Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Brexpiprazole in Treatment of Children and Adolescents With Irritability Associated With Autism Spectrum Disorder

Summary

EudraCT number	2019-000723-40
Trial protocol	Outside EU/EEA
Global end of trial date	09 September 2022

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	331-201-00148

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04174365
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	Krista Martinko, Otsuka Pharmaceutical Development & Commercialization, Inc., 1 8446878522, clinicaltransparency@otsuka-us.com
Scientific contact	Krista Martinko, Otsuka Pharmaceutical Development & Commercialization, Inc., 1 8446878522, 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	09 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to find out about the potential benefits and safety 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	30 October 2019
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: 119
Worldwide total number of subjects	119
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)	86
Adolescents (12-17 years)	33
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 40 sites in the United States from 30 October 2019 to 9 September 2022.

Pre-assignment

Screening details:

A total of 260 subjects were screened, of which 119 subjects were randomised to receive brexpiprazole or placebo.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Brexpiprazole

Arm description:

Subjects received flexible doses of brexpiprazole 0.25 to 3 milligram per day (mg/day), orally, once daily (QD) up to Week 8. For subjects with body weight < 50 kilograms (kg) the dose was titrated up from 0.25 mg/day on Days 1 to 3, followed by 0.5 mg on Days 4 to 7, and to 1 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5 mg/day after Day 15. The dose was fixed after Week 6 and administration continued for another 2 weeks until Week 8.
For subjects with body weight ≥ 50 kg the dose was titrated up from 0.5 mg/day 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 3 mg/day after Day 15. The dose was fixed after Week 6 and administration continued for another 2 weeks until Week 8.

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 8.

Arm title	Placebo

Arm description:

Subjects received brexpiprazole matching placebo orally, QD, in the same way as brexpiprazole up to Week 8.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Brexpiprazole matching placebo tablets were administered orally up to Week 8.

Number of subjects in period 1	Brexpiprazole	Placebo
Started	60	59
Randomised Sample	60	59
Safety Sample	58	57
Efficacy Sample	58	56
Completed	52	52
Not completed	8	7
Disease Relapse	1	-
Adverse Event	2	1
Reason Not Specified	-	1
Lost to follow-up	1	2
Subject Withdrew Consent To Participate	1	-
Subject Was Withdrawn From Participation By Parent	2	1
Protocol deviation	1	-
Lack of efficacy	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole
Reporting group description:	
Subjects received flexible doses of brexpiprazole 0.25 to 3 milligram per day (mg/day), orally, once daily (QD) up to Week 8. For subjects with body weight < 50 kilograms (kg) the dose was titrated up from 0.25 mg/day on Days 1 to 3, followed by 0.5 mg on Days 4 to 7, and to 1 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5 mg/day after Day 15. The dose was fixed after Week 6 and administration continued for another 2 weeks until Week 8. For subjects with body weight ≥ 50 kg the dose was titrated up from 0.5 mg/day 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 3 mg/day after Day 15. The dose was fixed after Week 6 and administration continued for another 2 weeks until Week 8.	
Reporting group title	Placebo
Reporting group description:	
Subjects received brexpiprazole matching placebo orally, QD, in the same way as brexpiprazole up to Week 8.	

Reporting group values	Brexpiprazole	Placebo	Total
Number of subjects	60	59	119
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	9.8	10.0	
standard deviation	± 2.9	± 3.2	-
Gender categorical Units: Subjects			
Female	6	9	15
Male	54	50	104
Ethnicity Units: Subjects			
Hispanic or Latino	8	7	15
Not Hispanic or Latino	52	52	104
Unknown or Not Reported	0	0	0
Race Units: Subjects			
White	49	45	94
Black or African American	3	10	13
American Indian or Alaska Native	0	0	0
Asian	2	3	5
Native Hawaiian or Other Pacific Islander	1	0	1
Other	5	1	6

End points

End points reporting groups

Reporting group title	Brexpiprazole

Reporting group description:

Subjects received flexible doses of brexpiprazole 0.25 to 3 milligram per day (mg/day), orally, once daily (QD) up to Week 8. For subjects with body weight < 50 kilograms (kg) the dose was titrated up from 0.25 mg/day on Days 1 to 3, followed by 0.5 mg on Days 4 to 7, and to 1 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5 mg/day after Day 15. The dose was fixed after Week 6 and administration continued for another 2 weeks until Week 8.
For subjects with body weight ≥ 50 kg the dose was titrated up from 0.5 mg/day 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 3 mg/day after Day 15. The dose was fixed after Week 6 and administration continued for another 2 weeks until Week 8.

Reporting group title	Placebo

Reporting group description:

Subjects received brexpiprazole matching placebo orally, QD, in the same way as brexpiprazole up to Week 8.

Primary: Mean Change From Baseline to Week 8 in Aberrant Behavior Checklist - Irritability (ABC-I) Subscale Score

End point title	Mean Change From Baseline to Week 8 in Aberrant Behavior Checklist - Irritability (ABC-I) Subscale Score

End point description:

ABC, a parent-reported scale 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 4-point scale from 0=not at all a problem to 3=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:all randomised subjects who took at least 1 dose of brexpiprazole or placebo & had baseline & at least 1 post-baseline assessment of primary efficacy variable ABC-I subscale score during double-blind treatment phase. Number of subjects analysed indicates number of subjects with data available for analysis.

End point type	Primary

End point timeframe:

Baseline to Week 8

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	46		
Units: score on a scale				
least squares mean (standard error)	-10.1 (± 1.28)	-8.87 (± 1.25)		

Statistical analyses

Statistical analysis title	Brexpiprazole, Placebo
Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4597 [1]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Least squares (LS) mean Difference
Point estimate	-1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.49
upper limit	2.05

Notes:

[1] - MMRM method with model terms: treatment, trial site, baseline body weight stratum, visit, treatment-by-visit and baseline-by-visit interaction.

Secondary: Mean Change From Baseline to Week 8 in Clinical Global Impression - Severity (CGI-S) Score

End point title	Mean Change From Baseline to Week 8 in Clinical Global Impression - Severity (CGI-S) Score

End point description:

The CGI-S is a 7-point clinician rated scale to assess severity of subject's current illness state with a focus on symptoms of irritability. The investigator (or rater) answered the following question: "Considering your total clinical experience with this particular population, how ill was the subject at this time with regard to symptoms of irritability? Response choices were from 1 (normal - not ill at all) to 7 (among the most extremely ill patients). Higher score = more severe illness. A negative change from baseline indicates improvement. Efficacy sample included all randomised subjects who took at least 1 dose of brexpiprazole or placebo and had baseline and at least 1 post-baseline assessment of the primary efficacy variable ABC-I subscale score during the double-blind treatment phase. Number of subjects analysed indicates the number of subjects with data available for analysis of this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	46		
Units: score on a scale				
least squares mean (standard error)	-1.16 (± 0.15)	-1.09 (± 0.15)		

Statistical analyses

Statistical analysis title	Brexpiprazole, Placebo
Comparison groups	Brexpiprazole v Placebo

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7315 [2]
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.32

Notes:

[2] - MMRM method with model terms: treatment, trial site, baseline body weight stratum, visit, treatment-by-visit and baseline-by-visit interaction.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose through 21 (±2) days after last dose of study drug (up to approximately Week 11)

Adverse event reporting additional description:

Safety sample included all enrolled subjects who received at least 1 dose of brexpiprazole or placebo.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Brexpiprazole

Reporting group description:

Subjects received flexible doses of brexpiprazole 0.25 to 3 mg/day, orally, QD up to Week 8. For subjects with body weight < 50 kg the dose was titrated up from 0.25 mg/day on Days 1 to 3, followed by 0.5 mg on Days 4 to 7, and to 1 mg on Days 8 to 14. Based on the investigator's judgment the dose was increased to 1.5 mg/day after Day 15. The dose was fixed after Week 6 and administration continued for another 2 weeks until Week 8.
For subjects with body weight ≥ 50 kg the dose was titrated up from 0.5 mg/day 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 3 mg/day after Day 15. The dose was fixed after Week 6 and administration continued for another 2 weeks until Week 8.

Reporting group title	Placebo

Reporting group description:

Subjects received brexpiprazole matching placebo orally, QD, in the same way as brexpiprazole up to Week 8.

Serious adverse events	Brexpiprazole	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Brexpiprazole	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 58 (22.41%)	5 / 57 (8.77%)	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 58 (10.34%)	1 / 57 (1.75%)	
occurrences (all)	7	2	

Somnolence subjects affected / exposed occurrences (all)	7 / 58 (12.07%) 8	3 / 57 (5.26%) 3	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 4	1 / 57 (1.75%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2019	-Revised Week 2 visit to occur in-clinic. -Clarified caregiver and subject interacting for virtual visit. -Clarifications provided for details around urogenital assessment, procedures on clinical laboratory tests at screening and use of propanolol. -Visits were adjusted for prolactin, clinical laboratory tests, electrocardiogram (ECG), extrapyramidal symptoms (EPS) scales, thyroid stimulating hormone (TSH), and coagulation assessments. -Clarification provided that ECGs done at screening do not need to be repeated if within normal ranges. -The pharmacogenomic and future biospecimen research (FBR) sampling should be taken with pharmacokinetic (PK) draws. -Added additional tests under hematology assessments. -Washout days updated for washout medications. -Revised the appendices and corresponding protocol sections containing normal ranges for glucose levels, TSH, free thyroxine (T4), prothrombin time, activated partial thromboplastin time, and international normalized ratio.
22 November 2019	- Added bicarbonate to the laboratory tests at screening, baseline, and Week 8. Parameters and criteria also added to Appendix 2.
12 February 2020	- Revised lower limit of adolescent systolic blood pressure. - Revised glycosylated hemoglobin laboratory value of potential relevance. - Added assessments and laboratory value of potential relevance for adrenocorticotropic hormone and cortisol.
06 July 2020	- A COVID-19 Addendum was introduced for any protocol specified activities that are not able to be performed or cannot be performed due to COVID-19 considerations. - Corrected PK parameter values in the Introduction. - Excluded the simultaneous participation of siblings or unrelated members of the same residence. - Stated that the Kiddie-Schedule for Affective Disorders and Schizophrenia - Present and Lifetime version (K-SADS-PL) does not need to be repeated at the screening visit for subjects that are rescreened. - Allowed for the extension of the screening period to accommodate repeating clinical laboratory tests or ECGs.
07 July 2022	- Revised the treatment effect assumption from 5.5 to 6.0, resulting in a new sample size of 102 randomised subjects. - 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. - Introduced an estimand. - 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. Clarified/added abbreviations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported