (BUN) Calcium Chloride Cholesterol (total, LDL, and HDL) CPK Creatinine Gamma Glutamyl Transferase (GGT) Glucose Lactic Dehydrogenase (LDH) Potassium Prolactin[a] 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 HbA1c

HDL = high-density lipoprotein; LDL = low-density lipoprotein

[a]Results blinded.

No more than 24.5 mL of blood will be taken at each visit designated in Table 3.7-1 for the purposes of clinical laboratory assessments, serum pregnancy tests, PK and PGx analyses. The laboratory tests to be evaluated in this trial are listed in Table 3.7.3.2-1.

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 collected at screening and predose on Day 1, Week 6, and ET. 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 one 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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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) $> 3 \times$ the upper limit of normal (ULN)
6) Alanine aminotransferase (ALT) $> 3 \times$ the ULN
7) Creatinine ≥ 2 mg/dL
8) HbA1c $\geq 7.0\%$
9) Creatine phosphokinase (CPK) $> 3 \times$ ULN
10) Abnormal free T_4, unless discussed with and approved by Medical Advisor. (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 relevant, 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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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 screening urogenital exam is required, which could have been performed up to one calendar year prior to the date of the ICF or informed assent form (IAF) being signed or can be performed during the screening period. The urogenital examination may be performed by the subject's primary care provider or pediatrician as long as the source records are obtained, and the findings documented. Post-baseline, medically relevant questions about the urogenital body system must be asked of the subject at all protocol-required physical exams, with answers documented accordingly in the source. The extent and scope of any part of the physical examination is to be left to the discretion of the investigator as deemed appropriate for each subject.

The following 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.[17]

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

- 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 should 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 relevant, 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 at 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 ECG will be repeated if any results are considered to be clinically significant.

A screening ECG finding of QTcF or QTcN $\geq$ 450 msec for males and $\geq$ 470 msec for females based on the results from the central reader is exclusionary (see Table 3.4.3-1). 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.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Appendix 3 is provided as a guide for determining potentially clinically relevant ECG abnormalities. Central reader results for verification of exclusion criteria at the baseline visit will not be available prior to randomization; therefore, subjects will be randomized based on screening ECG results from the central reader and baseline ECG results from the trial site.

3.7.3.5 Other Safety Assessments

It is required that a trained and experienced clinician administer the safety assessments, including the EPS scales (SAS, AIMS, and BARS) and C-SSRS. 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 Bracket.

3.7.3.5.1 Simpson Angus Scale

The SAS[18] (Appendix 10) 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 in eSource.

3.7.3.5.2 Abnormal Involuntary Movement Scale

The AIMS[16] assessment (Appendix 11) 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,

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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 in 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[19] (Appendix 12) 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 in 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 study to satisfy regulatory authority requirements. 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 13.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

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 study to satisfy regulatory authority requirements. 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 has been used in previous clinical studies with adolescent schizophrenia to detect the cognitive side effects of antipsychotic treatment. It is specifically designed to be used in pediatric populations (ages 12-17), but can be utilized with other age groups as appropriate. The clinician-administered NY-AACENT will be completed at all post-screening visits.

The clinician form is provided in Appendix 14.

3.7.3.5.6 Suicidality

Suicidality will be monitored during the trial using the 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 subjects at the baseline visit to determine eligibility (prior to the first dose). Any subject with active suicidal ideation or suicidal behaviors within the last year, or who in the clinical judgment of the investigator presents a serious risk of suicide 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 should be excluded from the trial (see Table 3.4.3-1). The "Since Last Visit" C-SSRS form will be completed at all postbaseline visits. Copies of the C-SSRS forms are provided in Appendix 15.

3.7.3.5.7 Psychiatric History

The K-SADS-PL[20] will be performed during screening by an adequately trained rater to confirm the diagnosis of schizophrenia or other related psychiatric disorders.

3.7.4 Pharmacokinetic/Pharmacogenomic Assessments

A total of 3 plasma PK samples will be collected from each subject: 1 sample on Day 1 (baseline) and at Weeks 4 and 6. Each sample will be taken at least 1 hour postdose. Subjects should take their IMP at approximately the same time each day. The time of IMP administration and the time of each PK blood draw should be recorded accurately on

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

days when PK samples are obtained. Every effort should be made to obtain the PK sample at the same time during the trial. Blood samples will be analyzed for brexpiprazole (OPC-34712) and metabolite concentrations.

A PGx sample will be collected at the time point presented in the Schedule of Assessments, (Table 3.7-1). The PGx blood sample will be taken in order to extract deoxyribonucleic acid (DNA) and determine the CYP2D6 genotype and predicted phenotype. Genotypes for other genes related to absorption, distribution, metabolism, and excretion will also be determined. Details for drawing and processing PK and PGx samples, and handling and shipping instructions, are provided in Appendix 4.

3.7.5 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 screen in eSource for the last subject completing or withdrawing from the trial.

3.7.6 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 or Treatment Arm(s)

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

3.8.2 Individual Site

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

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 2 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 via eSource and also recorded as a protocol deviation (Section 3.13).

3.8.3.2 Treatment Discontinuation

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

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

3.8.3.3 Documenting Reasons for Treatment Discontinuation

Subjects meeting any of the following criteria must discontinue IMP and be withdrawn from the trial:

a) occurrence of any AE, intercurrent illness or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial;
b) treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator;
c) subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures (see Section 3.12);

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

d) at the request of the subject, investigator, sponsor or designee, or regulatory authority;
e) subject becomes pregnant (see Section 5.5);
f) subject cannot tolerate the assigned dose of IMP;
g) subject is lost to follow-up;
h) death;
i) subject withdraws informed consent; or
j) termination of all or part of the trial by the sponsor.

The investigator will notify the sponsor promptly when a subject is withdrawn. Subjects withdrawn prior to Week 6 must complete the Week 6 evaluations at the time of withdrawal. In addition, all subjects who withdraw prematurely from the trial will be assessed by a telephone assessment 21 (± 2) days after the last dose of IMP for evaluation of safety. Withdrawn subjects will not be replaced.

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 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).

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

- 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, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.1 and 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 treatment, whether through randomization or open assignment. For the purposes of this trial, treatment begins with the first dose of double-blind IMP at the baseline visit. If a subject fails to qualify for the trial during screening for a reason other than a positive screen for drugs of abuse, he/she is permitted to be rescreened at a later date. In the event that a screen failure is rescreened for trial participation after the 28-day screening period expires, a new ICF must be signed and a new screening number assigned.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of IMP. Subjects who are evaluated at the last scheduled

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete the Week 6 visit will be defined as trial completers. Protocol specified post-treatment follow-up contacts will not qualify as the "last scheduled visit." Subjects who are not completers are defined as those who "discontinued the trial."

3.11 Definition of Subjects Lost to Follow-Up

Subjects who cannot be contacted on or before the Week 6 visit 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 (ie, brexpiprazole, aripiprazole, and placebo) 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 after counseling (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 at the earliest possible time by telephone. The investigator and sponsor will come as quickly as

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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 discontinue all prohibited medications during the screening period in order to meet the protocol-specified washout periods. Table 4.1-1 provides the required duration of washout for selected prohibited medications. All other prohibited medications must be discontinued at least 24 hours before the first dose of double-blind IMP. Other therapies prohibited prior to enrollment and during the trial are presented in Section 4.2. The Medical Advisor must approve the use of all supplements, vitamins, and over-the-counter medications with the exception of episodic use of ibuprofen, acetaminophen/paracetamol, naproxen, or equivalent.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Table 4.1-1 Washout of Prohibited Medications Required Before the Trial

Medication	Required Washout Prior to Dosing
Antipsychotics	
Oral aripiprazole	14 days
Oral antipsychotics (other than cariprazine and clozapine)	7 days
Depot or long-acting injectable antipsychotics	5 × half-life of the medication prior to screening
Cariprazine (Vraylar) and clozapine	6 months
Antidepressants	
Fluoxetine or Symbyax	28 days[a]
MAOIs	14 days
Citalopram and escitalopram	8 days
Venlafaxine and desvenlafaxine	3 days
All other antidepressants	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	12 hours before scales[c]
Other benzodiazepines	14 days
CYP2D6 inhibitors and CYP3A4 inhibitors and inducers (see Table 4.1-4)	14 days

MAOIs = monoamine oxidase inhibitors.

[a]If 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 in eSource.

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Table 4.1-2	**List of Medications Prohibited During the Trial**
1.	All psychotropic agents including, but not limited to, the following: a) Antipsychotics, including IR IM and depot or long-acting injectable formulations b) Antidepressants (including MAOIs) c) Symbyax d) Mood stabilizers (ie, lithium or anticonvulsants) e) Benzodiazepines, except specific benzodiazepines when used as rescue therapy[a] f) Stimulants with the diagnosis of ADHD and treatment with stimulants within 28 days, otherwise washout of > 5× half- life for subjects without diagnosis of ADHD g) Other psychotropics (ie, atomoxetine)
2.	Ramelteon and other non-benzodiazepine sleep aids, except for limited use of specific medications for the treatment of insomnia[b]
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]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 in eSource.

.

Table 4.1-3	**Oral Benzodiazepine Rescue Therapy During the Trial**		
Oral Benzodiazepine	**Maximum Allowable Dose (mg/day)**		
	Screening	**Baseline to Week 2 Visit**	**After Week 2 Visit to Week 6 Visit**
Lorazepam[a]	3	3	3
Oxazepam[a]	45	45	45
Diazepam[a,b]	15	15	15
Clonazepam[a,b]	1.5	1.5	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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

scales is not feasible, the scales should still be administered and the use of benzodiazepine documented, including a notation of the drug name, dose, and time of administration in eSource.

[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 dosing and for the duration of the trial.

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

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Use of intramuscular (IM) benzodiazepines is prohibited throughout the trial. Continual use of oral benzodiazepines is not permitted during the trial and subjects must discontinue routine benzodiazepine use, except those allowed per Table 4.1-3, for at least 2 weeks prior to the baseline visit. Subjects must not be on more than one benzodiazepine beyond screening. If a subject is receiving two benzodiazepines at screening (eg, lorazepam and oxazepam), attempts should be made to discontinue one of the benzodiazepines, if clinically warranted, to allow potential subjects to enter the trial. The second benzodiazepine should be tapered off over an appropriate amount of time within the 28-day screening period to prevent withdrawal effects prior to the first dose of IMP. Short-term use of specific oral benzodiazepines is allowed during the trial (including the prerandomization washout period) 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 (defined as more days than not) 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 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.

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 331-10-234 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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

medication documented, including a notation of the drug name, dose, and time of administration in 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 (eg. minor surgery, dental surgery, orthopedic surgery) 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, new-onset psychotherapy is prohibited during the trial. In other words, except for inpatient group therapy, 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 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.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs would not include information recorded as medical history at screening for preplanned 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.

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

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires 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 an SAE.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

If a subject is experiencing an EPS, the specific EPS must be indicated on the AE screen in 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 screen in 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 screen in eSource if there is an abnormality or complication.

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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 in eSource provided by the sponsor. The AE 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 in eSource.

Note: Normal pregnancy is not an AE and should not be recorded as one in 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, 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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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 in eSource.

5.5 Pregnancy

For females and for men who are sexually active, there must be a documented agreement that the subject or their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. 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 provide assent or e-sign the electronic ICF stating that the above-mentioned risk factors and the consequences were discussed with her.

A urine or serum pregnancy test for human chorionic gonadotropin will be performed at screening on all female subjects. At any time during the trial if a urine test is performed and is positive, the investigator will follow up with a confirmatory serum test.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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 or infants.

5.6 Procedure for Breaking the Blind

The investigator is encouraged to contact the sponsor/Clinical Research Organization (CRO) medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

24 hours of opening the code. If the blind is broken, the Clinical Safety and Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

5.7 Follow-up of Adverse Events

Post-trial follow-up is not required for eligible subjects who enter the optional open-label trial.

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 screen in eSource with the current status noted. For this trial, information on AEs will be followed for up to 21 (± 2) days after the last dose of IMP has been administered. All nonserious events that are ongoing at the last scheduled contact will be recorded as ongoing in 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 and as described below in Section 5.7.3.

Serious adverse events that are **identified or ongoing at the last scheduled contact** must be recorded on the AE screen in eSource 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.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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

Blood sampling for population PK analysis will be performed on Day 1 (baseline) and Weeks 4 and 6. The sample on Day 1 will be taken at least 1 hour postdose; the other samples are to be drawn within 1–6 hours postdose when possible. Samples will be analyzed for brexpiprazole and metabolite concentrations. The data will be combined with other trials in a population PK/PD analysis to be reported separately.

7 Statistical Analysis

7.1 Sample Size

A sample size of 105 subjects per arm is considered adequate for this trial. It will provide at least 80% power at a nominal 2-sided alpha level of 0.05 to detect a −7.4-point reduction in PANSS Total Score change from baseline to Week 6 for brexpiprazole vs placebo assuming a standard deviation (SD) of 19. With a 1:1:1 allocation ratio, the overall sample size of this trial is planned to be 315 subjects. This will provide a sample size comparable to other similar trials.[21,22]

7.2 Datasets for Analysis

The following analysis samples are defined for this trial:

- Randomized Sample: All subjects who are randomized into the trial.
- Safety Sample: All subjects who are randomized into the trial and who receive at least 1 dose of IMP.
- Efficacy Sample: All subjects who are randomized into the trial who take at least 1 dose of IMP and who have a baseline and at least 1 postbaseline efficacy evaluation for the PANSS Total Score.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

The core dataset for all efficacy analyses is based on the intent-to-treat (ITT) population, which is defined in the Efficacy Sample above. The observed case (OC) dataset will be used in the primary analysis of efficacy endpoints. As described below, in order to handle missing data and restrictions imposed by different types of analyses (eg, change from baseline analysis), datasets derived from the ITT population will be used for the efficacy analyses.

7.3 Handling of Missing Data

The PANSS scale is utilized as the primary efficacy assessment in this trial. The PANSS Total Score is the sum of the rating scores for 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale items from the PANSS panel in eSource. If fewer than 24 of the 30 items are recorded, the PANSS Total Score is not evaluable. If 24 to 29 of the 30 items are recorded, the PANSS Total Score is equal to the mean of the recorded items multiplied by 30 and then rounded to the first decimal place.

In general, missing data will be handled by analysis of mixed model repeated measures (MMRM) methodology based on all data from protocol-specified visits in the ITT population under the assumption of missing at random (MAR), which is a reasonable assumption in longitudinal clinical trials with psychiatric drugs. However, the possibility of "missing not at random" (MNAR) data can never be ruled out. As sensitivity analyses, multiple imputation (MI) will be used to explore data missing mechanisms of MNAR and investigate the response profile of dropout reasons. Details of these exploratory analyses will be provided in the Statistical Analysis Plan (SAP).

The OC dataset will consist of actual observations recorded at each visit during double-blind treatment and no missing data will be imputed. An MMRM will be performed on the OC dataset.

In order to assess sensitivity of results due to missing data, a last observation carried forward (LOCF) analysis will be performed as a sensitivity analysis. In contrast to the OC dataset, the LOCF dataset will include data recorded at a scheduled visit, ie, all OC data, or, if no observation is recorded at that visit, data carried forward from the previously scheduled visit. Baseline data will not be carried forward to impute missing values for the LOCF dataset.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

7.4 Primary and Secondary Endpoint Analyses

7.4.1 Primary Endpoint Analysis

The primary efficacy variable in this trial is the change from baseline to Week 6 in PANSS Total Score.

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

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

- Target Population: Adolescent subjects 13 to 17 years of age with schizophrenia who met the protocol-defined inclusion/exclusion criteria and were qualified for the Efficacy Sample
- Endpoint: Change from Baseline to Week 6 in the PANSS Total Score
- Intercurrent Events: Refers to premature treatment discontinuation (ie, early dropout) prior to Week 6 attributable to adverse events, lack of efficacy, withdrawal of consent/assent, or any other causes
- Measure of Intervention Effect: Difference in endpoint means between the brexpiprazole arm and the placebo arm.

In this hypothetical strategy, the event of withdrawing IMP is considered MAR, and the primary endpoint of the trial could be considered as a combination of the responses of on treatment completers at Week 6 and the imputation of the endpoint to Week 6 following the trend in each treatment group, using the MMRM method to impute missing data for

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

subjects who withdraw IMP during the trial. All data collected during the trial treatment period will be used for statistical analysis. For the primary efficacy analysis, the treatment effect will be estimated using the MMRM method described below. Under the MAR assumption, MMRM provides an unbiased estimate of treatment effect for the treatment period. Analyses with missing values imputed by MI under MNAR and other methods will be performed as sensitivity analyses.

The primary statistical comparison of interest is brexpiprazole 2–4 mg versus placebo. With the assumption of MAR, an MMRM analysis with fixed-effect factors of treatment, trial site, visit, treatment by visit interaction, and fixed effect covariates of baseline and baseline by visit interaction will be applied to the change from baseline from Week 1 to Week 6 in PANSS Total Score based on all available data (OC dataset). The data will be modeled using an unstructured variance covariance matrix for the within subject variation. A statistical test of the least squares (LS) mean differences at Week 6 of the MMRM analysis will serve as the analysis of the primary endpoint. The Efficacy Sample will be used in the analysis of the primary endpoint. The comparison will be tested at a significance level of 0.05 (2-side).

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

In order to explore the robustness of the primary analysis based on the MAR assumption, sensitivity analysis of the primary efficacy endpoint under the MNAR assumption will be conducted, using a pattern-mixture model.

Additional details, including pooling of small trial sites are provided in the SAP.

7.4.2 Secondary Endpoint Analysis

For all continuous secondary endpoints (CGI-S, CGI-I, CGAS, PANSS Positive Subscale score, and PANSS Negative Subscale score), an MMRM analysis with factors of treatment, trial site, visit, treatment by visit interaction, and baseline and baseline by visit interaction as covariates with an unstructured variance covariance structure to the visits will be applied to these endpoints based on all available data (OC dataset). The CGI-I score at endpoint will be analyzed at the last visit using the Cochran-Mantel-Haenszel

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

(CMH) row mean scores differ test controlling for trial site. The CMH general association test controlling for trial site will be applied to the analysis of percentage of subjects achieving response and remission by week on LOCF data, for the Efficacy Sample. Response is defined as reduction of ≥ 30% from baseline in PANSS Total Score or CGI-I score of 1 or 2. Remission is defined as a score of ≤ 3 on each of the following specific PANSS items: delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerisms/posturing (G5), blunted affect (N1), passive/apathetic social withdrawal (N4), and lack of spontaneity and conversation flow (N6).

7.4.3 Exploratory Endpoint Analysis

The change in the P-Q-LES-Q total score (ie, 14 items) will be summarized using an MMRM analysis with factors of treatment, trial site, visit, treatment by visit interaction, and baseline and baseline by visit interaction as covariates, with an unstructured variance covariance structure. All available data (OC dataset) will be applied in the model. Additionally, change from baseline in the overall score of P-Q-LES-Q will be summarized using the CMH row mean scores differ test controlling for trial site.

Hospitalization data will be summarized by 2 categories: hospitalization due to worsening schizophrenia and hospitalizations due to other causes.

Additional details for exploratory endpoint analysis are provided in the SAP.

7.4.4 Interim Analysis

No formal unblinded interim analysis is planned for this trial.

7.5 Analysis of Demographic and Baseline Characteristics

Demographic characteristics, disease severity, and psychiatric and medical history at (predose) baseline will be summarized by descriptive statistics, eg, proportion, mean, median, SD, and minimum and maximum values. These summary statistics will be reviewed to identify any potential lack of balance between the treatment groups in the Randomized Sample.

7.6 Safety Analysis

Standard safety variables to be analyzed include AEs, clinical laboratory tests, vital signs, ECGs, body weight, waist circumference, and body mass index. In addition, data from the following safety scales will be evaluated: SAS, AIMS, BARS, and C-SSRS. The safety analysis will be conducted based on the Safety Sample which is defined in

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Section 7.2. In general, baseline of a safety variable is defined as the last observation of the variable before taking the first dose of IMP, unless specified otherwise. Details of the safety analysis will be provided in the SAP.

7.6.1 Adverse Events

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

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

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

7.6.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the routine clinical laboratory measurements, prolactin concentrations, HbA1c, and TSH will be provided. In addition, potentially clinically relevant results in laboratory tests identified using prospectively defined criteria, such as liver function tests for cases of potential serious hepatotoxicity, will be summarized.

7.6.3 Physical Examination, Waist Circumference, and Vital Signs Data

By-patient listings will be provided for physical examination data. Summary statistics for changes from baseline in vital signs, body weight, waist circumference, and BMI will be provided. Potentially clinically relevant results in vital signs and body weight will also be summarized. In addition, z-scores for height, body weight, and BMI from baseline will also be summarized by visit. Additional details will be provided in the SAP.

7.6.4 Electrocardiogram Data

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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: $QTcN = QT/(RR)^{0.37}$

7.6.5 Other Safety Data

Change from baseline in scores for the SAS, AIMS, and BARS scales will be evaluated using Analysis of covariance (ANCOVA) with baseline value as covariate and treatment as factor. The OC datasets of the Safety Sample will be used in the analyses of these EPS scales.

Suicidality monitored during the trial using the C-SSRS will be summarized as the number and percentage of subjects reporting any suicidal behavior, ideation, behavior by type (4 types), ideation by type (5 types), and treatment-emergent suicidal behavior and ideation, based on the Safety Sample.

Additional details about other safety data will be provided in the SAP.

8 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the brexpiprazole IB.[12]

8.1 Packaging and Labeling

Trial medication will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. The IMP (brexpiprazole, aripiprazole, and placebo) will be supplied as child-resistant blister cards, each containing sufficient tablets for the window visit. Each blister card 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. When requested by the site, an IWRS will assign a specific blister card to be dispensed to a subject.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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, aripiprazole, and placebo 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 (brexpiprazole, aripiprazole, and placebo) 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 designee agent, or destroyed at the trial sites. 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 and 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)

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

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

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

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

8.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, telephone 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 complaint sample is available for return. If complaint sample is available for return, return it in the product retrieval package, which will be provided by the sponsor.

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

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. 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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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. Per regulatory guidelines, sites must retain any documents that are uploaded to eSource.

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.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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

10 Quality Control and Quality Assurance

10.1 Monitoring

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

10.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent 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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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, or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

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

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent 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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

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.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

15 References

1 Messias E, Chen CY, Eaton WW. Epidemiology of schizophrenia: Review of findings and myths. Psychiatr Clin North Am. 2007;30(3):323-338.

2 McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30:67-76.

3 van Os J, Kapur S. Schizophrenia. Lancet. 2009;374(9690):635-645.

4 American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. J Clin Psychiatry. 2004;65(2):267-272.

5 David SR, Taylor CC, Kinon BJ, Breier A. The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia. Clin Ther. 2000;22(9):1085-1096.

6 Volavka J, Czobor P, Cooper TB, Sheitman B, Lindenmayer JP, Citrome L, et al. Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol. J Clin Psychiatry. 2004;65(1):57-61.

7 Hollis C. Adult outcomes of child- and adolescent-onset schizophrenia: Diagnostic stability and predictive validity. Am J Psychiatry. 2000;157(10):1652-1659.

8 Sikich L. Efficacy of atypical antipsychotics in early-onset schizophrenia and other psychotic disorders. J Clin Psychiatry. 2008;69(Suppl 4):21-25.

9 Lay B, Blanz B, Hartmann M, Schmidt MH. The psychosocial outcome of adolescent-onset schizophrenia: A 12-year followup. Schizophr Bull. 2000;26(4):801-816.

10 Findling RL, Johnson JL, McClellan J, Frazier JA, Vitiello B, Hamer RM, et al. Double-blind maintenance safety and effectiveness findings from the treatment of early-onset schizophrenia spectrum (TEOSS) study. J Am Acad Child Adolesc Psychiatry. 2010;49(6):583-594.

11 Otsuka Pharmaceutical Co, Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., H. Lundbeck A/S. REXULTI® (brexpiprazole) Investigator's Brochure, Edition 12. Otsuka Report, issued 18 Aug 2016.

12 Brexpiprazole (OPC-34712) Investigator's Brochure, Otsuka Pharmaceutical Development & Commercialization, Inc. Version No. 9, 09 Sep 2013.

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

[14] Kay SR, Fiszbein A, Opler LA. Positive and Negative Syndrome Scale (PANSS) Technical Manual. North Tonawanda, NY: Multi-Health Systems; 2006.

[15] Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A children's global assessment scale (CGAS). Arch Gen Psychiatry. 1983;40(11):1228-1231.

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

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

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

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

[20] Kaufman J, Birmaher B, Brent D, Rao U, Ryan N. Kiddie-Sads-Present and Lifetime Version (K-SADS-PL). Version 1.0 of Oct 1996 ed. Pittsburgh, PA: Department of Psychiatry, University of Pittsburgh School of Medicine; 1996.

[21] US Food and Drug Administration. Clinicaltrial.gov register. Efficacy and Safety of Cariprazine in the Treatment of Adolescent Participants (13 to 17 Years of Age) With Schizophrenia. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03817502. Assessed on 08 March 2022.

[22] European Medicines Agency/59804/2021. Committee for Medicinal Products for Human Use (CHMP). Latuda Assessment Report. 23 July 2020. Procedure No. EMEA/H/C/002713/II/0029.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

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).

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST (SGOT)	≥ 3 x ULN
ALT (SGPT)	≥ 3 × ULN
Alkaline phosphatase	≥ 3 × ULN
LDH	≥ 3 × 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 × 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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

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 or QTcN ≥ 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.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

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; 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

Collect PK blood samples using 4-mL draw green-top Vacutainer® evacuated collection tubes containing sodium heparin. After obtaining the blood sample, mix the collection tube thoroughly by slowly inverting it several times before placing it in an ice/water bath. Within 45 minutes of collection, process collection tubes in a refrigerated centrifuge set at approximately 2000 x G for 15 minutes at approximately 5°C ± 3°C. Transfer duplicate plasma aliquots of approximately equal volume, using standard laboratory technique, into 2 appropriately labeled storage tubes. Within 90 minutes of collection, store both plasma aliquot samples in a freezer set to maintain a temperature −70°C ± 10°C. Specimens must be neatly packed and restrained in an insulated container appropriate for dry ice, and organized by subject where possible. Completely fill the insulated container and avoid air spaces that allow evaporation of the dry ice. Samples must be shipped via an overnight carrier, Monday through Thursday, to the central laboratory. Shipments should not be made on Fridays, Saturdays, or any day prior to a holiday. Plasma Aliquot 1 samples should be shipped preferably on the day of collection or else within 1 week of sample collection. Plasma Aliquot 2 specimens should be shipped to the central laboratory using the same procedure, once confirmation is received that the Plasma Aliquot 1 specimen was received.

Pharmacogenomics Sample

Blood samples for pharmacogenomic analysis will be collected into one 6-mL K2EDTA Vacutainer® tube. Each tube should be gently inverted 10 times to ensure proper mixing with the anticoagulant. Samples should be refrigerated in an upright position at 4°C for at least one day (no longer than 4 days). The samples should then be stored at -20°C or below prior to shipment. If refrigerating is not possible, samples may be frozen directly

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

from ambient. Samples must be shipped to the central laboratory via an overnight carrier, Monday through Thursday, preferably on the day of collection or else within 1 week of sample collection. Shipments should not be made on Fridays, Saturdays, or any day prior to a holiday.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Appendix 5 Positive and Negative Syndrome Scale (PANSS)

This scale consists of symptom constructs, each to be rated on a 7-point scale of severity.

For each symptom, please mark the rating which best describes the patient's present condition (from 1 = absent to 7 = extreme).

1=absent	2=minimal	3=mild	4=moderate
5=moderate severe	6=severe	7=extreme	

POSITIVE SCALE (P)

1. DELUSIONS	Beliefs that are unfounded, unrealistic, and idiosyncratic. **Basis for Rating:** thought content expressed during the interview and its influence on social relations, and behavior, as reported by primary care workers or family.
2. CONCEPTUAL DISORGANIZATION	There is a disorganized thinking process characterized by goal-directed sequencing disruption (eg circumstantiality, tangentiality, loose associations, non-sequiturs, gross illogicality, or thought block). **Basis for Rating**: cognitive verbal processes observed during the interview.
3. HALLUCINATORY BEHAVIOR	Verbal report or behavior indicate perceptions that are not generated by external stimuli. These occurrences may be auditory, visual, olfactory, or somatic. **Basis for Rating**: Verbal report and physical manifestations during the interview as well as behavior reports by primary care workers or family.
4. EXCITEMENT	Hyperactivity is reflected in accelerated motor behavior, heightened responsivity to stimuli, hypervigilance, or excessive mood lability. **Basis for Rating**: behavioral manifestations during the interview, as well as behavior reports by primary care workers or family.
5. GRANDIOSITY	There exists an exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power, and moral righteousness. **Basis for Rating**: thought content expressed in the interview and its influence on behavior as reported by primary care workers or family.
6. SUSPICIOUSNESS/ PERSECUTION	Unrealistic or exaggerated ideas of persecution are shown, as reflected in guardedness, a distrustful attitude, suspicious hypervigilance, or frank delusions that others mean harm. **Basis for Rating**: thought content expressed in the interview and its influence on behavior as reported by primary care workers or family.
7. HOSTILITY	There are verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behavior, verbal abuse, and assaultiveness. **Basis for Rating**: interpersonal behavior observed during the interview and reports by primary care workers or family.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

NEGATIVE SCALE (N)

1. BLUNTED AFFECT	There is diminished emotional responsiveness characterized by a reduction in facial expression, modulation of feelings, and communicative gestures. **Basis for Rating**: observation of the patient's affective tone and emotional responsiveness during the interview.
2. EMOTIONAL WITHDRAWAL	There is a lack of interest in, involvement with, and affective commitment to life's events. **Basis for Rating**: reports of functioning from primary care workers or family, and interpersonal behavior observations during the interview.
3. POOR RAPPORT	There is a lack of interpersonal empathy, a lack of openness in conversation, and also a minimal sense of closeness, interest or involvement with the interviewer. Poor rapport is evidenced by interpersonal distancing and reduced verbal and nonverbal communication. **Basis for Rating**: interpersonal behavior during the interview.
4. PASSIVE/APATHETIC AND SOCIAL WITHDRAWAL	Diminished interest and initiative in social interactions due to passivity, apathy, anergy, or avolition leading to reduced interpersonal involvements and neglect of daily living activities. **Basis for Rating**: social behavior reports from primary care workers or family.
5. DIFFICULTY IN ABSTRACT THINKING	The patient shows impairment using the abstract-symbolic thinking mode, as demonstrated by difficulty with classification, forming generalizations, and moving beyond concrete or egocentric thinking in problem-solving tasks. **Basis for Rating**: responses to questions on similarities and proverb interpretation, and use of concrete vs. abstract mode during the interview.
6. LACK OF SPONTANEITY AND FLOW OF CONVERSATION	There is a reduction in the normal flow of communication associated with apathy, avolition, defensiveness, or cognitive deficit. This disruption in normal flow is manifested by diminished fluidity and productivity of the verbal interactional process. **Basis for Rating**: cognitive-verbal processes observed during the interview.
7. STEREOTYPED THINKING	There is decreased fluidity, spontaneity, and flexibility of thinking, as evidenced in rigid, repetitious, or barren thought content. **Basis for Rating**: cognitive-verbal processes observed during the interview.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

GENERAL PSYCHOPATHOLOGY SCALE (G)

1. SOMATIC CONCERN	There are physical complaints or beliefs about bodily illness or malfunctions. This patient's concerns may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease. **Basis for Rating**: thought content expressed in the interview.
2. ANXIETY	There are subjective experiences of nervousness, worry, apprehension, or restlessness, ranging from excessive concern about the present or future to feelings of panic. **Basis for Rating**: verbal report during the interview and corresponding physical manifestations.
3. GUILT FEELINGS	The patient exhibits a sense of remorse or self-blame for real or imagined misdeeds in the past. **Basis for Rating**: verbal reports of guilt feelings during the interview and the influence of these feelings on the patient's attitudes and thoughts.
4. TENSION	There are overt physical manifestation of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating, and restlessness. **Basis for Rating**: verbal report attesting to anxiety and, thereupon, the severity of physical manifestations of tension observed during the interview.
5. MANNERISM AND POSTURING	Unnatural movements or posture are shown as characterized by an awkward, stilted, disorganized, or bizarre appearance. **Basis for Rating**: observation of physical manifestations during the interview as well as reports from primary care workers or family.
6. DEPRESSION	There are feelings of sadness, discouragement, helplessness, and pessimism. **Basis for Rating**: verbal report of depressed mood during the interview and its observed influence on the patient's attitude and behavior as reported from primary care workers or family.
7. MOTOR RETARDATION	There is a reduction in motor activity reflected by the slowing or lessening of movements and speech, diminished responsiveness to stimuli, and reduced body tone. **Basis for Rating**: manifestations during the interview as well as reports from primary care workers or family.
8. UNCOOPERATIVENESS	There is an active refusal to comply with the will of significant others, including the interviewer, hospital staff, or family, perhaps associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility, or belligerence. **Basis for Rating**: interpersonal behavior observed during the interview as well as reports from care workers or family.
9. UNUSUAL THOUGHT CONTENT	Thinking is characterized by strange, fantastic, or bizarre ideas, ranging from those that are remote or atypical to those that are distorted, illogical, and patently absurd. **Basis for Rating**: thought content expressed during the interview.
10. DISORIENTATION	There is a lack of awareness of one's relationship to one's surroundings, including persons, places, and time that may be due to confusion or withdrawal. **Basis for Rating**: responses to interview questions on orientation.
11. POOR ATTENTION	Poor focused alertness is manifested by poor concentration, distractibility from internal and external stimuli, and difficulty in harnessing, sustaining, or shifting focus to new stimuli.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

		Basis for Rating: manifestations during the interview.
12.	LACK OF JUDGMENT AND INSIGHT	There is an impaired awareness or understanding of one's own psychiatric condition and life situation. This impairment is evidenced by the patient's inability to recognize past or present psychiatric illness or symptoms, denial of his or her need for psychiatric hospitalization or treatment, decisions characterized by poor anticipation of the consequences, and unrealistic short-term and long-range planning. **Basis for Rating**: thought content expressed during the interview.
13.	DISTURBANCE OF VOLITION	There is disturbance in the willful initiation, sustenance, and control of one's thoughts, behavior, movements, and speech. **Basis for Rating**: thought content and behavior manifested during the interview.
14.	POOR IMPULSE CONTROL	There is disordered regulation and control when acting on inner urges, resulting in sudden, unmodulated, arbitrary, or misdirected discharge of tension and emotions without concern about the consequences. **Basis for Rating**: the patient's behavior during the interview and reports from primary care workers or family.
15.	PREOCCUPATION	There is absorption with internally generated thoughts and feelings or with autistic experiences to the detriment of reality orientation and adaptive behavior. **Basis for Rating**: interpersonal behavior observed during the interview.
16.	ACTIVE SOCIAL AVOIDANCE	There is diminished social involvement associated with unwarranted fear, hostility, or distrust. **Basis for Rating**: social functioning reports from primary care workers or family.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Appendix 6 Children's Global Assessment Scale (CGAS)

The C-GAS is a 100-point rating scale measuring psychological, social, and school functioning for children aged 6-17. It was adapted from the Adult Global Assessment Scale and is a valid and reliable tool for rating a child's general level of functioning on a health-illness continuum.

100-91	**Superior functioning** in all areas (at home, at school and with peers), involved in a range or activities and has many interests (e.g., has hobbies or participates in extracurricular activities or belongs to an organized group such as Scouts, etc.). Likable, confident, "everyday" worries never get out of hand. Doing well in school, no symptoms
90-81	**Good functioning in all areas.** Secure in family, school and with peers. There may be transient difficulties and "everyday" worries that occasionally get out of hand (e.g. mild anxiety associated with an important exam, occasional "blow ups" with siblings, parents or peers).
80-71	**No more than slight impairment in functioning** at home, at school, or with peers. Some disturbance of behavior or emotional distress may be present in response to life stresses (e.g., parental separations, deaths, births of a sib) but these are brief and interference with functioning is transient. Such children are only minimally disturbing to others who are not considered deviant by those who know them.
70-61	**Some difficulty in a single area, but generally functioning pretty well**, (e.g., sporadic or isolated antisocial acts, such as occasionally playing hooky or petty theft; consistent minor difficulties with school work, mood changes of brief duration; fears and anxieties which do not lead to gross avoidance behavior; self doubts). Has some meaningful interpersonal relationships. Most people who do not know the child well would not consider him/her deviant but those who do know him/her well might express concern.
60-51	**Variable functioning with sporadic difficulties or symptoms** in several but not all social areas. Disturbance would be apparent to those who encounter the child in a dysfunctional setting or time but not those who see the child in other settings.
50-41	**Moderate degree of interference in functioning in most social areas or severe impairment of functioning in one area**, such as might result from, for example, suicidal preoccupations and ruminations, school refusal and other forms of anxiety, obsessive rituals, major conversion symptoms, frequent anxiety attacks, frequent episodes of aggressive or other antisocial behavior with some preservation of meaningful social relationships.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

40-31	**Major impairment in functioning in several areas and unable to function in one of these areas,** i.e.**,** disturbed at home, at school, with peers, or in the society at large, e.g., persistent aggression without clear instigation; markedly withdrawn and isolated behavior due to either mood or thought disturbance, suicidal attempts with clear lethal intent. Such children are likely to require special schooling or hospitalization or withdrawal from school (but this is not a sufficient criterion for inclusion in this category).
30-21	**Unable to function in almost all areas,** e.g., stays at home, in ward or in bed all day without taking part in social activities OR severe impairment in reality testing OR serious impairment in communication (e.g., sometimes incoherent or inappropriate).
20-11	**Needs considerable supervision** to prevent hurting other or self, e.g., frequently violent, repeated suicide attempts OR to maintain personal hygiene OR gross impairment in all forms of communication, e.g., severe abnormalities in verbal and gestural communication, marked social aloofness, stupor, etc.
10-1	**Needs constant supervision** (24-hour care) due to severely aggressive or self-destructive behavior or gross impairment in reality testing, communication, cognition, affect, or personal hygiene.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Appendix 7 Clinical Global Impression - Severity of Illness Scale (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed	4 = Moderately ill
1 = Normal, not at all ill	5 = Markedly ill
2 = Borderline mentally ill	6 = Severely ill
3 = Mildly ill	7 = Among the most extremely ill patients

Guy, W. ed. ECDEU Assessment Manual for Psychopharmacology. US Dept of HEW, Publication No. (Adm): 76-338, 1976.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Appendix 8 Clinical Global Impression - Improvement scale (CGI-I)

Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to his/her condition at baseline, how much has patient changed?

0 = Not assessed	4 = No change
1 = Very much improved	5 = Minimally worse
2 = Much improved	6 = Much worse
3 = Minimally improved	7 = Very much worse

Guy, W. ed. ECDEU Assessment Manual for Psychopharmacology. US Dept of HEW, Publication No. (Adm): 76-338, 1976.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Appendix 9 Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-Q-LES-Q)

INSTRUCTIONS: This survey asks for your views about your general health, well-being, and feelings about your life. Please answer EVERY question by circling the number for your response. If you are not sure about how to answer a question, please give the best answer you can. Remember, there are no right or wrong answers.

	Very Poor	Poor	Fair	Good	Very Good
Over the past week, how have things been with...					
1. Your health?	1	2	3	4	5
2. Your mood or feelings?	1	2	3	4	5
3. School or learning?	1	2	3	4	5
4. Helping out at home?	1	2	3	4	5
5. Getting along with friends?	1	2	3	4	5
6. Getting along with your family?	1	2	3	4	5
7. Play or free time?	1	2	3	4	5
8. Getting things done?	1	2	3	4	5
9. Your love or affection?	1	2	3	4	5
10. Getting or buying things?	1	2	3	4	5
11. The place where you live?	1	2	3	4	5
12. Paying attention?	1	2	3	4	5
13. Your energy level?	1	2	3	4	5
14. Feelings about yourself?	1	2	3	4	5
15. Overall, how has your life been?	1	2	3	4	5

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Appendix 10 Simpson Angus Scale (SAS)

Circle the appropriate score for each item:	
1.	**GAIT** The patient is examined as he walks into the examining room; his gait, the swing of arms, his general posture; all form the basis for an overall score for this item. This is rated as follows:
0	Normal
1	Mild diminution in swing while the patient is walking
2	Obvious diminution in swing suggesting shoulder rigidity
3	Stiff gait with little or no arm swing noticeable
4	Rigid gait with arms slightly pronated; or stooped-shuffling gait with propulsion and retropulsion.
2.	**ARM DROPPING** The patient and the examiner both raise their arms to shoulder height and let them fall to their sides, in a normal subject a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly.
0	Normal, free fall with loud slap and rebound
1	Fall slowed slightly with less audible contact and little rebound
2	Fall slowed, no rebound
3	Marked slowing, no slap at all
4	Arms fall as though against resistance; as though through glue
3.	**SHOULDER SHAKING** The subject's arms are bent at a right angle at the elbow and taken one at a time by the examiner who grabs one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint
4.	**ELBOW RIGIDITY** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to the procedure is rated. (The presence of cogwheel rigidity is noted separately.)
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

5.	**WRIST RIGIDITY** The wrist is held in one hand and then the fingers held by the examiner's other hand with the wrist moved to extension, and both ulnar and radial deviation. The resistance to this procedure is rated:
0	Normal
1	Slight stiffness and resistance
2	Moderate stiffness and resistance
3	Marked rigidity with difficulty in passive movement
4	Extreme stiffness and rigidity with almost a frozen joint
6.	**HEAD ROTATION** The patient sits or stands and is told that you are going to move his head from side to side, that it will not hurt and that he should try and relax. (Questions about pain in the cervical area or difficulty in moving his head should be obtained to avoid causing any pain.) Clasp the patient's head between the two hands with fingers on back of the neck. Gently rotate the head in a circular motion 3 times and evaluate the muscular resistance to the movement.
0	Loose, no resistance
1	Slight resistance to movement although the time to rotate may be normal
2	Resistance is apparent and time of rotation is slowed
3	Resistance is obvious and rotation is slowed
4	Head appears stiff and rotation is difficult to carry out
7.	**GLABELLA TAP** Subject is told to open his eyes and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:
0	0-5 blinks
1	6-10 blinks
2	11-15 blinks
3	16-20 blinks
4	21 and more blinks
8.	**TREMOR** Patient is observed walking into examining room and then is examined for this item:
0	Normal
1	Mild finger tremor, obvious to sight and touch
2	Tremor of hand or arm occurring spasmodically
3	Persistent tremor of one or more limbs
4	Whole body tremor
9.	**SALIVATION** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:
0	Normal
1	Excess salivation so that pooling takes place if the mouth is open and the tongue raised
2	Excess salivation is present and might occasionally result in difficulty in speaking
3	Speaking with difficulty because of excess salivation
4	Frank drooling

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

10.	**AKATHISIA** Patient is observed for restlessness. If restlessness is noted, ask: "Do you feel restless or jittery inside; is it difficult to sit still?" Subjective response is not necessary for scoring but patient report can help make the assessment.
0	No restlessness reported or observed
1	Mild restlessness observed
2	Moderate restlessness observed
3	Restlessness is frequently observed
4	Restlessness persistently observed

Adapted and used with permission by: Simpson GN, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica. 1970;45(suppl 212):11-9.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Appendix 11 Abnormal Involuntary Movement Scale (AIMS)

Movement ratings: rate highest severity observed. Rate movements that occur upon activation one **less** than those observed spontaneously.		**Code for items 1-7:** **0** = None **1** = Minimal, may be extreme normal **2** = Mild **3** = Moderate **4** = Severe					
		(Circle One)					
FACIAL AND ORAL MOVEMENTS:	**1.** **MUSCLES OF FACIAL EXPRESSION** e.g. movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing	**0**	**1**	**2**	**3**	**4**
	2. **LIPS AND PERIORAL AREA** e.g. puckering, pouting, smacking.	**0**	**1**	**2**	**3**	**4**
	3. **JAW** e.g. biting, clenching, chewing, mouth opening, lateral movement.	**0**	**1**	**2**	**3**	**4**
	4. **TONGUE** Rate only increase in movement both in and out of mouth, not inability to sustain movement.	**0**	**1**	**2**	**3**	**4**
EXTREMITY MOVEMENTS:	**5.** **UPPER (ARMS, WRISTS, HANDS, FINGERS)** include choreic movements (i.e. rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e. slow, irregular, complex, serpentine). Do not include tremor (i.e. repetitive, regular, rhythmic).	**0**	**1**	**2**	**3**	**4**
	6. **LOWER (LEGS, KNEES, ANKLES, TOES)** e.g. lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	**0**	**1**	**2**	**3**	**4**
TRUNK MOVEMENTS:	**7.** **NECK, SHOULDERS, HIPS** e.g. rocking, twisting, squirming, pelvic gyrations	**0**	**1**	**2**	**3**	**4**
GLOBAL JUDGMENTS:	**8.** Severity of abnormal movements	None, normal **0** Minimal **1** Mild **2** Moderate **3** Severe **4**					
	9. Incapacitation due to abnormal movements	None, normal **0** Minimal **1** Mild **2** Moderate **3** Severe **4**					
	10. Patient's awareness of abnormal movements Rate only subject's report.	No awareness **0** Aware, no distress **1** Aware, mild distress **2** Aware, moderate distress **3** Aware, severe distress **4**					
DENTAL STATUS:	**11.** Any current problems with teeth or dentures?	No **0** Yes **1**					
	12. Does patient usually wear dentures?	No **0** Yes **1**					

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

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Appendix 12 Barnes Akathisia Rating Scale (BARS)

Instructions

Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs
1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging one leg while sitting, *or* rocking from foot to foot or "walking on the spot" when standing, *but* movements present for less than half the time observed
2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
3 Patient is constantly engaged in characteristic restless movements, or has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness
0 Absence of inner restlessness
1 Non-specific sense of inner restlessness
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, or complains of inner restlessness aggravated specifically by being required to stand still
3 Awareness of intense compulsion to move most of the time or reports strong desire to walk or pace most of the time

Distress related to restlessness
0 No distress
1 Mild
2 Moderate
3 Severe

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Global clinical assessment of akathisia

0 *Absent*. No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia

1 *Questionable*. Non-specific inner tension and fidgety movements

2 Mild akathisia. Awareness of restlessness in the legs or inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress

3 *Moderate akathisia*. Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing

4 *Marked akathisia*. Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing

5 *Severe akathisia*. The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia

Reproduced from: Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-6.

© 1989 The Royal College of Psychiatrists.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Appendix 13 Udvalg for Kliniske Undersogelser (UKU)

The UKU is used to assess side effects of subjects being treated with antipsychotic drugs and to determine whether there is a causal relationship. Assessment of the individual symptoms is best accomplished by a semi structured interview with the subject during which the scale is gone through point by point as well as obtaining information from case records and clinical observation.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

THE UKU SIDE EFFECTS RATING SCALE FOR THE REGISTRATION OF UNWANTED EFFECTS OF PSYCHOTROPICS MANUAL ENGLISH VERSION, October 1986

(UKU)

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Patient Information													
Personal Notes													

Psychic									
Category of side effects	**Symptom**	**Not Ass.**	**Degree last 3 days (see manual)**				**Causal relationship**		
		9	0	1	2	3			
1		☐	☐	☐	☐	☐	☐	☐	☐
2		☐	☐	☐	☐	☐	☐	☐	☐
3		☐	☐	☐	☐	☐	☐	☐	☐
4		☐	☐	☐	☐	☐	☐	☐	☐
5		☐	☐	☐	☐	☐	☐	☐	☐
6		☐	☐	☐	☐	☐	☐	☐	☐
7	Increased Duration of Sleep	☐	☐	☐	☐	☐	☐	☐	☐
8	Reduced Duration of Sleep	☐	☐	☐	☐	☐	☐	☐	☐
9	Increased Dream Activity	☐	☐	☐	☐	☐	☐	☐	☐
0	Emotional Indifference	☐	☐	☐	☐	☐	☐	☐	☐

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Neurologic									
Category of side effects	Symptom	Not Ass.	Degree last 3 days (see manual)				Causal relationship		
		9	0	1	2	3	[illegible]	[illegible]	[illegible]
2.1	Dystonia	☐	☐	☐	☐	☐	☐	☐	☐
2.2	Rigidity	☐	☐	☐	☐	☐	☐	☐	☐
2.3	Hypokinesia/Akinesia	☐	☐	☐	☐	☐	☐	☐	☐
2.4	Hyperkinesia logic	☐	☐	☐	☐	☐	☐	☐	☐
2.5	Tremor	☐	☐	☐	☐	☐	☐	☐	☐
2.6	Akathisia	☐	☐	☐	☐	☐	☐	☐	☐
2.7	Epileptic Seizures	☐	☐	☐	☐	☐	☐	☐	☐
2.8	Paraesthesias	☐	☐	☐	☐	☐	☐	☐	☐

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Autonomic									
Category of side effects	Symptom	Not Ass.	Degree last 3 days (see manual)				Causal relationship		
		9	0	1	2	3			
1		☐	☐	☐	☐	☐	☐	☐	☐
2		☐	☐	☐	☐	☐	☐	☐	☐
3		☐	☐	☐	☐	☐	☐	☐	☐
4		☐	☐	☐	☐	☐	☐	☐	☐
5		☐	☐	☐	☐	☐	☐	☐	☐
6		☐	☐	☐	☐	☐	☐	☐	☐
7		☐	☐	☐	☐	☐	☐	☐	☐
8		☐	☐	☐	☐	☐	☐	☐	☐
9		☐	☐	☐	☐	☐	☐	☐	☐
10		☐	☐	☐	☐	☐	☐	☐	☐
11		☐	☐	☐	☐	☐	☐	☐	☐

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Other									
Category of side effects	Symptom	Not Ass.	Degree last 3 days (see manual)				Causal relationship		
		9	0	1	2	3	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	☐	☐						
[illegible]	[illegible]			☐	☐	☐	☐	☐	☐
[illegible]	[illegible]			☐	☐	☐	☐	☐	☐
[illegible]	[illegible]			☐	☐	☐	☐	☐	☐
[illegible]	[illegible]			☐	☐	☐	☐	☐	☐
[illegible]	[illegible]			☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐
[illegible]	[illegible]	☐	☐	☐	☐	☐	☐	☐	☐

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Other-continued									
Category of side effects	Symptom	Not Ass.	Degree last 3 days (see manual)				Causal relationship		
		9	0	1	2	3			
4		☐	☐	☐	☐	☐	☐	☐	☐
5		☐	☐	☐	☐	☐	☐	☐	☐
6		☐	☐	☐	☐	☐	☐	☐	☐
7		☐	☐						
4				☐	☐	☐	☐	☐	☐
5				☐	☐	☐	☐	☐	☐
4				☐	☐	☐	☐	☐	☐
8		☐	☐	☐	☐	☐	☐	☐	☐
9		☐	☐	☐	☐	☐	☐	☐	☐

Global assessment of the interference by existing side effects with the patient's daily performance:		Assessed by	
		Patient	Doctor
0		☐	☐
1		☐	☐
2		☐	☐
3		☐	☐

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Consequence		
0	[illegible]	☐
1	[illegible]	☐
2	[illegible]	☐
3	[illegible]	☐

	[illegible]	[illegible]		[illegible]		[illegible]		[illegible]		[illegible]		[illegible]	
Signature													

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Appendix 14 New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY AACENT)

Description: The NY-AACENT is intended to be 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), but can be utilized with other age groups as appropriate. Each of the seven items is derived from the seven domains identified by MATRICS[1].

[1] Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, Fenton WS, Frese F, Goldberg TE, Heaton RK, Keefe RS, Kern RS, Kraemer H, Stover E, Weinberger DR, Zalcman S, Marder SR. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. Biol Psychiatry. 2004; 56(5):301-7.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Clinician Form: Please complete each section below:

1. Working memory: Trouble remembering things that people (parents, teachers, friends) have just said?

☐ Present during past week ☐ Not present in past week	☐ Evident During Visit ☐ Not Evident During Visit	☐ Not drug related ☐ Due to study drug ☐ Other drug ☐ Drug/drug interaction ☐ Not applicable	☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐ Not applicable	☐ Functional/ Role Impairment ☐ No Functional/ Role Impairment ☐ Not applicable

2. Attention/Vigilance: Trouble paying attention in class, home, or while playing games, watching TV, browsing the internet or using computers?

☐ Present during past week ☐ Not present in past week	☐ Evident During Visit ☐ Not Evident During Visit	☐ Not drug related ☐ Due to study drug ☐ Other drug ☐ Drug/drug interaction ☐ Not applicable	☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐ Not applicable	☐ Functional/ Role Impairment ☐ No Functional/ Role Impairment ☐ Not applicable

3. Verbal Learning/Memory: Difficulty remembering or learning words to things (book, songs, TV shows)? Trouble coming up with words in conversation?

☐ Present during past week ☐ Not present in past week	☐ Evident During Visit ☐ Not Evident During Visit	☐ Not drug related ☐ Due to study drug ☐ Other drug ☐ Drug/drug interaction ☐ Not applicable	☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐ Not applicable	☐ Functional/ Role Impairment ☐ No Functional/ Role Impairment ☐ Not applicable

4. Visual Learning/Memory: Patient has difficulty recalling how things look, such as shapes and colors?

☐ Present during past week ☐ Not present in past week	☐ Evident During Visit ☐ Not Evident During Visit	☐ Not drug related ☐ Due to study drug ☐ Other drug ☐ Drug/drug interaction ☐ Not applicable	☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐ Not applicable	☐ Functional/ Role Impairment ☐ No Functional/ Role Impairment ☐ Not applicable

5. Reasoning & Problem Solving: Trouble doing classwork or homework, solving math problems, doing puzzles?

☐ Present during past week ☐ Not present in past week	☐ Evident During Visit ☐ Not Evident During Visit	☐ Not drug related ☐ Due to study drug ☐ Other drug ☐ Drug/drug interaction ☐ Not applicable	☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐ Not applicable	☐ Functional/ Role Impairment ☐ No Functional/ Role Impairment ☐ Not applicable

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

6. Speed of Processing: Feeling "slowed down", does it take you longer than usual to do things?

☐ Present during past week ☐ Not present in past week	☐ Evident During Visit ☐ Not Evident During Visit	☐ Not drug related ☐ Due to study drug ☐ Other drug ☐ Drug/drug interaction ☐ Not applicable	☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐ Not applicable	☐ Functional/ Role Impairment ☐ No Functional/ Role Impairment ☐ Not applicable

7. Social Cognition: Trouble understanding what other people intend, participating in social situations, or interacting with others?

☐ Present during past week ☐ Not present in past week	☐ Evident During Visit ☐ Not Evident During Visit	☐ Not drug related ☐ Due to study drug ☐ Other drug ☐ Drug/drug interaction ☐ Not applicable	☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐ Not applicable	☐ Functional/ Role Impairment ☐ No Functional/ Role Impairment ☐ Not applicable

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Appendix 15 Columbia-Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:
This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

© 2008 The Research Foundation for Mental Hygiene, Inc.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal	Past 1 month
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation*** Past 6 Months ***- Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Lifetime: Time He/She Felt Most Suicidal	Past 1 month
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____	____

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 1 year**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐	**Yes** **No** ☐ ☐

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/ First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code*	*Enter Code*	*Enter Code*
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code*	*Enter Code*	*Enter Code*

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

© 2008 The Research Foundation for Mental Hygiene, Inc.

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Completed Suicide:	**Yes** **No** ☐ ☐

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

Protocol 331-10-234

Appendix 16 Tanner Scale

Classification of Sex Maturity Stages in Girls

Stage	Pubic Hair	Breasts
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; areolar diameter increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant but amount less than adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature; nipple projects, areola part of the general breast contour

Classification of Sex Maturity Stages in Boys

Stage	Pubic Hair	Penis	Testes
1	None	Preadolescent	Preadolescent
2	Scanty, long, slightly pigmented	Slight enlargement	Enlarged scrotum, pink texture altered
3	Darker, starts to curl, small amount	Longer	Larger
4	Resembles adult type but less in quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult Size

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

Protocol 331-10-234

Agreement

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

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

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

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

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

_____	_____	_____
Principal Investigator Print Name	Signature	Date

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.

This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

Document Name: 331-10-234_Country Specific Protocol Amendment 1_Hungary

Document Number: CCI [redacted]

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Clinical Approval	04-Jun-2019 16:12:45
PPD	Biostatistics Approval	04-Jun-2019 16:46:07

Until the information herein is released by Otsuka to the public domain, the contents of this document are Otsuka confidential information and should not be duplicated or re-distributed without prior written consent of Otsuka.