Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Brexpiprazole (OPC-34712)

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

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Statistical Analysis Plan

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
CDC	Center for Disease Control and Prevention
CGAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impression – Improvement scale
CGI-S	Clinical Global Impression – Severity of illness scale
COVID-19	Coronavirus Disease of 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
ECG	electrocardiogram
EPS	extrapyramidal symptoms scale
ET	early termination
IMP	investigational medicinal product
LOCF	last observation carried forward
NY-AACENT	New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment
OC	observed case
PANSS	Positive and Negative Syndrome Scale
PT	preferred term
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SBP	systolic blood pressure
SD	standard deviation
SI	International System of Units
SOC	system organ class
TEAE	treatment-emergent adverse event
UKU	Udvalg for Kliniske Undersogelser
ULN	upper limit of normal
US	United States

1 Introduction

This statistical analysis plan (SAP) expands the statistical section of Protocol 331-10-236 Amendment 5,[1] and documents in detail the statistical methodologies and data analysis algorithms and the conventions to be applied to the analysis and reporting of safety and tolerability data collected in the trial. All amendments to the protocol have been taken into consideration in developing this SAP.

2 Trial Objectives

The primary objective of this trial is to assess the long-term safety and tolerability of oral brexpiprazole as monotherapy in adolescents (13 to 17 years old) with schizophrenia. Efficacy outcomes such as the Positive and Negative Syndrome Scale (PANSS) ratings over a long-term period will also be assessed, but of secondary interest.

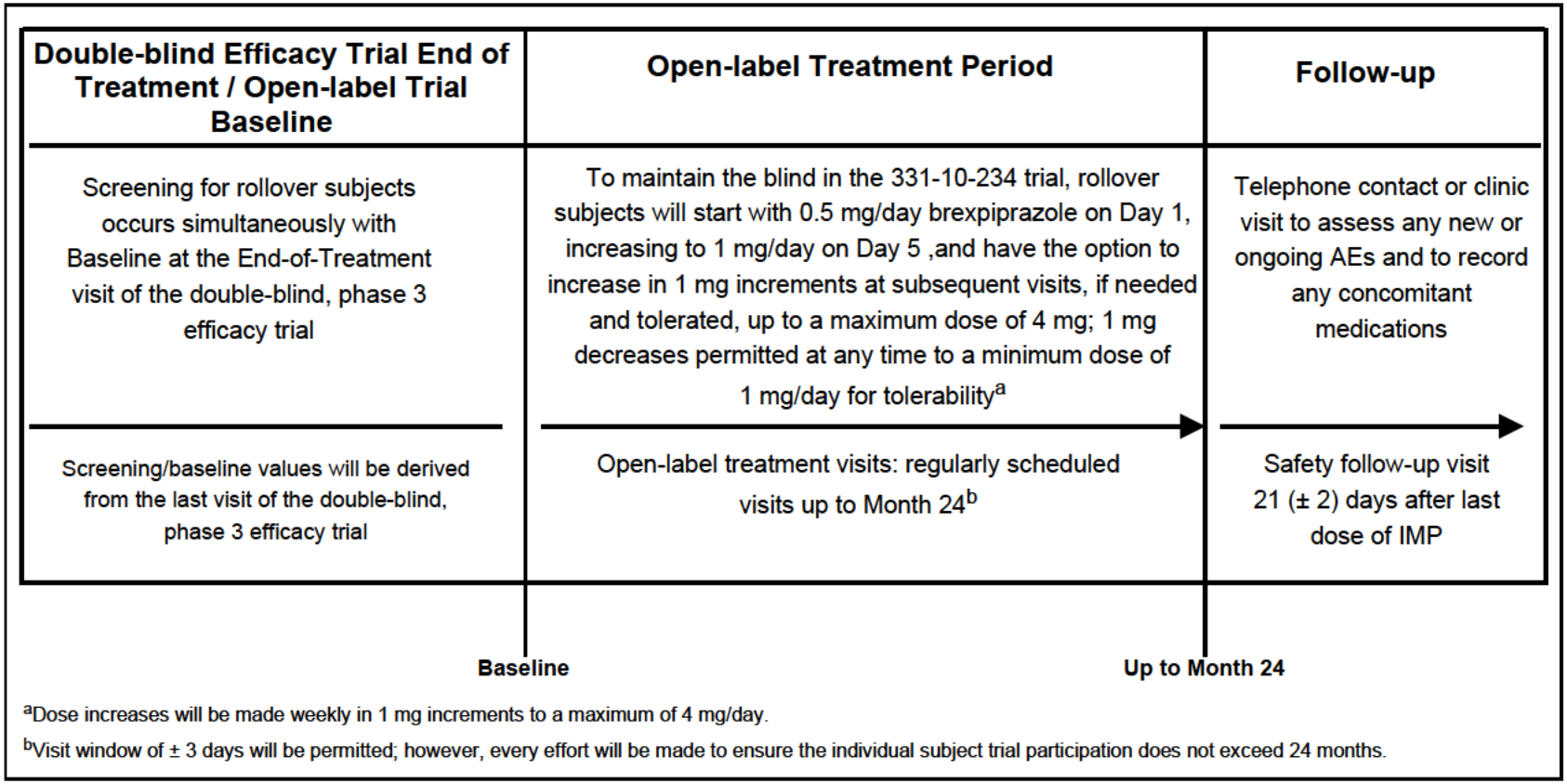
3 Trial Design

This is a long-term (24-month), multicenter, single-arm, open-label trial designed to examine the long-term safety and tolerability of brexpiprazole (1 to 4 mg/day) in adolescent subjects, aged 13 to 17 years at the time of informed consent/assent, with a Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) diagnosis of schizophrenia. Enrollment into the trial will be drawn from eligible subjects who, in the investigator's judgment, could potentially benefit from monotherapy treatment with oral brexpiprazole for schizophrenia and will include rollover subjects from the double-blind, phase 3 efficacy Trial 331-10-234 and de novo subjects from select sites. De novo subjects must have a Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version (K-SADS-PL) confirmed DSM-5 diagnosis of schizophrenia. Subjects who roll over from Trial 331-10-234 who turned 18 years old during that trial are also permitted to enroll in Trial 331-10-236. The trial will be conducted on an outpatient basis.

Rollover subjects are restricted to those who are able to rollover within ≤ 7 days of the Week 6 visit of Trial 331-10-234. Subjects who are only able to rollover from Trial 331-10-234 after > 7 days from the Week 6 visit may be allowed to enter Trial 331-10-236 as de novo subjects following approval by the medical monitor.

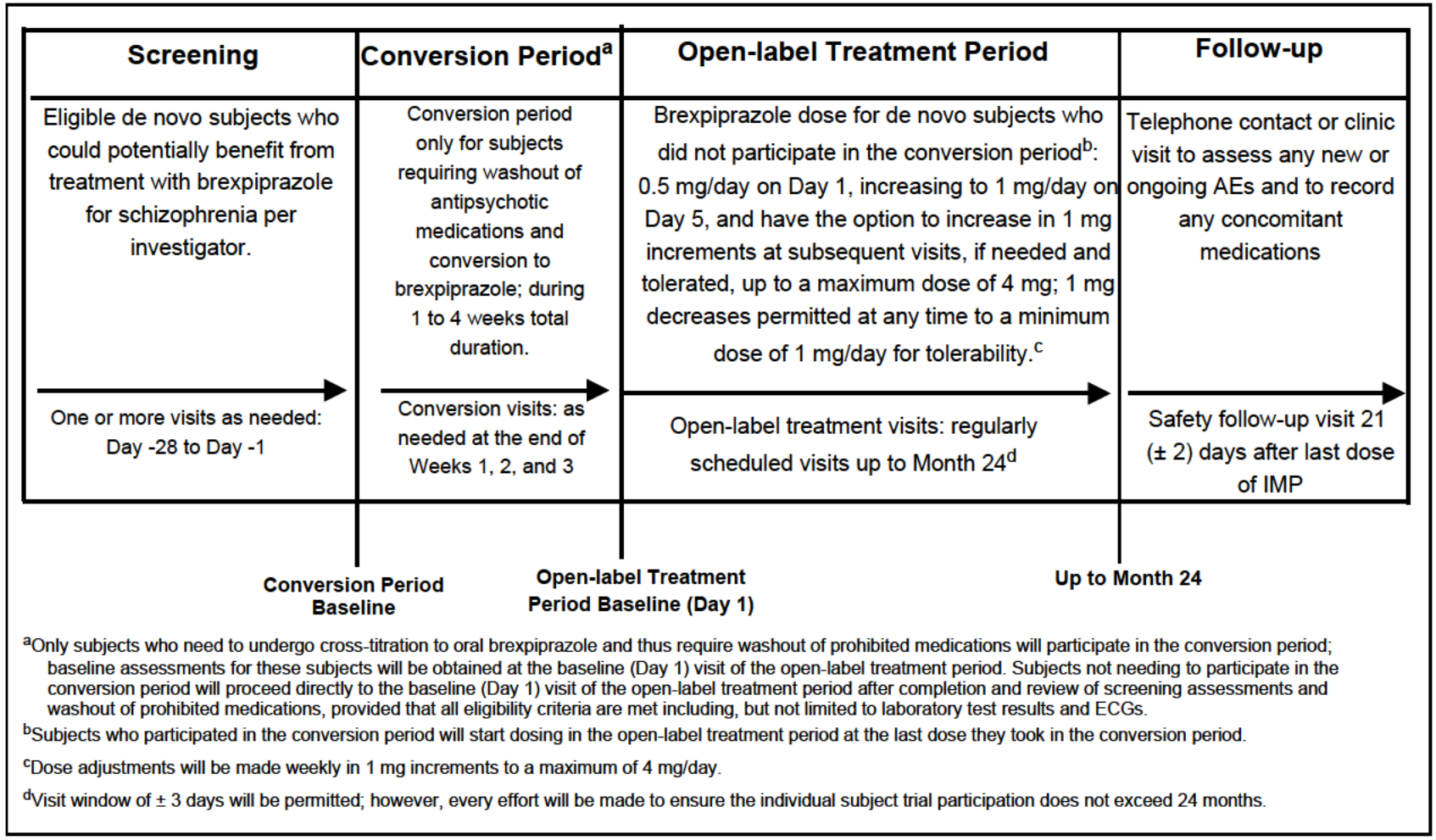
For rollover subjects, Trial 331-10-236 will consist of a 24-month open-label treatment period and a 21-day follow-up period. For de novo subjects, Trial 331-10-236 will consist of a 3- to 28-day screening phase, a 1-to 4-week conversion phase (if applicable), a 24-month open-label treatment phase, and a 21-day follow-up period.

A schematic of the trial design is provided in Figure 3-1 for rollover subjects and in Figure 3-2 for de novo subjects.



AE = adverse event; IMP = investigational medicinal product.

Figure 3-1 Trial Design Schematic - Rollover Subjects from Trial 331-10-234



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

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

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

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

Figure 3-2 Trial Design Schematic - De Novo Subjects

4 Sample Size and Power

The sample size for this trial is not based on considerations of statistical power.

Approximately 350 adolescent subjects are anticipated to be enrolled into this 24-month open-label trial with the expectation that at least 100 subjects will have had at least 12 months of exposure to the investigational medicinal product (IMP), brexpiprazole, at the conclusion of the trial.

Enrolled subjects will come from approximately 31 clinical sites across 7 countries.

It is to be noted that following the sample size reduction of the parent Trial 331-10-324 to 315 subjects (Protocol Amendment 3^2), less than 350 subjects are expected in Trial 331-10-236.

5 Analysis Populations

To adequately describe the statistical analyses and reporting, three analysis populations are defined as follows.

- Enrolled Sample: consists of all consented/assented subjects who were screened for eligibility and deemed eligible (ie, deemed to have met all the inclusion and none of the exclusion criteria for the current trial).
- Safety Sample: consists of all enrolled subjects who received at least one dose of IMP (brexpiprazole). Subjects will be excluded from this population only if there was documented evidence that the subject did not take any IMP (ie, number of tablets dispensed = number of tablets returned or no IMP dispensed). If a subject was dispensed IMP, but lost to follow-up, the subject will be considered exposed to the IMP.
- Efficacy Sample: consists of all subjects in the Safety Sample who had a baseline assessment and at least one postbaseline assessment of the PANSS Total Score.

Statistical analyses (including summaries) will be performed on the Enrolled Sample for demographics, baseline characteristics, and subject disposition data; on the Safety Sample for adverse events (AEs) and other safety parameters; and on the Efficacy Sample for efficacy parameters.

To facilitate separate analysis and reporting for the 2 sequential periods (ie, the 1- to 4-week conversion period and the 24-month open-label treatment period), 2 subpopulations of the Enrolled Sample and 2 subpopulations of the Safety Sample will be derived as described below.

There are 2 subpopulations of the Enrolled Sample: (1) Enrolled Sample for the open-label treatment period, which consists of (i) rollover subjects; (ii) those de novo subjects directly enrolled into the open-label treatment period; and (iii) those de novo subjects that, as required, underwent a cross-titration conversion period and became eligible for enrollment into the open-label treatment period; and (2) Enrolled Sample for the conversion period, which consists of those de novo subjects that were enrolled in the conversion period, regardless of their eventual eligibility for the subsequent open-label treatment period.

The 2 subpopulations of the Safety Sample are: (1) Safety Sample for the open-label treatment period, and (2) Safety Sample for the conversion period.

6 Trial Conduct

6.1 Subject Disposition, Completion Rate, and Reasons for Discontinuation

Subject disposition (such as “Enrolled”, “Treated”, “Discontinued”, “Completed”, etc) will be summarized for the Enrolled Sample for the 24-month open-label treatment period. Trial completion rate and reasons for discontinuation will also be summarized.

For purposes of this trial, subjects who complete the end-of-trial visit (ie, the Month 24 visit) in the open-label treatment period will be defined as trial completers. The summary will also be repeated for subgroups defined by prior treatment status, gender, race, age group (< 15 years, ≥ 15 years) and country/region. In particular, the number and percentage of subjects whose discontinuation was directly or indirectly related to the Coronavirus Disease of 2019 (COVID-19) pandemic will be presented.

Similarly, subject disposition (now restricted to “Enrolled”, “Treated” and “Enrolled into the Open-label Period”) will be summarized for the Enrolled Sample for the 1- to 4-week cross-titration conversion period.

6.2 Treatment Compliance

Treatment compliance score will be calculated and summarized only for the 24-month open-label treatment period.

Based on the IMP panel of the eSource, an individual subject’s overall compliance score with respect to taking IMP will be calculated by dividing the number of days with IMP tablets taken by the total number of days in the observed treatment period (ie, from Day 1 to the actual Last Dose date, inclusive), then multiply by 100. The numeric overall compliance score with respect to IMP will be summarized for the Safety Sample for the 24-month open-label treatment period by using descriptive statistics for continuous

variables. The overall compliance score will also be categorized (ie, into categories such as ≥ 100%, ≥ 80% and < 100%, ≥ 60% and < 80%, etc) and will be tabulated by category. Refer to Section 10.6 for descriptive statistics.

6.3 Protocol Deviations

Protocol deviations including types of deviations or violations (eg, deviations in entry criteria, dosing, concomitant medications, procedurals, etc) will be summarized for the Enrolled Sample separately for the open-label treatment period and the preceding conversion period. The summary will be made by country, trial site, and prior treatment group (if the parent trial data are unblinded). In addition, a subject listing of protocol deviations will also be provided describing the type or the nature of the deviation or violation on each subject.

A flagging variable taking values of "yes" or "no" will be created to indicate whether the deviation or violation was related to the COVID-19 pandemic.

7 Analysis and Reporting of Demographics and Baseline Characteristics

Baseline characteristics data include those of age, body weight, height, PANSS Total Score, PANSS Positive subscale score, PANSS Negative subscale score, Clinical Global Impression – Severity of illness (CGI-S) score, Children's Global Assessment Scale (CGAS) score, etc.

Demographics and baseline characteristics data will be summarized separately for 2 periods: (1) the 24-month open-label treatment period, on all subjects entering the open-label treatment, and (2) wherever appropriate and data are available, for the 1- to 4-week conversion period, on a set of de novo subjects that participated in a cross-titration conversion period.

7.1 Definition of the Baseline Value

7.1.1 Baseline for the 24-month Open-Label Treatment Period

Subjects entering the 24-month open-label treatment period come from three sources: (1) rollover subjects, (2) de novo subjects who skipped over a cross-titration conversion period and directly entered the open-label treatment period, and (3) de novo subjects who were required to participate in the conversion period to achieve a brexpiprazole monotherapy target starting dose of 1, 2, or 3 mg daily at any time after Week 1, and to achieve the required washout of prohibited medications. Once these goals have been achieved as deemed by the investigator, the subject will proceed to the baseline (Day 1)

visit of the open-label treatment period. It is possible that some de novo subjects cannot achieve these goals and thus will not enter the open-label treatment period.

For rollover subjects, baseline for the 24-month open-label treatment period is simply defined as the assessment value taken on the subject at the last visit (ie, the Week 6 visit) of the double-blind treatment period of the parent trial, whereas for de novo subjects (regardless of participating in the conversion period or not), baseline is defined as the last assessment value prior to the first dose of IMP upon entering the 24-month open-label treatment period. In other words, for de novo subjects, the data imputation rule last observation carried forward (LOCF) applies in determining the baseline value pertinent to the open-label treatment period. Note that there will be no imputation of baseline values for rollover subjects.

Note that there could be a small subset of subjects who completed the parent trial but could not directly rollover to the current trial due to the COVID-19 pandemic related pause of enrollment. These impacted subjects may be allowed to enroll later on as de novo subjects into the current trial (as mentioned in Section 3). If such a de novo subject enters the open-label treatment period without undergoing a conversion period, then his or her baseline values for the open-label treatment period will simply be the same as the assessments collected at the last visit (ie, the Week 6 visit) of the parent trial.

7.1.2 Baseline for the 1- to 4-week Conversion Period

The baseline value for the conversion period is applicable only to a subset of de novo subjects that were required to participate in the conversion period. The baseline is defined as the last assessment prior to the first dose of IMP in the conversion period. The LOCF rule applies. Specifically, the predose assessment at Day 1 of the conversion period will be taken as baseline; if unassessed or missing, then the assessment at screening will be taken as baseline.

7.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics variables including age, race, ethnicity, gender, weight, height, and body mass index (BMI) will be summarized for the Enrolled Sample by using descriptive statistics; eg, mean, median, standard deviation (SD), minimum and maximum values, percentage, etc. Of note, baseline BMI (unit: kg/m^2) will be derived by dividing baseline body weight (unit: kg) by the square of baseline height (unit: meter).

The data summary for the above-mentioned variables will be provided separately for 2 periods: (1) the 24-month open-label treatment period, on all subjects entering the open-label treatment, and (2) the 1- to 4-week conversion period, on a subset of de novo subjects that participated in the cross-titration conversion period.

7.3 Medical History and Baseline Psychiatric Evaluation

Baseline values in the following parameters related to psychiatric evaluation will be summarized on the Enrolled Sample by using descriptive statistics: PANSS Total Score, PANSS Positive subscale score, PANSS Negative subscale score, CGI-S score, and CGAS score. Medical history and psychiatric history data, updated for rollover subjects and collected for de novo subjects, will also be summarized.

The data summary for the above-mentioned parameters will be provided only for the 24-month open-label treatment period, since there are no pertinent assessments in the conversion period.

8 Analysis and Reporting of Safety Outcomes

All safety analyses specified in this section will be performed on the Safety Sample.

Standard safety variables to be analyzed include AEs, clinical laboratory tests (including prolactin), vital signs, electrocardiograms (ECGs), body weight, waist circumference, and BMI. In addition, data of extrapyramidal symptom (EPS) scales including the Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS) will be analyzed. Data of other scales of interest such as the Columbia-Suicide Severity Rating Scale (C-SSRS), Udvalg for Kliniske Undersogelser (UKU) Side Effects Rating Scale, New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT), and Tanner Staging assessment will also be analyzed.

For the parameter AE, the data summary will be provided separately for 2 periods: (1) the combined period of open-label treatment plus a 21-day follow-up, on all subjects entering the open-label treatment, and (2) the conversion period, on the subset of de novo subjects that participated in a cross-titration conversion period. Of course, the summary will be based on the Safety Sample pertinent to the period.

For the parameters such as vital signs, body weight, waist circumference, BMI, and C-SSRS, the data summary will be provided separately for 2 periods: (1) the open-label treatment period, on all subjects entering the open-label treatment, and (2) the conversion period, on the subset of de novo subjects that participated in a cross-titration conversion period.

For all other parameters as mentioned above (including clinical laboratories, ECG, EPS, UKU Side Effects Rating Scale, NY-AACENT, etc), there is no assessment in the conversion period; hence, the data summary will be provided only for the open-label treatment period.

8.1 Primary Safety Outcomes

The primary safety analysis is to estimate (1) the frequency and severity of AEs, (2) the frequency of serious treatment-emergent adverse events (TEAEs), and (3) the frequency of TEAEs that result in discontinuation of the IMP.

The incidence of AEs will be summarized for the following variables:

1) TEAEs by severity
2) TEAEs potentially causally related to the IMP
3) TEAEs with the outcome of death
4) Serious TEAEs
5) TEAEs leading to discontinuation of the IMP
6) EPS-related TEAEs.

Unless specified otherwise, data summaries of the above variables will present simple descriptive statistics such as count and percentage of subjects who had at least one incidence of the AEs of interest at various summarization levels. Of note, AEs that are sex-specific (eg, ovarian cancer) will have the incidence rate evaluated for the specific sex.

Incidence and occurrence (number of events) will be provided for serious TEAEs, potentially IMP-related serious TEAEs, and nonserious TEAEs.

The incidence of TEAEs by system organ class (SOC) and preferred term (PT) will be summarized for gender, race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, other), region (United States [US], Europe [continent], Mexico) and age (< 15 years, ≥ 15 years, based on Trial 331-10-236 entry) subgroups.

The following safety topics of interest will be provided (incidence by preferred term). The associated searching criteria base on preferred term is included in a separate document.

- EPS-related AEs (also EPS-related AEs, excluding akathisia)
- Neuroleptic malignant syndrome
- Prolactin
- QT prolongation

- Hepatic Impairment
- Effects on weight
- Effect on glucose
- Effect on lipids
- Rhabdomyolysis and CPK elevation
- Somnolence

The Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or newer will be used to code all AEs to an SOC and a PT.

8.1.1 Data Collected in the Open-label Treatment and the Follow-up Period

A TEAE in the open-label treatment period is defined as an AE that starts after the first dose of IMP upon entering the open-label treatment period, or an AE that is present at baseline of the open-label period and increases in intensity or becomes serious or IMP-related or results in death, discontinuation, interruption, or reduction of the IMP.

Any AEs occurring up to 30 days after the last dose of IMP in the open-label treatment period will be included in the AE summary tables. AEs having occurred 30 days after the last dose of IMP, if collected, will be reported in listings only.

In addition, a Kaplan-Meier curve will be plotted for the time (in months) from Day 1 of the open-label treatment to the discontinuation of IMP due to AEs or death. The subject will be censored if he or she discontinues the treatment due to any other causes (other than AEs or death) or loss to follow-up at any time points before the end of the open-label treatment period. In addition, subjects will be censored at the end (ie, the Month 24 visit) of the open-label treatment period if they stay in treatment beyond the end time point. A Kaplan-Meier curve will be plotted for the time (in months) from Day 1 of the open-label treatment to the discontinuation of IMP due to any reason.

8.1.2 Data Collected in the Conversion Period

The AE data are collected on a weekly basis on the de novo subjects that participated in the 1- to 4-week conversion period.

A TEAE in the conversion period is defined as an AE that starts after the first dose of IMP upon entering the conversion period, or an AE that is present at the baseline of the conversion period and increases in intensity or becomes serious or IMP-related or results in death, discontinuation, interruption, or reduction of the IMP.

Note that a Kaplan-Meier curve for time to discontinuation of the IMP due to AEs or death will not be plotted for the conversion period, due to the shorter length of the period and an anticipated small number of de novo subjects entering the cross-titration conversion period.

8.2 Secondary Safety Outcomes

8.2.1 Clinical Laboratory Data

A data summary will be provided for the 24-month open-label treatment period only, since there is no assessment of the clinical laboratory parameters in the conversion period.

During the 24-month open-label treatment period, clinical laboratory assessments in the fields of hematology, serum chemistry (including prolactin, glycosylated hemoglobin [HbA1c], and thyroid-stimulating hormone [TSH]), and urinalysis will be conducted at the following scheduled visits: Week 4 and Months 6, 12, 18, and 24. Refer to Table 3.7.3.2-1 of the protocol for a comprehensive list of laboratory tests (such as hemoglobin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], etc) conducted in this trial.

Assessment values and the change-from-baseline values in each laboratory test will be summarized on the observed case (OC) data by visit by using the descriptive statistics for continuous variables. Refer to Section 10.6 regarding descriptive statistics. Summary statistics will also be computed on the LOCF data for the last assessment visit.

The incidence of potentially clinically significant abnormal lab results will also be summarized. Refer to Appendix 2 of the protocol for the criteria for identifying laboratory values of potential clinical relevance. Data of laboratory test values with potential clinical relevance will be displayed in a data listing by subject, laboratory test, and visit.

Shift tables will be produced assessing status (low-normal-high) changes from baseline. The incidence of prolactin results > 1 × the upper limit of normal (ULN), > 2 × the ULN, and > 3 × the ULN will also be provided by gender.

An occurrence of potential serious hepatotoxicity (also referred to as potentially drug-induced liver injury) is defined as having concurrently met the following 2 criteria (ie, at the same visit) during the 24-month open-label treatment period:

1) ALT or AST ≥ 3 × the ULN or 3 × the baseline/screening value.
2) Increase in bilirubin ≥ 2 × the ULN or 2 × the baseline/screening value.

The incidence of potential serious hepatotoxicity will be summarized on the OC data by the specified visit as well as for the overall open-label treatment period. For the statistical summary of the overall open-label treatment period, the subject will be counted only once if he or she has multiple incidences of potential serious hepatotoxicity.

A by-subject listing of data of laboratory abnormalities that signal potential serious hepatotoxicity will also be provided.

Incidence of treatment-emergent potentially clinically relevant change in glucose and lipids will be summarized. The numerator in the incidence of treatment-emergent PCR is the number of subjects with 1 post-baseline potentially clinically relevant test abnormality observation (over the entire trial period) and their baseline values are normal or missing for a parameter; and the denominator is the total number of subjects with at least 1 post-baseline numeric laboratory results.

The criteria for treatment-emergent potential clinical relevance of glucose and lipids are provided in Appendix 1.

8.2.2 Physical Examinations Data

Physical examinations are scheduled at the Month 6, 12, 18, and 24 visits of the open-label treatment period, following the baseline/screening visit. Physical examination findings will be listed by subject and visit.

8.2.3 Body Weight, Waist Circumference, and Height Data

8.2.3.1 Data Collected in the Open-label Treatment Period

During the 24-month open-label treatment period, body weight and waist circumference will be assessed at the following scheduled visits: Weeks 1, 2, and 4 and Months 2, 3, 4, 6, 8, 10, 12, 15, 18, 21, and 24; whereas height will be assessed at the scheduled visits Months 6, 12, 18, and 24 only. For a postbaseline visit where both body weight and height are assessed, BMI (unit: kg/m^2) will be derived by dividing weight in kilograms by square of height in meters. For the postbaseline visits where body weight and height are not assessed on the same day, BMI will not be derived, and the values will be set to missing. Specifically for de novo subjects, if weight and height are both taken at Day 1 (predose), then weight and height from Day 1 will be used to calculate the baseline BMI. Otherwise, the most recent weight and height (taken on the same day) prior to Day 1 will be used to calculate the baseline BMI.

For the 24-month open-label period, change from baseline in each of the above 4 parameters will be summarized on OC data by visit and additionally on the LOCF data for the last assessment visit. The number and percentage of subjects having had

significant weight gain (defined as ≥ 7% increase in body weight relative to baseline) and significant weight loss (defined as ≥ 7% decrease in body weight relative to baseline) during the open-label treatment period will be respectively tabulated by visit as well as for the overall open-label treatment period.

Weight z-score is a variable of interest to be derived due to the natural growth of children and adolescent subjects. It describes how similar a subject is to his or her age and gender peers by determining a multiple of the SD from the expected weight. For each scheduled visit, weight z-score is calculated as the deviation of the subject's weight from the mean weight of the reference population divided by the SD for the reference population. Weight z-score and change from baseline in weight z-scores will be summarized by visit on the OC data by using descriptive statistics for continuous variables. Height z-score and BMI z-score will be similarly calculated and similarly summarized as that for weight, based on the OC data.

Furthermore, the number and percentage of subjects with a large magnitude of change such as ≥ 0.5 or ≤ −0.5 in BMI z-score (relative to baseline) will be tabulated by visit as well as for the overall 24-month open-label treatment period. Refer to Section 8.2.3.3 for the calculations of z-score for body weight, height, and BMI.

If a subject has repeat measures in a lab test for the same visit, the last repeat for the visit will be used for the analysis or summary. However, all data from the same visit, including repeats and unscheduled visits, will be included for the data listing.

8.2.3.2 Data Collected in the Conversion Period

Body weight and waist circumference will be assessed weekly on the subset of de novo subjects that underwent a 1- to 4-week cross-titration conversion period. The analysis and reporting of the data for the conversion period will be analogous to that for the open-label treatment period, with the exception that z-scores will not be calculated or reported for the conversion period.

8.2.3.3 Calculations of z-scores for Body Weight, Height, and BMI

Age and gender adjusted z-scores for body weight, height, and BMI will be calculated using the approach of the Center for Disease Control and Prevention (CDC), US. The CDC provides a reference dataset (CDCref_d.sas7bdat in sas data format or CDCref_d.csv in csv data format) and a sas program (cdc-source-code.sas) along with detailed instructions for the calculations at https://www.cdc.gov/growth-chart-training/hcp/computer-programs/sas.html.

The Z-scores are calculated as Z = [((value / M)**L) – 1] / (S * L) , in which ‘value’ is the child’s BMI, weight, height, etc. The L, M, and S values are in the reference dataset and vary according to the child’s sex and age. The following rules will be observed:

1) Age (in months) at the day of assessment, which is an input for the calculations, will be calculated as: (assessment date – birth date + 1)/(365.25/12).
2) In principle, BMI and its z-score will be calculated only if weight and height are both taken on the same day.
3) The above calculations are applicable in children and adolescents older than 24 months but younger than 20 years of age.

It is not anticipated that the CDC’s information (including the reference dataset, the SAS program, or the instructions for the calculations) will be updated in the short run. Nevertheless, the information at the CDC website will be re-checked for any updates within a month prior to the database lock, and updated information will be used if any.

8.2.4 Vital Signs Data

8.2.4.1 Data Collected in the Open-label Treatment Period

Vital signs will be assessed at all scheduled visits across the 24-month open-label treatment period. Vital signs parameters include body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse (ie, heart rate), of which SBP and DBP and pulse will be measured in the supine, sitting, and standing positions.

Measurements obtained in different positions will be treated as different parameters for purposes of the data summary. Thus, there are a total of 10 vital signs parameters for this trial.

For the 24-month open-label treatment period, assessment values and change from baseline values in each vital signs parameter will be summarized on the OC data by visit and additionally on the LOCF data for the last assessment visit.

Additionally, change from baseline to the lowest value postbaseline and to the highest value postbaseline in each parameter will be respectively summarized on the OC data for the overall 24-month open-label treatment period.

Potentially clinically significant vital signs abnormalities during the 24-month open-label treatment period will be identified, and the incident (ie, number and percentage of subjects who had such an abnormality) in each parameter will be tabulated by visit and at the subject level for the overall open-label treatment period. All potentially clinically significant vital signs abnormalities will be listed by prior treatment group, subject ID, visit, and vital signs parameter, along with baseline value, age, sex, body weight, and

dose at onset of the event of abnormality. Refer to Appendix 1 of the protocol for the criteria for identifying vital signs of potential clinical relevance. In addition to the protocol criteria, blood pressure criteria provided in Appendix 2 will be applied.

If a subject has repeat measures in a parameter at a visit, only the last repeat for the visit will be used for the analysis or summary. But all data from the same visit, including repeats and unscheduled visits, will be used for the data listing.

8.2.4.2 Data Collected in the Conversion Period

Vital signs data will be assessed weekly on the subset of de novo subjects that underwent a 1- to 4-week cross-titration conversion period. The analysis and reporting of the vital signs data for the conversion period will be analogous to that for the open-label treatment period.

8.2.5 Electrocardiogram Data

A data summary will be provided for the 24-month open-label treatment period only, since there are no ECG measurements in the conversion period.

The ECG measurements will be made at the Week 4 and Month 6, 12, 18, and 24 visits for all enrolled subjects during the 24-month open-label treatment period. The ECG measurements will also be obtained on Day 1 upon entering the open-label treatment period for de novo subjects.

Assessment values and change-from-baseline values in each of the quantitative ECG parameters will be summarized on the OC data by visit and LOCF data for the last assessment visit.

The incidence of clinically significant changes in each ECG parameter will be summarized on the OC data by visit, as well as for the overall open-label treatment period. Refer to Appendix 3 of the protocol for the criteria for identifying ECG measurements of potential clinical relevance. Data of clinically significant changes in ECG parameters will be listed by prior treatment group, subject number, sex, age, body weight, baseline value, visit, description of the findings, and dose at onset of the event.

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 Food and Drug Administration (FDA) Neuropharm Division formula: $QTcN=QT/(RR)^{0.37}$.

8.2.6 Other Safety Data

8.2.6.1 Special Pediatric Safety Assessments

A data summary will be provided for the 24-month open-label treatment period only, since in the conversion period there are no special pediatric safety assessments such as the NY-AACENT and UKU Side Effects Rating Scale assessment.

The NY-AACENT will be performed at the baseline visit, all protocol-specified scheduled visits, and at the early termination (ET) visit. The incidence of sign/symptom items as recorded in the NY-AACENT scale will be summarized. Specifically, the incidence (and severity) of the sign/symptom items will be tabulated by trial visit, based on the OC data. The summarization will be repeated for the subset of *drug-related* signs or symptoms and for the subset of *function-impaired* signs or symptoms, respectively. Additionally, change from baseline in the NY-AACENT total score will be summarized on the OC data by trial visit and on the LOCF data for the last assessment visit.
See Section 8.2.7 for the construction of the NY-AACENT total score.

The UKU Side Effects Rating Scale assessments will be administered at the baseline visit, all protocol-specified scheduled visits, and at the ET visit. The incidence (and severity) of the individual side effects and categories of side effects as recorded in the UKU Side Effects Rating Scale will be tabulated by trial visit, based on the OC data. The summarization will be repeated respectively for the subset of having “improbable”, “possible”, and “probably” connection to the IMP. In addition, a by-visit summarization will be provided for the following assessments: (i) the global assessment of the interference by existing side effects with the subject’s daily performance, and (ii) the consequence (ie, the measures taken with respect to the side effects).

8.2.6.2 Extrapyramidal Symptoms

A data summary will be provided for the 24-month open-label treatment period only, since there are no assessments of the EPS scales in the conversion period.

Three EPS scales including the SAS, AIMS, and BARS will be assessed at the baseline visit and the following visits in the 24-month open-label treatment period: Weeks 1, 2, and 4; Months 2, 3, 4, 6, 8, 10, 12, 15, 18, and 24; or an ET visit. Change from baseline in each of the 3 EPS variables (SAS total score, AIMS total score, and BARS global clinical assessment score) will be summarized on the OC data by visit and on the LOCF data for the last assessment visit. In addition, the BARS global clinical assessment will be treated as a categorical variable taking values (categories) of “Absent”, “Questionable”,

"Mild Akathisia", "Marked Akathisia", and "Severe Akathisia", and thus will be summarized on OC data by visit for each severity category, by using count and frequency.

8.2.6.3 Suicidality

Suicidality will be monitored during the trial (including the 1- to 4-week conversion period but excluding the 21-day follow-up period) by using the C-SSRS. A data summary will be provided separately for the open-label treatment period and for the conversion period.

Suicidality data (including suicidal ideation, suicidal behavior) will be collected at all scheduled visits and the ET visit.

Suicidal ideation has 5 types or levels, with increasing severity from "wish to be dead" to "active suicidal ideation with specific plan and intent". The incidence of each type of suicidal ideation will be summarized for the reporting period (ie, separately for the open-label period and for the conversion period). Suicidal behavior has several types or levels ranging from "actual attempt", "interrupted attempt", "aborted attempt" to "completed suicide". The incidence of each type of suicidal behavior will be summarized for the reporting period.

Additionally, the incidence of each of the following 4 categories of treatment-emergent suicidality will be summarized for the reporting period: (1) Emergence of suicidal ideation, which is defined as having an occurrence of any suicidal ideation during the reporting period while having no suicidal ideation at the baseline (relative to the reporting period); (2) Emergence of serious suicidal ideation, which is defined as having an observation of suicidal ideation severity rating of 4 or 5 during the reporting period while having no suicidal ideation at the baseline (relative to the reporting period); (3) Worsening of suicidal ideation, which is defined as having had a suicidal ideation severity rating that is more severe compared to the baseline (relative to the reporting period); and (4) Emergence of suicidal behavior, which is defined as reporting of any suicidal behavior during the reporting period while there was no suicidal behavior at the baseline (relative to the reporting period). Specifically, for each category of treatment-emergent suicidality as defined above, the number and percentage of subjects having experienced the event of interest during the reporting period will be tabulated.

8.2.6.4 Tanner Stage

A data summary will be provided for the 24-month open-label treatment period only. There are no ratings of the Tanner Staging (a classification of sexual maturity stages) in the conversion period.

The Tanner Staging scores are collected at baseline and at the following scheduled visits in the 24-month open-label treatment period: Months 6, 12, 18, and 24. The shifting frequency in Tanner Staging score (an ordinal score of 1 to 5) between baseline and each postbaseline visit will be tabulated separately for boys and girls by using cross-frequency. If the subject is rated "5" at a visit before Month 24 and is not rated thereafter, missing ratings at the subject's subsequent visits will be imputed with the value of "5".

8.2.7 Computational Details for Safety Scales

1) The SAS total score is the sum of rating scores over 10 items from the SAS panel in the eSource. The SAS total score is treated as unevaluable if fewer than 8 of the 10 items are recorded. If 8 or 9 of the 10 items are recorded, the SAS total score will be calculated as the mean of the recorded items multiplied by 10 and then rounded to the first decimal place.
2) The AIMS movement total score is the sum of rating scores for facial and oral movements (ie, items 1 - 4), extremity movements (ie, items 5 - 6), and trunk movements (ie, item 7). The AIMS total score will be treated as unevaluable if fewer than 6 of the 7 items are recorded. If 6 of the 7 items are recorded, the total score will be calculated as the mean of the recorded items multiplied by 7 and then rounded to the first decimal place.
3) The BARS score is based only on the item of "Global Clinical Assessment of Akathisia". The BARS consists of 4 items related to akathisia as follows. Item 1: objective observation of akathisia by the investigator; Item 2: subjective feelings of restlessness by the subject; Item 3: subjective distress due to akathisia; and Item 4: global clinical assessment of akathisia. The first 3 items will be rated on a 4-point Likert scale from 0 to 3, with 0 representing the absence of symptoms and 3 representing a severe condition. The BARS global clinical assessment score refers to the ratings from the fourth item Global Clinical Assessment of Akathisia, which is a 6-point Likert scale from 0 to 5, with 0 representing absence of symptoms and 5 representing severe akathisia. Thus, the BARS global clinical assessment score ranges from 0 to 5.
4) 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 to 17), though can be utilized with other age groups as appropriate. Each of the 7 items are derived from the 7 domains as follows: Working Memory, Attention/Vigilance, Verbal Learning/Memory, Visual Learning/Memory, Reasoning and Problem Solving, Speed of Processing, and Social Cognition. Each item score is derived as follows: 0 = not present in the past week; 1 = present (during past week) and mild; 2 = present (during past week) and moderate; 3 = present (during past week) and severe; and 4 = present (during past week) and extreme; and the item score is set to missing/unknown if otherwise.

   The NY-AACENT total score is calculated by summing up the 7 individual item scores at the subject-visit level. If 3 or more than 3 individual item scores are missing/unknown, the NY-AACENT total score cannot be calculated and will be

set to missing; if 1 or 2 individual item scores are missing/unknown, the NY-AACENT total score equals the average score of the non-missing items multiplied by 7 and then rounded to the first decimal place.

5) Each item (ie, each symptom) of the UKU Side Effects Rating Scale is defined by the means of a 4-point-scale (0-1-2-3) if it is assessed. In general, Degree 0 means "not or doubtfully present", and Degrees 1, 2, and 3 indicate that the symptom is present to a mild, moderate, or severe degree, respectively.

8.3 Concomitant Medications

Concomitant medications will be coded using the latest version of the World Health Organization (WHO) drug dictionary. The number and percentage of subjects taking concomitant medications prior to the 24-month open-label treatment period, during the 24-month open-label treatment period, and during the follow-up period will be respectively tabulated by drug class and medication generic name, based on the Safety Sample.

8.4 Extent of Exposure to the IMP

The extent of exposure to IMP will be summarized separately for the Safety Sample for the 24-month open-label treatment period, and for the Safety Sample for the conversion period.

8.4.1 Exposure Data for the 24-month Open-label Treatment Period

An individual subject's days of exposure to IMP for the open-label treatment period is calculated as: date of last dose in the open-label treatment period – date of first dose in the open-label treatment period + 1, regardless of any treatment gaps such as dose interruptions or omissions. An individual subject's average daily dose (unit: mg/day) will be calculated as: total dose (in mg) divided by days of exposure, where total dose is the summation of the actual daily doses (in mg) taken over the entire open-label treatment period.

The number and percentage of subjects having had IMP exposure of ≥ 3, 6, 12, 15, 18, and 24 months will be respectively tabulated and the descriptive statistics (eg, mean) of the average daily dose will be calculated based on the subset of subjects having had exposure in the corresponding exposure interval (eg, "≥ 6 months" refers to a semi-open exposure interval).

For calculating the percentage, the number of subjects having had any IMP exposure in the 24-month open-label treatment period will be used as the denominator.

Days of exposure and the average daily dose will be summarized for the Safety Sample for the 24-month open-label treatment period by using descriptive statistics (such as mean, SD).

8.4.2 Exposure Data for the 1- to 4-week Cross-titration Conversion Period

An individual subject's days of exposure to IMP for the conversion period is calculated as: date of last dose in the conversion period – date of first dose in the conversion + 1, regardless of any treatment gaps such as dose interruptions or omissions. An individual subject's average daily dose (unit: mg/day) will be calculated as: total dose (in mg) divided by days of exposure, where total dose is the summation of the actual daily doses (in mg) taken over the conversion period.

The number and percentage of subjects exposed to IMP will be tabulated by trial week. The average daily dose will be calculated for each week and will be summarized by trial week.

9 Analysis and Reporting of Efficacy Outcomes

All efficacy analyses specified in this section will be performed on the Efficacy Sample. For each efficacy variable, the analysis (eg, data summary) and reporting will be provided for the 24-month open-label treatment period only, since there is no efficacy assessment in the conversion period on the de novo subjects that underwent a cross-titration conversion.

For both rollover and de novo subjects, efficacy assessments will be collected at Week 4 and Months 2, 3, 4, 6, 8, 10, 12, 18, and 24 during the 24-month open-label treatment period. Additionally, for the de novo subjects, efficacy assessments (with the exception of the Clinical Global Impression – Improvement scale [CGI-I]) will also be collected at Day 1 of the 24-month open-label treatment period.

All efficacy assessments will be treated as secondary outcomes (endpoints) for this trial.

9.1 Secondary Endpoints

The secondary endpoints for this trial pertain to the following efficacy variables: PANSS Total Score, PANSS Positive subscale score, PANSS Negative subscale score, CGI-S score, and CGI-I score. Each of these 5 variables and the change from baseline in each of them (except the CGI-I score) will be summarized on the OC data by visit and additionally on the LOCF data for the last assessment visit by using descriptive statistics for continuous variables. Note that change from baseline in CGI-I score is not meaningful and hence will not be calculated for the statistical summary.

Additionally, the number and percentage of subjects having had either "very much improved" (with CGI-I score of 1) or "much improved" (with CGI-I score of 2) in the variable CGI-I score will be tabulated on the OC data by visit and on the LOCF data for the last assessment visit.

The number and percentage of responders (defined as a reduction of ≥ 30% from baseline to the last visit in PANSS Total Score or having a CGI-I score of 1 or 2 at the last visit) will be provided.

The PANSS Total Score will also be summarized for gender, race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, other), region (US, Europe [continent], Mexico) and age (< 15 years, ≥ 15 years, based on Trial 331-10-236 entry) subgroups.

Refer to Section 10.3 for the definition of baseline value. Note that the CGI-I assessment is not administered at the screening or Day 1 visits in the 24-month open-label treatment period; thus, there is no baseline value for the CGI-I score.

9.2 Interim Analysis

There will be an interim data reporting when approximately 100 subjects have had at least 6 months of exposure to the IMP in the 24-month open-label treatment period. An additional interim analysis will be performed approximately 6 months after the last subjects enters the trial.

All collected data including all safety and efficacy data will be reported for the interim data reporting. Database lock will be executed for the interim data reporting.

The final analysis will be performed upon completion of the trial. Database lock will be executed for the final analysis.

9.3 Multiplicity Adjustment

Not applicable.

9.4 Computational Details for Efficacy Scales

1) Observed case data will be used for the efficacy analyses for all scheduled (protocol-specified) visits, including the end-of-trial visit at Month 24, and LOCF data will be used only for the derived "last assessment visit".

2) The PANSS Total Score is the sum of the rating scores over 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale items from the PANSS panel in the eSource. If fewer than 24 of the 30 items are recorded, the PANSS Total Score will be unevaluable and thus set to missing. If 24 to 29 of the 30 items are recorded, the PANSS total is equal to the mean of the recorded items multiplied by 30 and rounded to the first decimal place.
3) The PANSS Positive subscale score is the sum of the rating scores over the 7 positive scale items from the PANSS panel in the eSource. The PANSS Negative subscale score is the sum of the rating scores for the 7 negative scale items from the PANSS panel in eSource. If fewer than 6 of the 7 items of the PANSS subscale scale are recorded, the PANSS subscale score will be unevaluable, thus missing. If 6 of the 7 items are recorded, the PANSS subscale score is equal to the mean of the recorded items multiplied by 7 and rounded to the first decimal place.
4) The CGI-S and CGI-I scores with a value (score) of zero (0) should be set to missing because the 0-score means "Not Assessed."

10 Conventions and Handling of Missing Data

10.1 Trial Day

The trial day that is associated with an observation or an assessment will be used for purposes of (1) data reporting (eg, data listing), and (2) determining whether an AE is a TEAE relative to the trial period (eg, the conversion period or the open-label treatment period).

The trial day in relation to the open-label treatment period will be derived as follows:

1) Trial day = assessment date – first dose date + 1, for assessment date ≥ first dose date;
2) Trial day = assessment date – first dose date, for assessment date < first dose date.

Note that, the "first dose date" above refers to the first dose date for the open-label treatment. Specifically, for a rollover subject the first dose date is the next day after the last assessment visit (ie, the Week 6 visit) from the parent Trial 331-10-234, and for the de novo subject that underwent a 1- to 4-week conversion period, the first dose date (with respect to the open-label treatment period) coincides with the date of the last assessment visit in the conversion period.

The trial day in relation to the conversion period will be derived similarly and is applicable only to the de novo subjects that entered a cross-titration conversion period. Of course, in the derivation of the trial day in relation to the conversion period, the "first dose date" should be the first dose date upon entering the conversion period.

10.2 Visit Window and the Derived Analysis Visit

The variable analysis visit will be derived to facilitate a by-visit analysis (including summary) and reporting. For efficacy parameters (eg, PANSS and CGI-S) and the 3 EPS parameters (ie, SAS, AIMS, and BARS), the analysis visit will be derived per Table 10.2-1 below. For all other parameters, the protocol-specified scheduled visit as recorded on the eSource *per se* will be simply taken as the analysis visit, and observations or assessments collected at any unscheduled visits will be programmatically mapped to an analysis visit per Table 10.2-1 below.

Protocol Amendment 5 (04 Aug 2021) updated the definition of a month duration for the purpose of scheduling monthly trial visits. The protocol month duration was changed from 4 weeks to 31 days (± 3 days). However, for analysis purposes, the same windowing will apply to all subjects, regardless of whether the assessment occurred before or after the amendment.

1) Observations will be mapped to an analysis visit for the 24-month open-label period based on the visit windows shown in Table 10.2-1.

Table 10.2-1 Visit Window for the 24-month Open-label Treatment Period

Analysis Visit	Trial Day	
	Allowed in Protocol	Window Specified in SAP
Day 1	1	1
Week 1	7 ± 3	2 to 10
Week 2	14 ± 3	11 to 20
Week 4	28 ± 3	21 to 44
Month 2	62 ± 3	45 to 76
Month 3	93 ± 3	77 to 104
Month 4	124 ± 3	105 to 160
Month 6	186 ± 3	161 to 216
Month 8	248 ± 3	217 to 272
Month 10	310 ± 3	273 to 328
Month 12	372 ± 3	329 to 412
Month 15	465 ± 3	413 to 496
Month 18	558 ± 3	497 to 580
Month 21	651 ± 3	581 to 664
Month 24	744 ± 3	665 to 790

Note: If the observation occurs 7 days after the last dose date, then Table 10.2-1 should not be used.

2) A subset of de novo subjects will undergo a 1- to 4-week conversion period to cross-titrate to brexpiprazole monotherapy from other antipsychotic medications. Observations in the conversion period will be mapped to an analysis visit of the conversion period based on the first dose date for the conversion period as shown in Table 10.2-2.

Table 10.2-2 Visit Window for the Conversion Period

Analysis Visit	Allowed in Protocol	Specified in SAP
Day 1 (Conversion Period)	Day 1 in the conversion period	Same as that in protocol
Week 1 (Conversion Period)	Day 4 to 10 in the conversion period	Day 2 to 10 in the conversion period
Week 2 (Conversion Period)	Day 11 to 17 in the conversion period	Same as that in protocol
Week 3 (Conversion Period)	Day 18 to 24 in the conversion period	Same as that in protocol
Week 4 (Conversion Period)	Day 25 to 31 in the conversion period	Same as that in protocol

Note: Day # in the conversion period = observation date in the conversion period – date of the first dose of IMP in the conversion period + 1.

The above algorithm ensures that all observations that are obtained at unscheduled visits will be mapped to an analysis visit. In case that multiple observations of the same parameter on the same subject are mapped to the same analysis visit, only the last observation (in the visit window) will be used for the by-visit analyses, but all observations will be included for the data listing.

10.3 Baseline Value

If a parameter (such as AE, C-SSRS, vitals, etc) is assessed during both the conversion period and the subsequent open-label treatment period for the de novo subjects that were enrolled into both of the periods, there will be 2 baseline values: one pertinent to the conversion period and the other pertinent to the open-label treatment period.

Refer to Section 7.1 for details.

10.4 Trial Completer

A trial completer is defined as those subjects in the efficacy sample who completed the scheduled assessment at the end-of-trial visit (ie, the Month 24 visit) in the 24-month open-label treatment period.

10.5 Data Imputation for the Last Assessment Visit

A landmark time point for the trial is the end-of-trial visit (the Month 24 visit) in the open-label treatment period of the trial. For some reason, a subject may be discontinued early from treatment before the end-of-trial visit. Such a subject will be invited to an ET visit where the assessments originally scheduled for the Month 24 visit will be collected.

It is anticipated that there will be many ongoing subjects at the time of the interim analysis database lock. For purposes of the interim data reporting, the LOCF rule will be applied to all subjects (including all ongoing subjects) in deriving the last visit's value for the subjects. If this trial is completed to the extent that the last enrolled subject has had an

opportunity to complete 24 months' open-label treatment, then the value at the 24-month visit or at the ET visit will be taken as the value for the last visit.

In deriving the last visit data, the LOCF rule will be applied to the following parameters: PANSS (including Total Score, Positive subscale score, Negative subscale score), CGI, SAS, AIMS, BARS, body weight, waist circumference, height, BMI, vital signs, ECG, clinical laboratory tests, CGAS, NY-AACENT, UKU Side Effects Rating Scale, Tanner Staging, and pregnancy tests. The LOCF rule will also be applicable to the individual PANSS items in deriving the last visit data. Note that only the postbaseline data can be carried forward in deriving the last visit data.

In general, the by-visit analysis (eg, summary) of a variable will also include the analysis for the derived last visit.

10.6 Descriptive Statistics for Continuous and Categorical Variables

For continuous variables, descriptive statistics include N (ie, number of subjects with non-missing value), mean, SD, median (Med), quartile, minimum (Min), and maximum (Max). For categorical (eg, nominal or dichotomous) variables, descriptive statistics refer to frequency distribution (eg, count and percentage).

In general, ordinal variables with fewer categories (say, ≤ 4) will be handled as categorical variables, whereas ordinal variables of ≥ 5 categories (such as assessment scores on many of the scales used in this trial) will be treated as continuous.

Unless specified otherwise, the denominator used for calculating percentage will be the number of unique subjects (or say, the number of subjects "at risk") in the analysis sample (or its subgroup of interest). And whenever applicable, a row of "Missing/Unknown" will be presented along with rows of recorded outcomes for the tabulation of the categorical variables.

10.7 Display of Statistical Output Tables and Listings

The data analysis (including summary) for the open-label treatment period will be performed on the analysis sample in aggregate as well as separately on 4 subgroups defined by prior treatment status as follows: (1) rollover subjects from Trial 331-10-234 who received the treatment with brexpiprazole 2 to 4 mg/day; (2) rollover subjects from Trial 331-10-234 who received the treatment with aripiprazole 10 to 20 mg/day; (3) rollover subjects from Trial 331-10-234 who received the treatment with placebo; and (4) de novo subjects. Thus, a statistical output table for the open-label treatment period will generally display the following 5 columns: (1) prior brexpiprazole, (2) prior aripiprazole, (3) prior placebo, (4) de novo, and (5) all.

However, in the situation where prior treatment cannot be unblinded (eg, for the interim data reporting before Trial 331-10-234 unblinding), statistical output tables will display the following 3 columns: (1) rollover, (2) de novo, and (3) all, where the "rollover" column pools together all 3 treatment groups from the parent Trial 331-10-234. It is anticipated that, at the time of data lock for the first interim data reporting, the parent trial will remain blinded.

In the situation where the number of de novo subjects participating in the cross-titration conversion period is 5 or fewer, statistical output tables will not be provided for the conversion period, but all the assessments, observations, or events collected in the conversion period will be included for data listings.

In general, data listings will not be presented separately for the open-label treatment period and the conversion period. Wherever appropriate, the listings should present a flagging variable (column) that indicates whether the listed observation is from the conversion period or not.

Wherever feasible, data listings should be sorted by trial period, prior treatment status, subject ID, date of assessment, visit, etc. And in general, the listing should present the sorting variables, baseline demographics, and all the variables of interest.

All statistical analysis and reporting will be generated using SAS® version 9.3 or higher.

10.8 Other Conventions

Percentage change from baseline is calculated as the change from baseline divided by the baseline value, then multiplied by 100. If the baseline value is zero, the percentage change will be undefined. If the baseline value is missing, the percentage change from baseline will be missing.

The International System of Units (Système international d'unités or SI) is the current international standard metric system. The SI units will be used for the reporting in all tables/figures/listings for this trial.

11 References

1 Otsuka Pharmaceutical Development & Commercialization, Inc. A long-term, multicenter, open-label trial to evaluate the safety and tolerability of flexible-dose brexpiprazole as maintenance treatment in adolescents (13-17 years old) with schizophrenia. Otsuka Protocol 331-10-236, issued 04 May 2017, amended 01 Dec 2017, 13 Sep 2018, 03 Jun 2019, 16 Jun 2020, and 04 Aug 2021.

2 Otsuka Pharmaceutical Development & Commercialization, Inc. 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. Otsuka Protocol 331-10-234, issued 10 Mar 2017, amended 24 Aug 2018, 31 May 2019, 16 Jun 2020, and 05 Jul 2022.

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Appendix 1 Criteria for Metabolic Change

Incidence of Treatment-Emergent Significant Change in Lipids

Parameters	Baseline	Anytime post baseline
Total Cholesterol, fasting (mg/dl)	Normal < 170	High ≥ 200
	Borderline 170 - < 200	High ≥ 200
	Normal/Borderline < 200	High ≥ 200
	Normal < 170	Borderline/High ≥ 170
LDL-cholesterol, fasting (mg/dl)	Normal < 110	High ≥ 130
	Borderline 110 - < 130	High ≥ 130
	Normal/borderline < 130	High ≥ 130
	Normal < 110	Borderline/High ≥ 110
HDL-cholesterol, fasting (mg/dl)	Normal > 45	Low < 40
	Borderline 45 - ≥ 40	Low < 40
	Normal/Borderline ≥ 40	Low < 40
	Normal > 45	Borderline/Low ≤ 45
Triglycerides, fasting (mg/dl)	Normal < 90	High ≥ 130
	Borderline 90 - < 130	High ≥ 130
	Normal/borderline < 130	High ≥ 130
	Normal < 90	Borderline/High ≥ 90

Incidence of Treatment-Emergent Significant Change in Glucose

Parameters	Baseline	Anytime post baseline
Glucose fasting, serum (mg/dl)	Normal < 100	High ≥ 126
	Impaired 100 - < 126	High ≥ 126
	Normal/impaired < 126	High ≥ 126
	Any Value	increased ≥10

Appendix 2 Additional Criteria for Blood Pressure

Parameter	Criteria	Change Relative to Baseline
Systolic Blood Pressure (Any position)	< 90 mmHg or > 120 mmHg	Increase or decrease of ≥ 15 mmHg
Diastolic Blood Pressure (Any position)	< 60 mmHg or > 85 mmHg	Increase or decrease of ≥ 15 mmHg