Clinical trial results:
A Phase 3, Multicenter, Open Label Trial to Evaluate the Long-term Safety and Tolerability of Brexpiprazole in Treatment of Children and Adolescents With Irritability Associated With Autism Spectrum Disorder

Summary

EudraCT number	2018-004899-35
Trial protocol	Outside EU/EEA
Global end of trial date	16 March 2023

Results information

Result version number	v1 (current)
This version publication date	24 October 2024
First version publication date	24 October 2024

Trial information

Trial identification

Sponsor protocol code	331-201-00191

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04258839
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, 20850
Public contact	Clinical Transparency, Otsuka Pharmaceutical Development & Commercialization, Inc., 1 8446878522,
Scientific contact	Clinical Transparency, Otsuka Pharmaceutical Development & Commercialization, Inc., 1 8446878522,
Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, 20850
Public contact	Clinical Transparency, Otsuka Pharmaceutical Development & Commercialization, Inc., clinicaltransparency@otsuka-us.com
Scientific contact	Clinical Transparency, Otsuka Pharmaceutical Development & Commercialization, Inc., clinicaltransparency@otsuka-us.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the long-term safety and tolerability of brexpiprazole in children and adolescent subjects, aged 5 to 17, with irritability associated with autism spectrum disorder.

Protection of trial subjects:

Written informed consent, assent, or both were obtained from a legally acceptable representative (eg, guardian) or from the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 95
Worldwide total number of subjects	95
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	68
Adolescents (12-17 years)	26
Adults (18-64 years)	1
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with irritability associated with autism spectrum disorder (ASD) were enrolled in the study at sites in the United States from 23 January 2020 to 16 March 2023.

Pre-assignment

Screening details:

A total of 95 eligible subjects who completed 8-week, double-blind treatment, in the parent study 331-201-00148 (NCT04174365) and, who in the investigator's judgment, could potentially benefit from receiving brexpiprazole were enrolled in this study. Data was summarised as per the treatment received in the parent study 331-201-00148 (NCT0417436).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Prior Brexpiprazole

Arm description:

Subjects who received brexpiprazole in the parent study 331-201-00148 (NCT04174365) received brexpiprazole based on the body weight for 26 weeks in this study.

Subjects with body weight < 50 kilograms (kg), received brexpiprazole tablets orally, once daily (QD) at dose of 0.25 mg on Days 1 to 3 followed by 0.5 mg on Days 4 to 7 and 1 mg on Days 8 to 14. Based on the investigator's judgment, the dose was increased to 1 or 1.5 mg starting from Day 15 until week 26.

Subjects with body weight ≥ 50 kg received brexpiprazole tablet orally, QD at dose of 0.5 mg on Days 1 to 3, followed by 1.5 mg on Days 4 to 7, and 2 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5, 2, or 3 mg starting from Day 15 until week 26.

Arm type	Experimental
Investigational medicinal product name	Brexpiprazole
Investigational medicinal product code	OPC-34712
Other name	LuAF41156
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Brexpiprazole tablets, flexible dosing from 0.25 to 3 mg/day administered orally up to Week 26.

Arm title	Prior Placebo

Arm description:

Subjects who received placebo matched to brexpiprazole in the parent study 331-201-00148 (NCT04174365) received brexpiprazole based on the body weight for 26 weeks in this study.

Subjects with body weight < 50 kg, received brexpiprazole tablets orally, QD at dose of 0.25 mg on Days 1 to 3 followed by 0.5 mg on Days 4 to 7 and 1 mg on Days 8 to 14. Based on the investigator's judgment, the dose was increased to 1 or 1.5 mg starting from Day 15 until week 26.

Subjects with body weight ≥ 50 kg received brexpiprazole tablet orally, QD at dose of 0.5 mg on Days 1 to 3, followed by 1.5 mg on Days 4 to 7, and to 2 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5, 2 or 3 mg starting from Day 15 until week 26.

Arm type	Experimental

Investigational medicinal product name	Brexpiprazole
Investigational medicinal product code	OPC-34712
Other name	LuAF41156
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Brexpiprazole tablets, flexible dosing from 0.25 to 3 mg/day administered orally up to Week 26.

Number of subjects in period 1	Prior Brexpiprazole	Prior Placebo
Started	49	46
Safety Sample	49	46
Efficacy Sample	48	46
Completed	39	31
Not completed	10	15
Adverse Event	2	4
Withdrawal by Subject	1	2
Lost to follow-up	2	-
Withdrawal by Caregiver	5	6
Reason not Specified	-	1
Lack of efficacy	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Prior Brexpiprazole

Reporting group description:

Subjects who received brexpiprazole in the parent study 331-201-00148 (NCT04174365) received brexpiprazole based on the body weight for 26 weeks in this study.

Subjects with body weight < 50 kilograms (kg), received brexpiprazole tablets orally, once daily (QD) at dose of 0.25 mg on Days 1 to 3 followed by 0.5 mg on Days 4 to 7 and 1 mg on Days 8 to 14. Based on the investigator's judgment, the dose was increased to 1 or 1.5 mg starting from Day 15 until week 26.

Subjects with body weight ≥ 50 kg received brexpiprazole tablet orally, QD at dose of 0.5 mg on Days 1 to 3, followed by 1.5 mg on Days 4 to 7, and 2 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5, 2, or 3 mg starting from Day 15 until week 26.

Reporting group title	Prior Placebo

Reporting group description:

Subjects who received placebo matched to brexpiprazole in the parent study 331-201-00148 (NCT04174365) received brexpiprazole based on the body weight for 26 weeks in this study.

Subjects with body weight < 50 kg, received brexpiprazole tablets orally, QD at dose of 0.25 mg on Days 1 to 3 followed by 0.5 mg on Days 4 to 7 and 1 mg on Days 8 to 14. Based on the investigator's judgment, the dose was increased to 1 or 1.5 mg starting from Day 15 until week 26.

Subjects with body weight ≥ 50 kg received brexpiprazole tablet orally, QD at dose of 0.5 mg on Days 1 to 3, followed by 1.5 mg on Days 4 to 7, and to 2 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5, 2 or 3 mg starting from Day 15 until week 26.

Reporting group values	Prior Brexpiprazole	Prior Placebo	Total
Number of subjects	49	46	95
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	10.0	10.0	
standard deviation	± 3.1	± 3.1	-
Gender categorical Units: Subjects			
Female	4	8	12
Male	45	38	83
Ethnicity Units: Subjects			
Hispanic or Latino	6	8	14
Not Hispanic or Latino	43	38	81
Unknown or Not Reported	0	0	0
Race Units: Subjects			
White	37	38	75
Black or African American	8	2	10
Asian	1	3	4
Native Hawaiian or Other Pacific Islander	0	1	1
Other	3	2	5

Weight Units: kilogram (kg) arithmetic mean standard deviation	 41.6 ± 17.9	 44.2 ± 18.3	 -
Simpson Agnus Scale (SAS) Score			
SAS was used to evaluate extrapyramidal symptoms (EPS). The SAS 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). Severity of each item was rated on a 5-point Likert scale, with a score of 0 (absence of symptoms) to 4 (severe condition). The SAS total score is the sum of the scores of all 10 items, ranging from 0 to 40 where a higher score indicates a severe condition.			
Units: score on a scale arithmetic mean standard deviation	 ±	 ±	 -
Abnormal Involuntary Movement Scale (AIMS) Total Score			
AIMS is a 12-item scale. First 10 items are rated on Likert 5-point scale: 0 (best) to 4 (worst). 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". Item score of 4 means either "severe AIM" or "severe incapacitation due to AIM" or "being aware of, & severe distress caused by AIM". Items 11,12 are related to dental status, taking dichotomous response: 0=no & 1=yes. AIMS movement score is sum of ratings for first 7 items: possible total scores of 0-28, higher score indicates a severe condition.			
Units: score on a scale arithmetic mean standard deviation	 ±	 ±	 -
Barnes Akathisia Rating Scale (BARS) Score			
BARS consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items were rated on a 4-point Likert scale, with a score of 0 (absence of symptoms) to 3 (severe condition) & global clinical assessment was rated on a 6-point scale, with a score of 0 (absence of symptoms) to 5 (severe akathisia). Total score is the sum of the scores of all 4 items, ranging from 0 to 14. Lower scores indicate less symptoms.			
Units: score on a scale arithmetic mean standard deviation	 ±	 ±	 -

Subject analysis sets

Subject analysis set title	Safety Sample Subset
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Sample included all enrolled subjects who received at least one dose of the investigational medicinal product (IMP). 'Number analysed' indicates the number of subjects with data available for measure analysis, reported as the subset of Safety Sample.

Reporting group values	Safety Sample Subset		
Number of subjects	94		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	 ±	 	

Gender categorical Units: Subjects			
Female Male			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race Units: Subjects			
White Black or African American Asian Native Hawaiian or Other Pacific Islander Other			
Weight Units: kilogram (kg) arithmetic mean standard deviation	 ±		
Simpson Agnus Scale (SAS) Score			
SAS was used to evaluate extrapyramidal symptoms (EPS). The SAS 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). Severity of each item was rated on a 5-point Likert scale, with a score of 0 (absence of symptoms) to 4 (severe condition). The SAS total score is the sum of the scores of all 10 items, ranging from 0 to 40 where a higher score indicates a severe condition.			
Units: score on a scale arithmetic mean standard deviation	 0.3 ± 1.4		
Abnormal Involuntary Movement Scale (AIMS) Total Score			
AIMS is a 12-item scale. First 10 items are rated on Likert 5-point scale: 0 (best) to 4 (worst). 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". Item score of 4 means either "severe AIM" or "severe incapacitation due to AIM" or "being aware of, & severe distress caused by AIM". Items 11,12 are related to dental status, taking dichotomous response: 0=no & 1=yes. AIMS movement score is sum of ratings for first 7 items: possible total scores of 0-28, higher score indicates a severe condition.			
Units: score on a scale arithmetic mean standard deviation	 0.04 ± 0.25		
Barnes Akathisia Rating Scale (BARS) Score			
BARS consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items were rated on a 4-point Likert scale, with a score of 0 (absence of symptoms) to 3 (severe condition) & global clinical assessment was rated on a 6-point scale, with a score of 0 (absence of symptoms) to 5 (severe akathisia). Total score is the sum of the scores of all 4 items, ranging from 0 to 14. Lower scores indicate less symptoms.			
Units: score on a scale arithmetic mean standard deviation	 0.06 ± 0.35		

End points

End points reporting groups

Reporting group title	Prior Brexpiprazole

Reporting group description:

Subjects who received brexpiprazole in the parent study 331-201-00148 (NCT04174365) received brexpiprazole based on the body weight for 26 weeks in this study.

Subjects with body weight < 50 kilograms (kg), received brexpiprazole tablets orally, once daily (QD) at dose of 0.25 mg on Days 1 to 3 followed by 0.5 mg on Days 4 to 7 and 1 mg on Days 8 to 14. Based on the investigator's judgment, the dose was increased to 1 or 1.5 mg starting from Day 15 until week 26.

Subjects with body weight ≥ 50 kg received brexpiprazole tablet orally, QD at dose of 0.5 mg on Days 1 to 3, followed by 1.5 mg on Days 4 to 7, and 2 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5, 2, or 3 mg starting from Day 15 until week 26.

Reporting group title	Prior Placebo

Reporting group description:

Subjects who received placebo matched to brexpiprazole in the parent study 331-201-00148 (NCT04174365) received brexpiprazole based on the body weight for 26 weeks in this study.

Subjects with body weight < 50 kg, received brexpiprazole tablets orally, QD at dose of 0.25 mg on Days 1 to 3 followed by 0.5 mg on Days 4 to 7 and 1 mg on Days 8 to 14. Based on the investigator's judgment, the dose was increased to 1 or 1.5 mg starting from Day 15 until week 26.

Subjects with body weight ≥ 50 kg received brexpiprazole tablet orally, QD at dose of 0.5 mg on Days 1 to 3, followed by 1.5 mg on Days 4 to 7, and to 2 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5, 2 or 3 mg starting from Day 15 until week 26.

Subject analysis set title	Safety Sample Subset
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Sample included all enrolled subjects who received at least one dose of the investigational medicinal product (IMP). 'Number analysed' indicates the number of subjects with data available for measure analysis, reported as the subset of Safety Sample.

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) Graded By Severity, Serious TEAEs and Trial Discontinuation Due to TEAEs

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) Graded By Severity, Serious TEAEs and Trial Discontinuation Due to TEAEs[1]

End point description:

AE:untoward medical occurrence in clinical trial subject administered a medicinal product that does not necessarily have a causal relationship with the treatment.SAE:AE that results in appearance of (or worsening of any pre-existing) undesirable signs, symptoms,or is fatal, life-threatening, result in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, & requires inpatient hospitalisation or prolongation of existing hospitalisation.TEAE:AE that started after trial drug treatment; or if event was continuous from baseline & was worsening, serious, trial drug-related, or resulted in death, discontinuation, interruption, or reduction of trial therapy. TEAEs were graded Mild:Discomfort noticed, but no disruption to daily activity, Moderate:Discomfort sufficient to reduce or affect normal daily activity, & Severe: Inability to work or perform normal daily activity. Safety Sample included all enrolled subjects who received at least one dose of IMP.

End point type	Primary

End point timeframe:

From the first dose of study drug (in current study) up to 21 days after the last dose of study drug (up to approximately 29 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: subjects				
Subjects With TEAEs	23	24		
Subjects With Mild TEAEs	15	19		
Subjects With Moderate TEAEs	11	12		
Subjects With Severe TEAEs	2	2		
Subjects With Serious TEAEs	2	1		
Subjects With Trial Discontinuations due to TEAEs	2	4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Relevant Abnormalities in Vital Signs

End point title	Number of Subjects With Potentially Clinically Relevant Abnormalities in Vital Signs[2]

End point description:

Vital signs measurements included body weight, body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. Blood pressure (i.e., SBP, DBP) and heart rate were measured in the supine and standing positions after the subject had been in each position for at least 3 minutes. The subjects were categorized based on the clinically relevant vital sign values as per protocol-predefined criteria. The categories with at least one subject with clinically significant value outside the normal range for vital signs are reported. 'Number of subjects analysed' indicates the number of subjects with data available for this endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis of the specified parameter.

End point type	Primary

End point timeframe:

Baseline (current study) up to Week 26

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	46		
Units: subjects				
SBP Standing (mmHg): High (n = 47, 46)	4	5		
SBP Supine (mmHg): High (n = 48, 46)	1	5		
DBP Standing (mmHg): Low (n = 47, 46)	0	1		
DBP Standing (mmHg): High (n = 47, 46)	2	1		
DBP Supine (mmHg): Low (n = 48, 46)	1	1		
DBP Supine (mmHg): High (n = 48, 46)	1	3		
Heart Rate Standing (beats/min): High (n=47,46)	10	4		

Heart Rate Supine (beats/min): Low (n=48,46)	1	0		
Heart Rate Supine (beats/min): High (n=48,46)	3	1		
Body Temperature (n = 48, 46)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Relevant Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects With Potentially Clinically Relevant Electrocardiogram (ECG) Abnormalities[3]

End point description:

Criteria for identifying ECG measurements of potential clinical relevance included Rate:Tachycardia (Vent ≥110 beats per minute [bpm];increase ≥15bpm),Bradycardia (Vent ≤ 60bpm; decrease ≥15bpm);Rhythm: Sinus tachycardia (≥ 110bpm; an increase of ≥15 bpm),Sinus bradycardia (≤ 60bpm; a decrease of ≥15 bpm),Supraventricular premature beat (not present at baseline and present post-baseline),Conduction: Right bundle branch block (not present at baseline and present post-baseline)ST/T Morphology: Symmetrical T-Wave Inversion (not present at baseline and present post-baseline). Categories with at least 1 subject with clinically relevant ECG abnormalities are reported. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for this endpoint analysis 'Number analysed (n) indicates the number of subjects with data available for the analysis of the specified parameter.

End point type	Primary

End point timeframe:

Baseline (current study) up to Week 26

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: subjects				
Rate: Tachycardia (n = 43, 41)	1	2		
Rate: Bradycardia (n = 43, 41)	1	0		
Rhythm: Sinus Tachycardia (n = 43, 41)	1	2		
Rhythm: Sinus Bradycardia (n = 43, 41)	1	0		
Rhythm: Supraventricular Premature Beat (n =44,43)	1	0		
Conduction: Right Bundle Branch Block (n = 45, 43)	0	1		
ST/TMorphology:SymmetricalT-WaveInversion n=45,43	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Relevant Laboratory Test Abnormalities

End point title	Number of Subjects With Potentially Clinically Relevant Laboratory Test Abnormalities[4]

End point description:

Laboratory assessments included - serum chemistry including prolactin and thyrotropin, hematology, and urinalysis. Number of subjects with potentially clinically relevant laboratory test abnormalities were reported as per criteria defined in SAP. The categories with at least one subject with clinically relevant value outside the normal range for laboratory assessments are reported. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for this endpoint analysis. 'Number analysed (n)' indicates the number of subjects with data available for analysis of the specified parameter.

End point type	Primary

End point timeframe:

Baseline (current study) up to Week 26

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: subjects				
ActivatedPartialThromboplastinTime(sec)Highn=39,34	6	2		
Alanine Aminotransferase (U/L): High (n = 41, 42)	0	2		
Aspartate Aminotransferase (U/L): High(n=42, 42)	0	1		
Bicarbonate (mEq/L): Low (n = 41,42)	14	15		
Bilirubin (mg/dL): Low (n = 36, 31)	10	8		
Bilirubin (mg/dL): High (n = 36, 31)	0	1		
Calcium (mg/dL): Low (n = 42, 42)	0	1		
Chloride (mEq/L): High (n = 42, 41)	2	0		
Cortisol (ug/dL): Low (n = 36, 35)	7	9		
Creatinine (mg/dL): High (n = 42, 42)	1	0		
Glucose (mg/dL): Low (n = 42, 42)	0	1		
Glucose (mg/dL): High (n = 42, 42)	1	0		
Potassium (mEq/L): High (n = 42, 41)	1	3		
Sodium (mEq/L): High (n = 42, 41)	2	0		
Eosinophils/Leukocytes (%): High (n= 41, 42)	2	3		
Hematocrit (%): Low (n = 41, 42)	0	1		
Hematocrit (%): High (n = 41, 42)	1	0		
Hemoglobin (g/dL): Low (n = 41, 42)	1	0		
Hemoglobin A1C (%): High (n = 42, 41)	2	4		
Leukocytes (10^9/L): Low (n = 41, 42)	6	2		
Leukocytes (10^9/L): High (n = 41, 42)	0	1		
Neutrophils (10^9/L): High (n = 41, 42)	0	2		

Neutrophils/Leukocytes (%): Low (n = 41, 42)	8	2		
Neutrophils/Leukocytes (%): High (n = 41, 42)	0	2		
Platelets (10^9/L): High (n = 41, 42)	1	1		
Prothrombin Intl. Normalized Ratio: High(n=39,34)	5	2		
Prothrombin Time (sec): High (n = 39, 34)	3	2		
Protein, Urine: Low (n = 42, 39)	12	11		
Protein, Urine: High (n = 42, 39)	10	11		
Prolactin (ng/mL): Low (n = 42, 42)	3	4		
Prolactin (ng/mL): High (n = 42, 42)	1	2		
Thyrotropin (uIU/mL): High (n = 42, 42)	2	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Relevant Abnormal Physical Examination Values

End point title	Number of Subjects With Potentially Clinically Relevant Abnormal Physical Examination Values[5]

End point description:

Physical examination included measurement of height and the examination of the head, ears, eyes, nose, and throat (HEENT); thorax; abdomen; urogenital; extremities; neurological; and skin and mucosae. Subjects with abnormal values, as assessed by the investigator were reported. Safety Sample included all enrolled subjects who received at least one dose of IMP.

End point type	Primary

End point timeframe:

Baseline (current study) up to Week 26

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: subjects	6	4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Suicidality as Measured by Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Subjects With Suicidality as Measured by Columbia-Suicide Severity Rating Scale (C-SSRS)[6]

End point description:

Suicidality as defined as at least one occurrence of suicidal ideation or suicidal behavior, was assessed using C-SSRS.Assessment included yes/no responses for 5 questions,each related to suicidal ideation (wish to be dead,non-specific active suicidal thoughts,active suicidal ideation with any methods,active suicidal ideation with some intent,active suicidal ideation with specific plan) & suicidal behavior (preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt, suicide).Numeric ratings provided for suicidal ideation:1(wish to be dead) to 5(active suicidal ideation with specific plan and intent), higher total scores indicate more suicidal ideation; Suicidal behavior: 0(no suicidal behavior) to 4(actual suicide attempt), higher total scores indicate more suicidal behavior. Number of subjects with at least one occurrence of suicidal ideation or suicidal behavior was reported.Safety Sample included all enrolled subjects who received at least 1 one dose of IMP.

End point type	Primary

End point timeframe:

Baseline (current study) up to Week 26

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: subjects	4	2		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Simpson Angus Scale (SAS) Total Score at Week 2

End point title	Change From Baseline in Simpson Angus Scale (SAS) Total Score at Week 2[7]

End point description:

SAS was used to evaluate extrapyramidal symptoms (EPS). The SAS 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). Severity of each item was rated on a 5-point Likert scale, with a score of 0 (absence of symptoms) to 4 (severe condition). The SAS total score is the sum of the scores of all 10 items, ranging from 0 to 40 where a higher score indicates a severe condition. Negative change from baseline indicates absence of symptoms. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analyzed' indicates the number of subjects with data available for this endpoint analysis.

End point type	Primary

End point timeframe:

Baseline and Week 2

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	41		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.0 (± 0.5)	0.0 (± 0.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in SAS Total Score at Week 14

End point title	Change From Baseline in SAS Total Score at Week 14[8]

End point description:

SAS was used to evaluate extrapyramidal symptoms (EPS). The SAS 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). Severity of each item was rated on a 5-point Likert scale, with a score of 0 (absence of symptoms) to 4 (severe condition). The SAS total score is the sum of the scores of all 10 items, ranging from 0 to 40 where a higher score indicates a severe condition. Negative change from baseline indicates absence of symptoms. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis at specified time point.

End point type	Primary

End point timeframe:

Baseline and Week 14

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.1 (± 0.7)	0.2 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in SAS Total Score at Week 26

End point title	Change From Baseline in SAS Total Score at Week 26[9]

End point description:

SAS was used to evaluate extrapyramidal symptoms (EPS). The SAS 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). Severity of each item was rated on a 5-point Likert scale, with a score of 0 (absence of symptoms) to 4 (severe condition). The SAS total score is the sum of the scores of all 10 items, ranging from 0 to 40 where a higher score indicates a severe condition. Negative change from baseline indicates absence of symptoms. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data

available for endpoint analysis at specified time point.

End point type	Primary

End point timeframe:

Baseline and Week 26

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	28		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.1 (± 0.9)	-0.0 (± 0.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Abnormal Involuntary Movement Scale (AIMS) Total Score at Week 2

End point title	Change From Baseline in Abnormal Involuntary Movement Scale (AIMS) Total Score at Week 2[10]

End point description:

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. AIMS movement score is the sum of the ratings for the first seven items with possible total scores of 0 to 28, where a higher score indicates a severe condition. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis at specified time point.

End point type	Primary

End point timeframe:

Baseline and Week 2

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: score on a scale				
arithmetic mean (standard deviation)	0.0 (± 0.00)	0.14 (± 1.08)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in AIMS Total Score at Week 14

End point title	Change From Baseline in AIMS Total Score at Week 14[11]

End point description:

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. AIMS movement score is the sum of the ratings for the first seven items with possible total scores of 0 to 28, where a higher score indicates a severe condition. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis at specified time point.

End point type	Primary

End point timeframe:

Baseline and Week 14

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: score on a scale				
arithmetic mean (standard deviation)	0.0 (± 0.00)	0.16 (± 1.15)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in AIMS Total Score at Week 26

End point title	Change From Baseline in AIMS Total Score at Week 26[12]

End point description:

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. AIMS movement score is the sum of the ratings for the first seven items with possible total scores of 0 to 28, where a higher score indicates a severe condition. A negative change from baseline indicates less symptoms. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis at specified time point.

End point type	Primary

End point timeframe:

Baseline and Week 26

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	28		
Units: score on a scale				
arithmetic mean (standard deviation)	0.00 (± 0.00)	-0.04 (± 0.19)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Barnes Akathisia Rating Scale (BARS) Score at Week 2

End point title	Change From Baseline in Barnes Akathisia Rating Scale (BARS) Score at Week 2[13]

End point description:

The BARS consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items were rated on a 4-point Likert scale, with a score of 0 (absence of symptoms) to 3 (severe condition) and the global clinical assessment was rated on a 6-point scale, with a score of 0 (absence of symptoms) to 5 (severe akathisia). Total score is the sum of the scores of all 4 items, ranging from 0 to 14. Lower scores indicate less symptoms. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis at specified time point.

End point type	Primary

End point timeframe:

Baseline and Week 2

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: score on a scale				
arithmetic mean (standard deviation)	0.02 (± 0.26)	0.05 (± 0.30)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in BARS Score at Week 14

End point title	Change From Baseline in BARS Score at Week 14[14]

End point description:

The BARS consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items were rated on a 4-point Likert scale, with a score of 0 (absence of symptoms) to 3 (severe condition) and the global clinical assessment was rated on a 6-point scale, with a score of 0 (absence of symptoms) to 5 (severe akathisia). Total score is the sum of the

scores of all 4 items, ranging from 0 to 14. Lower scores indicate less symptoms and negative change from baseline indicate less symptoms. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis at specified time point.

End point type	Primary

End point timeframe:

Baseline and Week 14

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.05 (± 0.22)	0.05 (± 0.40)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in BARS Score at Week 26

End point title	Change From Baseline in BARS Score at Week 26[15]

End point description:

The BARS consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items were rated on a 4-point Likert scale, with a score of 0 (absence of symptoms) to 3 (severe condition) and the global clinical assessment was rated on a 6-point scale, with a score of 0 (absence of symptoms) to 5 (severe akathisia). Total score is the sum of the scores of all 4 items, ranging from 0 to 14. Lower scores indicate less symptoms and negative change from baseline indicate less symptoms. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis at specified time point.

End point type	Primary

End point timeframe:

Baseline and Week 26

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	28		
Units: score on a scale				
arithmetic mean (standard deviation)	0.00 (± 0.24)	-0.04 (± 0.19)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Potentially Clinically Relevant Changes in Weight up to Week 14

End point title	Percentage of Subjects With Potentially Clinically Relevant Changes in Weight up to Week 14[16]

End point description:

Percentage of subjects who had significant weight gain (≥ 7% increase in body weight relative to baseline) and significant weight loss (≥ 7% decrease in body weight relative to baseline) were reported. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Week 14

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	37		
Units: percentage of subjects				
number (not applicable)				
Weight Gain >= 7%	45.0	48.6		
Weight Loss >= 7%	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Potentially Clinically Relevant Changes in Weight up to Week 26

End point title	Percentage of Subjects With Potentially Clinically Relevant Changes in Weight up to Week 26[17]

End point description:

Percentage of subjects who had significant weight gain (≥ 7% increase in body weight relative to baseline) and significant weight loss (≥ 7% decrease in body weight relative to baseline) were reported. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for this outcome measure.

End point type	Primary

End point timeframe:

Baseline up to Week 26

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	30		
Units: percentage of subjects				
number (not applicable)				
Weight Gain >= 7%	71.8	76.7		
Weight Loss >= 7%	0.0	3.3		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Discontinuation Due to AE

End point title	Time to Discontinuation Due to AE[18]

End point description:

The time to discontinuation due to AE was defined as the total number of days between the enrolment date and the discontinuation date. The time to discontinuation was analyzed using the Kaplan Meier curve. Safety Sample included all enrolled subjects who received at least one dose of IMP. 'Number of subjects analysed' indicates the number of subjects with data available for this outcome measure.

End point type	Primary

End point timeframe:

Baseline (in current study) up to 21 days post last dose of study drug (up to approximately 29 weeks)

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypotheses were tested for this end point.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	4		
Units: days				
median (full range (min-max))	83 (14 to 152)	113 (54 to 140)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline to Week 26 in Aberrant Behavior Checklist - Irritability (ABC-I) Subscale Score

End point title	Mean Change From Baseline to Week 26 in Aberrant Behavior Checklist - Irritability (ABC-I) Subscale Score

End point description:

ABC is a parent-reported rating scale that evaluates treatment effects on problem behavior in subjects with intellectual disabilities. ABC scale has 58 items, divided in 5 subscales Irritability, Agitation; Lethargy, Social Withdrawal; Stereotypic Behavior; Hyperactivity, Noncompliance; & Inappropriate Speech. Each of 58 ABC items is rated on a 4-point scale from 0=not at all a problem to 3=the problem is severe in degree. ABC-I measures emotional & behavioral symptoms of ASD. ABC-I total score is sum of ratings over 15 ABC items. Individual scores were summed, thus ABC-I total score ranges from 0 to

45. Higher scores=worst condition. Negative change from baseline indicates improvement. Efficacy sample included all randomised subjects in the Safety Sample who had a baseline assessment and at least one post-baseline assessment of the ABC-I subscale score. ‘Number of subjects analysed’ indicates number of subjects with data available for this endpoint analysis.

End point type	Secondary

End point timeframe:

Baseline (current study), Week 26

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	27		
Units: score on a scale				
arithmetic mean (standard deviation)	-5.47 (± 8.06)	-7.00 (± 8.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline to Week 26 in Clinical Global Impression - Severity (CGI-S) Scale Score

End point title	Mean Change From Baseline to Week 26 in Clinical Global Impression - Severity (CGI-S) Scale Score

End point description:

The CGI-S scale is a clinician-rated assessment that evaluates the severity of a subject's condition with a focus on symptoms of irritability on a 7-point scale. The investigator (or rater) answered the following question: "Considering your total clinical experience with this particular population, how ill was the participant at this time with regard to symptoms of irritability?" Response choices were 0 = not assessed; 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients. The total score ranges from 0 to 7, where higher scores indicate worse condition. A negative change from baseline indicates less symptoms. Efficacy Sample included all subjects in the Safety Sample who had a baseline assessment and at least one post-baseline assessment of the ABC-I subscale score. 'Number of subjects analysed' indicates the number of subjects with data available for this endpoint analysis.

End point type	Secondary

End point timeframe:

Baseline (current study), Week 26

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	28		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.78 (± 0.99)	-0.68 (± 0.94)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug (in current study) up to 21 days after the last dose of study drug (up to approximately 29 weeks)

Adverse event reporting additional description:

Safety Sample included all enrolled subjects who received at least one dose of IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Prior Brexpiprazole

Reporting group description:

Subjects who received brexpiprazole in the parent study 331-201-00148 (NCT04174365) received brexpiprazole based on the body weight for 26 weeks in this study.

Subjects with body weight < 50 kg, received brexpiprazole tablets orally, QD at dose of 0.25 mg on Days 1 to 3 followed by 0.5 mg on Days 4 to 7 and 1 mg on Days 8 to 14. Based on the investigator's judgment, the dose was increased to 1 or 1.5 mg starting from Day 15 until week 26.

Subjects with body weight ≥ 50 kg received brexpiprazole tablet orally, QD at dose of 0.5 mg on Days 1 to 3, followed by 1.5 mg on Days 4 to 7, and 2 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5, 2, or 3 mg starting from Day 15 until week 26.

Reporting group title	Prior Placebo

Reporting group description:

Subjects who received placebo matched to brexpiprazole in the parent study 331-201-00148 (NCT04174365) received brexpiprazole based on the body weight for 26 weeks in this study.

Subjects with body weight < 50 kg, received brexpiprazole tablets orally, QD at dose of 0.25 mg on Days 1 to 3 followed by 0.5 mg on Days 4 to 7 and 1 mg on Days 8 to 14. Based on the investigator's judgment, the dose was increased to 1 or 1.5 mg starting from Day 15 until week 26.

Subjects with body weight ≥ 50 kg received brexpiprazole tablet orally, QD at dose of 0.5 mg on Days 1 to 3, followed by 1.5 mg on Days 4 to 7, and to 2 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5, 2 or 3 mg starting from Day 15 until week 26.

Serious adverse events	Prior Brexpiprazole	Prior Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 49 (4.08%)	1 / 46 (2.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Affective disorder			
subjects affected / exposed	0 / 49 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 49 (2.04%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Prior Brexpiprazole	Prior Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 49 (34.69%)	11 / 46 (23.91%)	
Investigations			
Weight increased			
subjects affected / exposed	5 / 49 (10.20%)	8 / 46 (17.39%)	
occurrences (all)	5	8	
Nervous system disorders			
Somnolence			
subjects affected / exposed	5 / 49 (10.20%)	1 / 46 (2.17%)	
occurrences (all)	5	2	
Psychiatric disorders			
Irritability			
subjects affected / exposed	3 / 49 (6.12%)	0 / 46 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 49 (6.12%)	0 / 46 (0.00%)	
occurrences (all)	3	0	
Viral influenza			
subjects affected / exposed	4 / 49 (8.16%)	0 / 46 (0.00%)	
occurrences (all)	4	0	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	2 / 49 (4.08%)	4 / 46 (8.70%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2019	- Removed trial 331-201-00084 and corresponding bipolar I disorder data. - Revised the Week 2 visit to occur in-clinic. - Add visit for extrapyramidal symptoms (EPS scales) - Add additional tests under hematology assessments - Removed references to Young Mania rating scale (YMRS), CGI-Bipolar Version (CGI-BP), Children's Depression rating scale revised (CDRS-R), Children's Global Assessment scale (CGAS), and the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) - Clarified details around urogenital assessment - Revised the appendix containing normal ranges for glucose levels - Thyroid stimulating hormone (TSH) and coagulation parameters added at screening/baseline and Week 26. Parameters and criteria also added to Appendix 2.
06 November 2019	- Updated serious hepatotoxicity criteria to align with trial 331-201-00148. - Accommodated FDA request to add bicarbonate and hemoglobin A1c (HbA1C) to the laboratory tests at Screening/Baseline weeks 14 and 26, requiring an update to Table 3.7.3.2-1. - Parameters and criteria also added to Appendix 2. - Added tests for TSH and prolactin at Week 14. - Added exclusion criteria regarding birth control and breastfeeding from the trial 331-201-00148 protocol.
12 February 2020	- Revised lower limit of adolescent systolic blood pressure - Revised HbA1c laboratory value of potential relevance - Added assessments and laboratory value of potential relevance for ddrenocorticotropic hormone (ACTH) and cortisol.
06 July 2020	- Introduced a COVID-19 Addendum for any protocol-specified activities that are not able to be performed or cannot be performed due to COVID-19 considerations. Refer to the COVID-19 Addendum for the appropriate measures to be followed. - Excluded the simultaneous participation of siblings or unrelated members of the same residence.
07 July 2022	- Allowed in clinic visits in lieu of virtual visits if investigators and caregivers feel that an in person visit may be more appropriate. This change reflects feedback/requests from the trial site staff and principal investigators. - Clarified that the ± 2 day visit window is applicable to the dose titration schedule. - Added clarifications to prohibited and permitted medications. - Updated information based on the latest Investigator Brochure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported