Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational New Drug

Brexpiprazole (OPC-34712)

Protocol 331-201-00191: A Phase 3, Multicenter, Open-label Trial to Evaluate the Long-term Safety and Tolerability of Brexpiprazole (OPC-34712) in the Treatment of Children and Adolescents with Irritability Associated with Autism Spectrum Disorder

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Statistical Analysis Plan

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CONFIDENTIAL - PROPRIETARY INFORMATION

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ABC	Aberrant Behavior Checklist
ABC-I	Aberrant Behavior Checklist - Irritability
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ASD	Autism Spectrum Disorder
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BMI	Body mass index
CDC	Center for Disease Control and Prevention
CGI-S	Clinical Global Impressions - Severity
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, 5th edition*
ECG	Electrocardiogram
EPS	Extrapyramidal symptoms
ET	Early termination
FDA	(United States) Food and Drug Administration
HbA1c	Glycosylated hemoglobin
HDL	High density lipoprotein
IAF	Informed assent form
ICF	Informed consent form
IMP	Investigational medicinal product
IRE	Immediately reportable event
LDL	Low density lipoprotein
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
OC	Observed Case
OPDC	Otsuka Pharmaceutical Development and Commercialization, Inc.
CCI	[redacted]
PE	Physical examination
CCI	[redacted]
PT	Preferred Term
QTc	Corrected QT interval
QTcF	QT interval as corrected for heart rate by Fridericia's formula
QTcN	QT interval as corrected for heart rate by the FDA Neuropharm Division
SAE	Serious adverse event
SAS	Simpson Angus Scale
SAS®	Statistical Analysis System®
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SOC	System Organ Class

Abbreviation	Definition
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WHO	World Health Organization

SAP 331-201-00191

1 Introduction

This statistical analysis plan (SAP) expands the statistical section of the protocol 331-201-00191 (version 6.0) and documents in detail the statistical methodologies and data analysis algorithms and conventions to be applied to the analysis and reporting of the safety and tolerability data collected in the study. All amendments to the protocol have been taken into consideration in developing this SAP.

2 Study Objectives

Primary: To assess the long-term safety and tolerability of brexpiprazole monotherapy in children and adolescents of 5 to 17 years old with irritability associated with autism spectrum disorder (ASD).

Secondary: To assess the long-term efficacy of brexpiprazole monotherapy in the same patient population.

3 Trial Details

3.1 Study Design

This is a phase 3, multicenter, single-arm, open-label extension trial designed to assess the long-term safety and tolerability of oral brexpiprazole monotherapy in children and adolescents with irritability associated with ASD. Enrollment into the trial will be drawn from eligible subjects who complete the double-blind treatment period of the phase 3 ASD trial (Trial 331-201-00148[1]), and in the investigator's judgment, could potentially benefit from continued investigational treatment with oral brexpiprazole.

The trial is planned to be conducted on an outpatient basis. Individual subjects' participation into the trial will be up to 29 weeks, including 26 weeks of open-label treatment, and 3 weeks of follow-up period. See Figure 3.1-1 for the design schematic of the trial. The trial will be organized as follows.

Screening Phase: Subjects who completed the double-blind treatment period of Trial 331-201-00148 (also referred to as the parent trial) and are deemed compliant with the protocol will be screened for eligibility at the last assessment visit of the double-blind treatment period. A separate fully executed informed consent/assent will be obtained for this open-label extension trial (Trial 331-201-00191[2]) before any procedures specific to this trial are performed. Unless specified otherwise, the assessments at the last visit in the double-blind treatment period of the parent trial will serve as the baseline measures for this open-label extension trial. Medical history will be updated for this trial, if necessary.

SAP 331-201-00191

Open-label Treatment Phase: Eligible subjects will receive 26 weeks of daily treatment with brexpiprazole in Trial 331-201-00191. Subject will start the open-label dosing of brexpiprazole - the investigational medicinal product (IMP) on the very next day of the last assessment visit of the double-blind treatment period in the parent trial. Subjects will be evaluated at baseline and all the scheduled visits which will occur at the end of Weeks 1, 2, 3, 4, 8, 14, 18, 22 and 26 during the treatment period. Visits are to occur within ± 2 days of the target visit date. All required evaluations as described in the Schedule of Assessments (see Table 3.7-1of the Protocol for Trial 331-201-00191) will be performed. If a subject discontinues from the trial before the end-of-trial visit at Week 26, assessments or procedures noted for the Week 26 visit must be completed at an early termination (ET) visit. Attempts should be made to complete all evaluations prior to the administration of any new medications or treatment. Of note, the baseline, Week 2, Week 14, and Week 26 visits will occur in the clinic. All other visits will be virtual or in clinic. Where the investigator and caregiver make the decision to conduct a visit virtually, the visit will be conducted by means of telecommunications technology.

Follow-up Phase: Subjects will have a follow-up contact 21 (± 2) days after the last dose of the IMP to assess any new or ongoing AEs and to record any concomitant medications. The follow-up contact also applies to the subjects who are prematurely withdrawn from the trial.

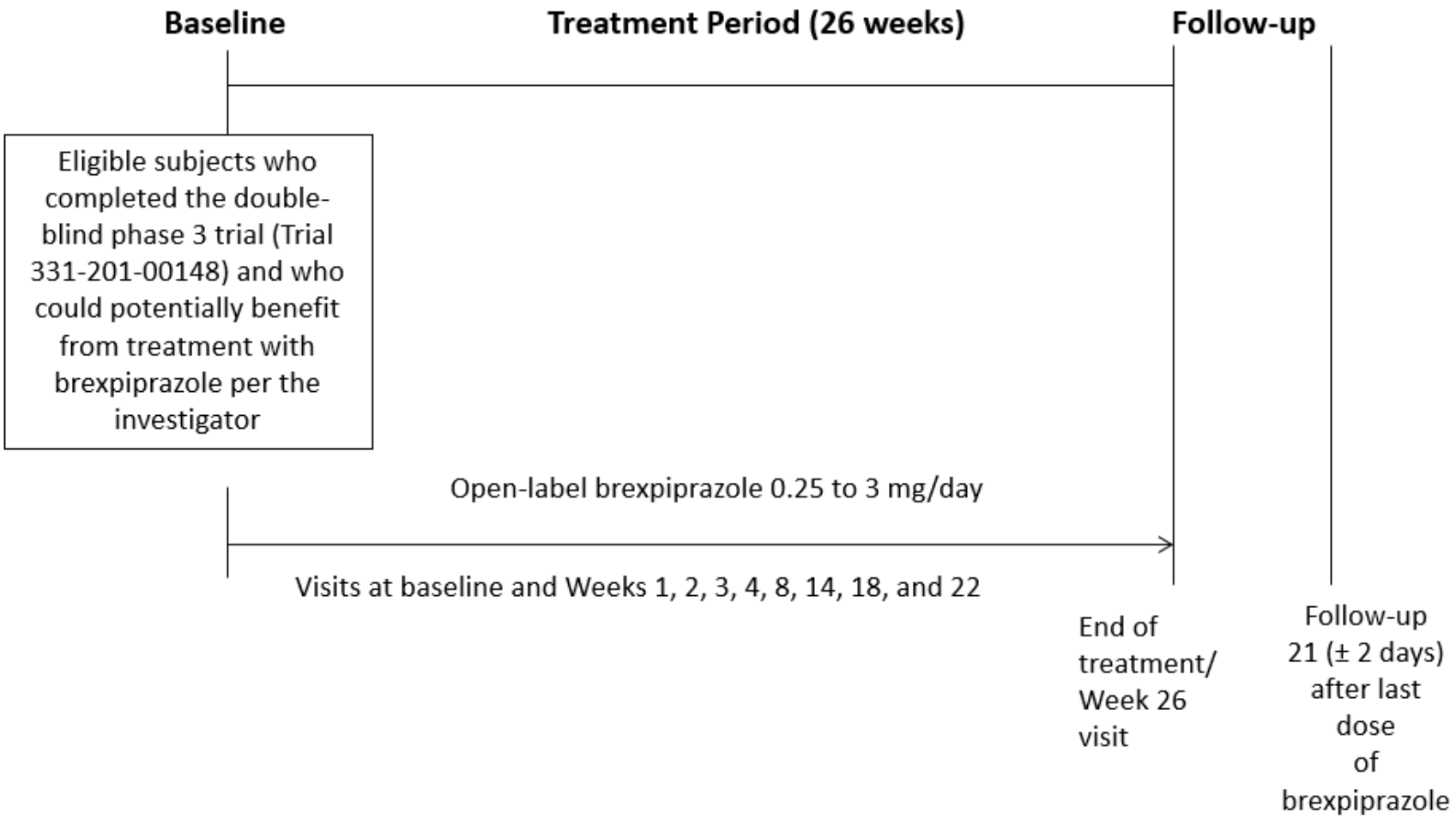

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

The first dose of open-label brexpiprazole will be taken the following day after the last dose of double-blind IMP is taken in the parent trial so that treatment continues without interruption. Whenever possible, it is anticipated that the last dose of IMP in the double blind, phase 3 efficacy trial will be taken on the day of the baseline visit for the open-label trial. Subjects should not be dosed using double-blind and open-label IMP on the same day. Throughout 26 weeks of treatment in this open-label extension trial, enrolled subjects will follow a titration/dosing schedule depending upon subject's body weight at the baseline visit. Subjects will receive a target dose range of 1 to 1.5 mg/day if body weight < 50 kg, and 1.5 to 3 mg/day if ≥ 50 kg. Refer to Table 3.2-1 of the Protocol for Trial 331-201-00191, which shows the titration/dosing schedule per subject's body weight stratum at baseline.

4 Sample Size and Power Justification

The sample size planned for this open-label extension trial is not based on considerations of statistical power.

Participants in this trial will be the subjects who completed the double-blind treatment period of the parent trial (Trial 331-201-00148) and who would likely benefit from a longer term of treatment with brexpiprazole in the judgement of the investigator. The sample size for this rollover trial will not exceed that of the parent trial (ie, 119 randomized subjects).

5 Data Sets for Analysis and Missing Data

5.1 Data Sets for Analysis

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

- Enrolled Sample: Consists of subjects who completed the double-blind treatment period of the parent trial and who gave consent/assent for participation into this open-label trial and who also met all the eligibility criteria for this trial.
- Safety Sample: Consists of all Enrolled subjects who took at least one dose of the IMP as indicated on the dosing records of this open-label extension trial. A subject will be excluded from this population only if there is documented evidence that the subject has not taken the IMP (ie, number of tablets/capsules dispensed = number of tablets/capsules returned, or no IMP dispensed). If a subject is dispensed trial medications but subsequently lost to follow-up, the subject will be considered exposed to the IMP.

- Efficacy Sample: All subjects in the Safety Sample who have a baseline assessment and at least one post-baseline assessment of the Aberrant Behavior Checklist - Irritability (ABC-I) subscale score.

Summary statistics of demographics, baseline characteristics and subject disposition variables will be computed on the Enrolled Sample. Summary statistics of adverse events and all other safety parameters will be computed on the Safety Sample, and summary statistics of all efficacy parameters will be computed on the Efficacy Sample.

5.2 Handling of Missing Data

For scoring via the aggregation of component items of the efficacy and safety scales, and how to handle the items with unrecorded (missing) ratings for the scoring, refer to Section 11 for details.

The Observed Case (OC) dataset for the parameters (eg, efficacy or safety variables) of interest will consist of all the actual observations or assessments of the parameters recorded at the visits during the open-label treatment period and the follow-up period. Note that if observations or assessments are unrecorded, thus missing, at a visit, the missing values will not be imputed. Subjects discontinued from treatment before Week 26 will have an ET visit where all assessments originally scheduled for the Week 26 visit will be made. Such data collected at the ET visit (or any other unscheduled visits, if any) will be mapped to a specific visit per the visit window algorithm given in Section 10.3. In the instances where a subject discontinues the treatment early but somehow does not subsequently attend the ET visit, all scheduled assessments after the timepoint of his or her treatment discontinuation will remain missing. All by-visit analysis (including summary) will be based on the OC dataset.

The Last-Observation-Carried-Forward (LOCF) dataset include all OC data and in addition the imputed data per a commonly used imputation rule (the LOCF rule) as follows: If no observation or assessment is recorded at a scheduled visit, the missing value for that visit will be imputed by carrying forward the last available (ie, the immediately preceding) observation or assessment (inclusive of the value at an ET visit, if any). Note that baseline data cannot be carried forward to impute post-baseline values.

Of particular interest is the timepoint of the end-of-trial visit at Week 26. Serving as a kind of supplementary evidence for the results, the analysis will be repeated on the Week 26 LOCF data for each analysis performed on the Week 26 OC data.

6 Study Conduct

6.1 Subject Disposition, Completion Rate and Reasons for Discontinuation

Subject disposition will be summarized on the Enrolled Sample by clinical center as well as by prior treatment group. Subject completion rate and reasons for discontinuation will be summarized on the Enrolled Sample by prior treatment group. Subjects who are evaluated at the last scheduled visit of the open-label treatment period will be defined as trial completers. For purposes of this trial, subjects who complete the Week 26 visit will be defined as trial completers.

6.2 Treatment Compliance

Based on the IMP panel of the Case Report Form (CRF), an individual subject's overall compliance score with respect to his/her taking IMP will be calculated by dividing the number of tablets/capsules (actually) taken by the total number of tablets/capsules scheduled to be taken for the observed treatment period, then multiply by 100. For the subject who is prematurely discontinued from treatment or lost to follow-up, the last dose date recorded on the subject will be used as the endpoint of the observed treatment period. The denominator (ie, number of tablets/capsules scheduled to be taken) will be downwardly adjusted for early treatment discontinuation.

6.3 Protocol Deviation

Protocol deviations including the types of deviations (eg, deviations in entry criteria, dosing, concomitant medications, procedurals, etc) will be summarized on the Enrolled Sample by trial center and prior treatment group. A listing of protocol deviations will also be provided.

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 Baseline Characteristics

7.1 Baseline Definition

An individual subject's baseline value is defined as the observation or assessment taken on the subject at the last visit of the double-blind treatment period in the parent trial. If a subject has separate screening visit(s) after end of the parent trial, then the last observation or assessment prior to the first dose of the open-label IMP will be considered

as baseline. For baseline values, there will be no imputation for missing or unknown values.

7.2 Demographic Characteristics

Demographic and baseline characteristics include age, sex, race, ethnicity, height, body weight, waist circumference, and body mass index (BMI). Demographic characteristics will be summarized on the Enrolled Sample by prior treatment group and for the overall analysis sample as well. Age, height, body weight, waist circumference and BMI will be treated as continuous variables, while sex, race and ethnicity will be treated as categorical variables. Refer to Section 10.4 for the conventions on using descriptive statistics for continuous and categorical variables.

7.3 Baseline Psychiatric Evaluations

Baseline psychiatric evaluations for this open-label extension trial are the ones taken at the last assessment visit of the parent trial. The baseline values in the following parameters will be summarized on the Enrolled Sample on the OC data using descriptive statistics: the ABC-I subscale score; all other ABC subscale scores; the CGI-S score; CCI

Refer to Section 11 for the scales and the scoring via the aggregation of component items of the scales.

7.4 Medical and Psychiatric History

Medical history and psychiatric history data will be summarized on the Enrolled Sample by prior treatment group using descriptive statistics.

8 Safety Analysis

All safety analyses specified in this section will be performed on the Safety Sample. The baseline of a safety variable is defined as the last observation or assessment in the variable prior to the first dose of the open-label IMP.

Safety is the primary objective for this study. Safety will be assessed by the following standard endpoints for clinical trials and trials of antipsychotic drugs:

- The frequency and severity of treatment-emergent adverse events (TEAEs), serious TEAEs, and discontinuation from trial due to AEs.
- Change from baseline to post-baseline time points in: a) vital sign measurements; b) electrocardiogram (ECG) parameters; c) clinical laboratory tests (including prolactin) and urinalysis; and d) physical examination findings.

- Analysis of potential suicide events recorded on the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Changes from baseline to post-baseline time points in results from extrapyramidal symptoms (EPS) scales (Simpson Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale [BARS]).
- Percentage of subjects with clinically significant changes in weight (gain or loss) from baseline to specified time points.
- Time to discontinuation.

8.1 Adverse Events (AEs)

All AEs will be coded by System Organ Class (SOC) and Preferred Term (PT) according to the latest version (Version 25.0 or newer) of Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as an AE that starts after the first dose of the open-label IMP or an AE that is present at baseline and increases in intensity or becomes serious or trial drug-related or results in death, discontinuation, interruption or reduction of the IMP. 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 listed only.

The incidence of the following AEs in Trial 331-201-00191 will be tabulated by prior treatment group and for the overall:

a) TEAEs
b) TEAEs by severity
c) TEAEs potentially causally related to the IMP
d) TEAEs with an outcome of death
e) Serious TEAEs
f) TEAEs leading to discontinuations of the IMP
g) EPS-related TEAEs

The above summaries (b), (e) and (f) will also be prepared for TEAEs potentially causally related to the IMP.

In addition, TEAE incidence with rate ≥ 2% at any SOC and PT levels in any of the two prior treatment groups will be provided. Incidence of TEAEs by SOC and PT will also be summarized for subgroups defined by sex, race, age, and body weight category at enrollment. Of note, AEs that are sex-specific, eg, ovarian cancer, will have the incidence rate evaluated for the specific sex.

8.2 Clinical Laboratory Tests

During the open-label treatment period, clinical laboratory assessments, including hematology, serum chemistry, urinalysis, serum bicarbonate, glycosylated hemoglobin (HbA1c), serum prolactin concentrations, thyroid stimulating hormone (TSH), and free T4 (if the TSH is abnormal) will be made in office at the Week 14 and 26 visits. Coagulation parameters will be assessed only at the end timepoint (the Week 26 visit) of the open-label treatment period. Of note, metabolic parameters (ie, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides) and serum glucose will be separately summarized for fasting and non-fasting tests, and serum prolactin concentrations will be separately summarized for male and female subjects.

The assessment value and the change from baseline value at each of the specified visits above in each of the above-mentioned clinical laboratory parameters will be summarized on the OC data by using the descriptive statistics for continuous variables. Likewise, the summary statistics will also be computed on the LOCF data for the last assessment visit.

Potentially clinically relevant laboratory measurement test results during the open-label treatment period will be identified and the number and percentage of subjects who had such a laboratory value will be tabulated by laboratory parameter and prior treatment group based on the observation from the scheduled and the unscheduled (if any) post-baseline visits. Criteria for Identifying Laboratory Values of Potential Clinical Relevance for the children and adolescent subjects enrolled into this study are provided in Appendix 2.

Potential serious hepatotoxicity is an immediately reportable adverse event of interest. The case of potential serious hepatotoxicity at a post-baseline visit is defined as having (1) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 2 times the upper limit of normal (ULN), and (2) the total Bilirubin ≥ 1.6 times the ULN. The incidence of potential serious hepatotoxicity (ie, the number and percentage of subjects who had a case of potential serious hepatotoxicity) will be tubulated by prior treatment group based on the observation from the scheduled and the unscheduled (if any) post-baseline visits.

All potentially clinically significant laboratory abnormalities will be listed by prior treatment group, patient ID, baseline value, age, sex, body weight, visit, and dose at onset of the event if applicable.

8.3 Vital Signs

Vital signs measurements will include body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. Blood pressure (ie, SBP, DBP) and heart rate will be measured in the supine and standing positions. Measurements at different positions will be treated as different parameters for purposes of data analysis. Thus, there will be 7 parameters for the vital signs.

The assessment value and the change from baseline value in each of the 7 vital signs parameters during the open-label treatment period will be summarized by visit on the OC data by using descriptive statistics for continuous variables. Likewise, the summary statistics will be computed for the last assessment visit based on the LOCF data.

Potentially clinically relevant vital signs abnormalities during the open-label treatment period will be identified, and the number and percentage of subjects who had such an abnormality in each of the vital signs will be tabulated by prior treatment group based on the observation from the scheduled and the unscheduled (if any) post-baseline visits.

All potentially clinically significant vital signs abnormalities will be listed by prior treatment group, patient ID, baseline value, age, sex, body weight, visit week, type of visit (virtual or in office), and dose at onset of the event if applicable.

Criteria for Identifying Vital Signs of Potential Clinical Relevance for subjects 5 to 17 years of age are provided in Appendix 1.

8.4 Electrocardiogram Data

Electrocardiogram (ECG) measurements will be made in office at 2 specified visits (Weeks 14 and 26 visits) during the open-label treatment period. The standard 12-lead measurements include QTc, heart rate, PR interval, and QRS complex. For the analysis of QT and QTc, data from three consecutive complexes (representing three consecutive heart beats) will be measured to determine average values. The following QT corrections will be used for reporting purposes:

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

For each of the quantitative ECG parameters, assessment value and change from baseline value will be summarized on the OC data for each of the specified visits above, as well as

on the LOCF data for the last assessment visit, by using descriptive statistics for continuous variables.

Criteria for identifying potentially clinically relevant ECG abnormality for subjects of 5 to 17 years of age are provided in Appendix 3. All potentially clinically relevant ECG abnormalities during the open-label treatment period will be listed by prior treatment group, patient number, sex, age, body weight, baseline value, visit, description of the findings, and dose at onset of the event if applicable. In addition, the number and percentage of patients who had a potentially clinically relevant ECG abnormality will be tabulated by prior treatment group based on the observation at the scheduled and the unscheduled (if any) post-baseline visits.

Categorical Change in ECG parameters during the open-label treatment period will be summarized based on the following criteria:

Table 8.4-1 Categorical Change Criteria in QT/QTc Parameters

Classification	Category	Criteria
QT	New onset (≥ 450 msec for men or ≥ 470 msec for women)	New onset in QT means a subject who attains a cut off value during treatment period but not at baseline.
QTc[a]	New onset (≥ 450 msec for men or ≥ 470 msec for women)	New onset in QTc means a subject who attains a cut-off value during treatment period but not at baseline.
	New onset (≥ 450 msec for men or ≥ 470 msec for women) and > 10% increase	New onset and > 10% increase in QTc means a subject who attains a cut off value and > 10% increase during treatment period but not at baseline
	New onset (> 500 msec)	New onset (> 500 msec) in QTc means a subject who attains a value > 500 msec during treatment period but not at baseline.
	Increase 30 - 60 msec	Increase from baseline value > 30 and ≤ 60 msec in QTc.
	Increase > 60 msec	Increase from baseline value > 60 msec in QTc.

[a]QTc categorical change criteria apply to QTcF and QTcN.

8.5 Physical Examinations

By-subject listings will be provided for physical examinations (PE), which is scheduled at the end (ie, the Week 26 visit) of the open-label treatment period, following the screening/baseline visit.

8.5.1 Body Weight, Waist Circumference and BMI

Measurements on body weight, waist circumference and height will be collected at two specified visits (ie, Weeks 14 and 26) in office at clinical site during the open-label treatment period. For each visit, BMI will be derived as: weight in kilograms divided by the square of height in meters.

Measurement value and change from baseline value at each of the two specified visits above during the open-label treatment period in each of the above-mentioned four parameters will be summarized on the OC data by using descriptive statistics for continuous variables. Likewise, the summary statistics will also be computed on the LOCF data for the last visit.

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

8.5.2 Z-score

Z-score is a variable of interest to be derived due to the natural growth of children and adolescent subjects. Weight z-score describes how similar a subject is to his/her age and gender peers by determining the number of standard deviations 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 standard deviation for the reference population. Weight z-score and change from baseline in weight z-scores will be summarized on the OC data by specified visit (ie, Weeks 14 and 26) and the last visit 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 and last visit. Refer to Section 8.5.2.1 for the calculation of z-score for body weight, height, and BMI. Furthermore, the number and percentage of subjects with the magnitude of change being ≥ 0.5 or ≤ −0.5 in BMI z-score (relative to baseline) will be tabulated on the OC data by specified visit (ie, Weeks 14 and 26) and the last visit.

8.5.2.1 Calculation 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), USA. 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[3].

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 CDC's information (including the reference dataset or 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 final database lock, and updated information will be used if any.

8.6 Extrapyramidal Symptoms Rating Scales (SAS, AIMS and BARS)

Extrapyramidal symptoms scales (SAS, AIMS and BARS) will be assessed in office at clinical site at three specified visits (Weeks 2, 14 and 26) during the open-label treatment period. The SAS total score, the AIMS total score, and the BARS global clinical assessment score (see Section 11.5, Section 11.6, and Section 11.7 for the construction of these scores) and the change from baseline in these scores will be respectively summarized on the OC data by visit above and on the LOCF for last visit by using descriptive statistics for continuous variables. For the AIMS individual item score on Item 8, 9 and 10, summary statistics will be computed analogously to the above.

In addition, incidence of BARS global clinical assessment during the open-label treatment period by severity category will be provided using summary statistics on OC data and last visit.

8.7 Columbia Suicide Severity Scale (C-SSRS)

Suicidality will be monitored during the trial (excluding the 21-day follow-up period) using the C-SSRS (Child Version). Suicidality data will be collected at all the visits including the scheduled visits and the ET visit.

Variables pertaining to suicidality assessments are categorical in nature. For each of the suicidality categories of interest, the number and percentage of subjects with the presence of suicidality will be tabulated (or say, summarized) by visit and for the overall treatment period. Note that, the presence of suicidality is defined as reporting of at least one occurrence of any types of suicidal ideation or behavior. Also note that, for the tabulation for the overall treatment period, a subject will be counted only once if he or she had multiple occurrences of suicidal ideation or behavior during the treatment period.

And the following four categories of treatment emergent suicidality will be analogously summarized: (1) Emergence of suicidal ideation, which is defined as reporting of any types of suicidal ideation during the treatment period while there was no suicidal ideation at baseline; (2) Emergence of serious suicidal ideation, which is defined as having observation of suicidal ideation severity rating of 4 or 5 during the treatment period while there was no suicidal ideation at baseline; (3) Worsening of suicidal ideation, which is defined as having a suicidal ideation severity rating that is more severe compared to baseline; (4) Emergence of suicidal behavior, which is defined as reporting of any types of suicidal behavior during the treatment period while there was no suicidal behavior at baseline. Specifically, for each of the above categories of treatment emergent suicidality, descriptive statistics in the form of count and percentage of the subjects who experienced such an event will be calculated on the OC data by visit and for the overall treatment period.

There are 4 specific types of suicidal behavior and 5 specific types of suicidal ideation. The number and percentage of subjects who experienced any of those types of behavior or ideation will be tabulated on the OC data by visit and for the overall treatment period.

Wherever applicable, assessments on all individual questionnaires pertaining to suicidal behavior or ideation will be summarized by visit by using the descriptive statistics for categorical variables.

8.8 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 open-label treatment period, during the open-label treatment period, and during the follow-up period will be respectively tabulated by drug classification, based on the Safety Sample.

8.9 Extent of Exposure

An individual subject's Total Days of Exposure to IMP is calculated as: last dose date − first dose date + 1, regardless of any gaps in treatment (such as dose interruption or omission) during the 26-week open-label treatment period. The variable Total Days of Exposure will be summarized on the Safety Sample by using descriptive statistics for a continuous variable.

The number and percentage of subjects who received the IMP during the open-label treatment will be calculated by dosing week. The dosing week will be based on the actual week since the start of the open-label dosing (ie, Days 1 to 7 as Week 1, Days 8 to 14 as

Week 2, etc). An individual subject's Average Daily Dosage will be derived for each dosing week by dividing the subject's total doses taken during the week by the number of his/her exposure days in that week. Note that the number of exposure days in a dosing week is not always equal to 7. It can be less than 7 for the week in which early treatment discontinuation occurs. Note that the number of exposure days in a week will not be adjusted for any gaps in treatment during the week. The variable Average Daily Dosage will be summarized by dosing week by using descriptive statistics.

9 Efficacy Analysis

All efficacy analysis will be performed on the Efficacy Sample.

9.1 The Secondary Endpoints

The secondary endpoints for this trial pertain to a few efficacy variables constructed from the rating scales (see Section 11). Two key efficacy variables are the ABC-I subscale score and the CGI-S score. Each of these variables and the change from baseline in each of them will be summarized on the OC data by visit and additionally on the LOCF data for the last visit at Week 26, by using descriptive statistics for continuous variables.

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9.3 Interim Analysis

No interim analysis is planned.

9.4 Multiplicity Adjustment

Not applicable.

10 Conventions

10.1 Software for Statistical Analysis and Reporting

The Statistical Analysis System® (SAS®, version 9.3 or newer) will be used for all statistical analysis and reporting.

10.2 Study Day

The open-label IMP dosing will start on the very next day after the last assessment visit of the double-blind period of the parent trial (Trial 331-201-00148).

For this trial, study day is derived as follows: (1) study day = observation date − IMP dosing start date + 1, for observation date ≥ IMP dosing start date; (2) study day = observation date − IMP dosing start date, for observation date < IMP dosing start date. The open-label IMP dosing start date is referred to as Day 1.

10.3 Visit Window and the Derived Analysis Visit

The analysis visit variable will be needed for the by-visit analysis (including summary). For efficacy parameters and selected safety parameters (including all ABC subscales, CGI-S, CCI [redacted] SAS, AIMS and BARS), the analysis visit will be derived per Table 10.3-1 below. Observations or assessments at the ET visit or any other unscheduled visit will be programmatically mapped to an analysis visit per Table 10.3-1 below. If an observation date is ≤ (the last dose date + 7), then the mapping algorithm in Table 10.3-1

below applies; else if an observation date > (the last dose date + 7), then the observation will be excluded from data analysis.

For all other parameters, the protocol-specified scheduled visit per se (as recorded on the eCRF) will be taken as the analysis visit.

Table 10.3-1 Mapping of the Analysis Visit for the Open-label Treatment Period

Analysis Visit	Target Study Day[a] per Protocol	Study Day[a] Interval (end points inclusive)
Day 1	1	1
Week 1	7	2 to 10
Week 2	14	11 to 17
Week 3	21	18 to 24
Week 4	28	25 to 42
Week 8	56	43 to 77
Week 14	98	78 to 112
Week 18	126	113 to 140
Week 22	154	141 to 168
Week 26	182	169 to 196

[a] See Study Day definition in Section 10.2.

The preceding algorithm ensures that all observations collected at the ET visit or any other unscheduled visit will be mapped to an analysis visit. In the instances where multiple observations (of same parameter on the same subject) fall into one study day interval, all values of the multiple observations in the study interval will be included for listings, but only the last observation (in the study day interval) will be used for the by-visit analysis.

10.4 Descriptive Statistics for Continuous and Categorical Variables

For continuous variables, descriptive statistics include N (which is number of subjects with non-missing value), mean, standard deviation, median, quartile, minimum and maximum. For categorical (eg, nominal or dichotomous) variables, descriptive statistics refer to frequency distribution (eg, count and percentage). Unless stated otherwise, ordinal variables such as assessment scores on all the scales used for this trial will be treated as continuous. Wherever possible, inferential statistics will be accompanied by descriptive statistics for presentation. Descriptive statistics can be used alone for data summary purpose, for example, for summarizing baseline demographic characteristics, medical history, etc. Unless specified otherwise, the denominator used for calculating percentage will be the number of unique subjects in the analysis sample (or its subgroups). And whenever applicable, a row of “Missing/Unknown” will be presented along with rows of recorded outcomes for the tabulation of the categorical variables.

10.5 Display of Statistical Outputs

Unless stated otherwise, data analysis and summary will be performed for the overall analysis sample (or the subgroups of interest) and separately for the two prior treatment groups. Thus, a statistical table output generated via SAS® programming will display the following three columns: (1) prior brexpiprazole; (2) prior placebo; and (3) all.

Wherever applicable statistical listings should be sorted by prior treatment group, subject ID, date of assessment, visit, etc. And in general, the listing should present the sorting variables, prior treatment, baseline demographics and all the variables of interest.

11 Scales: Rules for Scoring and Handling of Missing Data

11.1 ABC Subscales

The ABC scale has 58 items, which divide into 5 subscales as follows: (1) Irritability, Agitation; (2) Lethargy, Social Withdrawal; (3) Stereotypic Behavior; (4) Hyperactivity, Noncompliance; and (5) Inappropriate Speech. Each of the 58 ABC items is rated on a 4-point scale (0 = not at all a problem; 1 = the behavior is a problem, but slight in degree; 2 = the problem is moderately serious; 3 = the problem is severe in degree).

The Irritability subscale (ABC-I) subscale score is the sum of the ratings over 15 ABC items as follows. Item 2: injuries self on purpose; Item 4: verbally or physically aggressive to other children or adults; Item 8: scream inappropriately; Item 10: temper tantrums or outbursts; Item 14: irritable and whiny; Item 19: yells at inappropriate times; Item 25: depressed mood; Item 29: demands must be met immediately; Item 34: cries over minor annoyances and hurts; Item 36: mood changes quickly; Item 41: cries and screams inappropriately; Item 47: stamps feet or bangs objects or slam doors; Item 50: deliberately hurts himself/herself; Item 52: does physical violence to self; Item 57: has temper outbursts or tantrums when he/she does not get own way. Thus, ABC-I subscale score ranges from 0 to 45. For a visit, a subject's ABC-I subscale score will be unevaluable and set to missing if less than 12 of the 15 items are recorded for the visit. If 12, 13 or 14 of the 15 items are recorded, the ABC-I subscale score will be the mean of the recorded items multiplied by 15 and then rounded to the first decimal place. To state equivalently, if more than 20% of the component items have missing ratings (or say, not recorded), the ABC-I subscale score will be set to missing; otherwise, the total score will be the mean of the recorded items multiplied by 15.

The ABC subscale score on Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance, and Inappropriate Speech is respectively the sum of

ratings over 16, 7, 16 and 4 individual ABC items. For each of these 4 subscales, if more than 20% of the component items have missing ratings (of note, at the subject-visit level), the subscale score will be set to missing; otherwise, the subscale score will be the mean of the recorded items multiplied by the total number of component items for the subscale.

11.2 Clinical Global Impressions - Severity (CGI-S)

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

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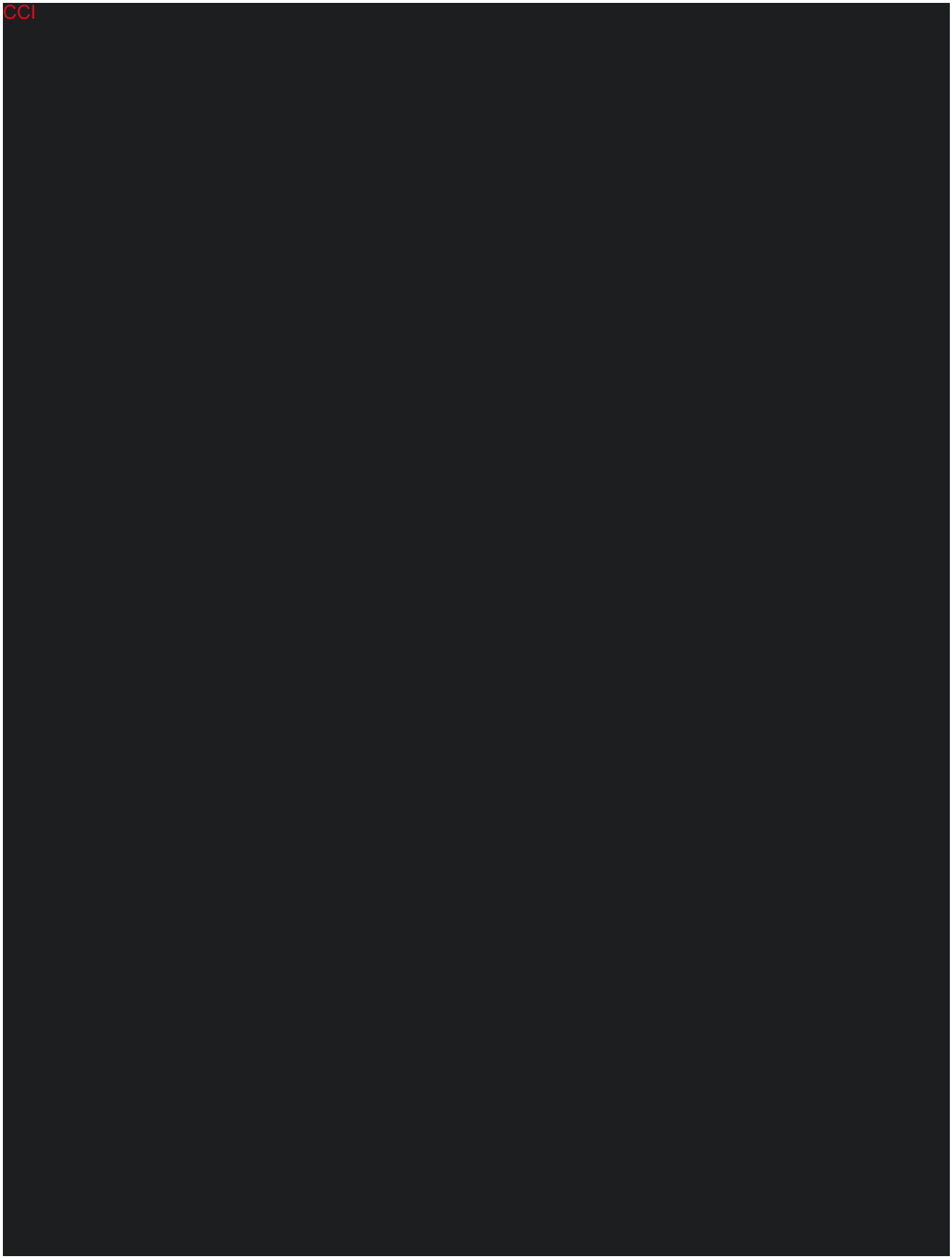

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11.5 Simpson Angus Scale (SAS)

The SAS will be used to evaluate extrapyramidal symptoms (EPS). It 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 Likert scale, with 0 representing absence of symptoms and 4 representing a severe condition. The SAS total score is the sum of ratings over all 10 items, with possible total score ranging from 0 to 40. The SAS total score will be un-evaluable if less than 8 of the 10 items are recorded. If 8 or 9 of the 10 items are recorded, the total score will be the mean of the recorded items multiplied by 10 and then rounded to the first decimal place.

11.6 Abnormal Involuntary Movement Scale (AIMS)

The AIMS is a 12-item scale. The first 10 items are rated on a Likert 5-point scale from 0 to 4 (0 = best, 4 = worst). An item score of 0, depending on specific item, means either "no abnormal Involuntary movement (AIM)" or "no incapacitation due to AIM" or "no awareness of AIM". An item score of 4 means either "severe AIM" or "severe incapacitation due to AIM" or "being aware of, and severe distress caused by AIM". Items 11 and 12 are related to dental status, taking dichotomous response: 0 = no and 1 = yes. The AIMS total score is the sum of the ratings over the first 7 items, with possible total score ranging from 0 to 28. The AIMS total Score will be un-evaluable if less than 6 of the first 7 items are recorded. If 6 of the items are recorded, then the total score will be the mean of the recorded items multiplied by 7 and then rounded to the first decimal place.

11.7 Barnes Akathisia Rating Scale (BARS)

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 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 0 to 5.

11.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored at all visits during the trial (excluding the 21-day follow-up period) using the C-SSRS (Child Version). The “Since Last Visit” of the scale will be completed for all subjects at all visits. For subjects in this trial, the pediatric version will be used and may be completed with caregiver assistance if required.

Suicidal ideation has 5 types of ideations with increasing severity from Type 1 to Type 5. A subject can report or can be rated with multiple types of ideations at the visit level. The most severe type of ideation on the subject at the visit level will be used for data summary purpose. The variable Intensity of Suicidal Ideation also has 4 other dimensions, which are the frequency of ideation, duration of ideation, controllability, and deterrents, each of which is rated on a scale of 0 to 5 or 1 to 5, with higher integers representing more worse clinical outcomes.

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Appendix 1 Criteria for Identifying Vital Signs Outside of Normal Values and of Potential Clinical Relevance

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

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

Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria (Normal Ranges) for Subjects 5 to 17 Years of Age
Chemistry	
AST	≥ 2 × ULN
ALT	≥ 2 × ULN
ALP	≥ 2 × ULN
Bicarbonate	
< 6 y	< 17.0 or > 26.0 mEq/L (17.0-26.0 mEq/L)
6 y to 12 y	< 19.0 or > 27.0 mEq/L (19.0-27.0 mEq/L)
≥ 12 y	< 19.3 or > 29.3 mEq/L (19.3-29.3 mEq/L)
BUN	≥ 24 mg/dL (≤ 4 mg/dL or ≥ 24 mg/dL)
Creatinine ≤ 12 y	≥ 0.7 mg/dL (≤ 0.2 mg/dL or ≥ 0.7 mg/dL)
≥ 13 y	≥ 1.1 mg/dL (≤ 0.3 mg/dL or ≥ 1.1 mg/dL)
Uric Acid	
≤ 12 y	≥ 6.7 mg/dL (≤ 1.6 mg/dL or ≥ 6.7 mg/dL)
≥ 13 y	≥ 8.2 mg/dL (≤ 2.2 mg/dL or ≥ 8.2 mg/dL)
Bilirubin (total)	≥ 1.6 mg/dL (≤ 0.2 mg/dL or ≥ 1.6 mg/dL)
CPK	≥ 2 × ULN
Prolactin	
≤ 12 y	≥ 21.00 ng/dL (≤ 2.63 ng/dL or ≥ 21.00 ng/dL)
≥ 13 y	≥ 39.00 ng/dL (≤ 2.52 ng/dL or ≥ 39.00 ng/dL)
Hematology	
Hematocrit	
≤ 12 y	≤ 33% (≤ 33% or ≥ 44%)
≥ 13 y	≤ 34% (≤ 34% or ≥ 54%)
Hemoglobin	
≤ 12 y	≤ 11.2 g/dL (≤ 11.2 g/dL or ≥ 15.5 g/dL)
≥ 13 y	≤ 11.6 g/dL (≤ 11.6 g/dL or ≥ 18.1 g/dL)
White blood count	≤ 4.35 × 10^3/uL (≤ 4.35 × 10^3/uL or ≥ 13.65 × 10^3/uL)
Eosinophils	
≤ 12 y	≥ 4.8%
≥ 13 y	≥ 4.1%
Neutrophils	≤ 40.5% (≤ 40.5% or ≥ 75.0%)
Absolute neutrophil count	
≤ 12 y	≤ 1.00 × 10^3/uL or ≥ 9.00 × 10^3/uL
≥ 13 y	≤ 1.35 × 10^3/uL or ≥ 8.15 × 10^3/uL
Platelet count	
≤ 12 y	≤ 130 × 10^3/uL (≤ 130 × 10^3/uL or ≥ 570 × 10^3/uL)
≥ 13 y	≤ 140 × 10^3/uL (≤ 140 × 10^3/uL or ≥ 400 × 10^3/uL)
Urinalysis	
Protein	Change from baseline
Glucose	Presence
Additional Criteria	
Chloride	≤ 94 mEq/L or ≥ 112 mEq/L
HbA1c	≥ 5.7%
ACTH	< 7.2 pg/mL - > 63.3 pg/mL
Cortisol	AM: 6.7 ug/dL - 22.60 ug/dL PM: < 10 ug/dL
Potassium	≤ 3.3 mEq/L or ≥ 5.2 mEq/L
Sodium	≤ 132 mEq/L or ≥ 148 mEq/L

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

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

Appendix 3 Criteria for Identifying ECG Measurement of Potential Clinical Relevance

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

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

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

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

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

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