Clinical trial results:
A Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Adult Subjects With Borderline Personality Disorder

Summary

EudraCT number	2019-002897-30
Trial protocol	ES
Global end of trial date	22 September 2021

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022

Trial information

Trial identification

Sponsor protocol code	331-201-00195

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04186403
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., clinicaltransparency@otsuka-us.com
Scientific contact	Global Clinical Development, 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	22 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of brexpiprazole in the treatment of subjects with a diagnosis of borderline personality disorder (BPD).

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Ukraine: 10
Country: Number of subjects enrolled	United States: 185
Worldwide total number of subjects	201
EEA total number of subjects	6

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	201
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 55 investigational sites in Spain, Ukraine, and the United States (US) from 13 January 2020 to 22 September 2021.

Pre-assignment

Screening details:

A total of 203 subjects with borderline personality disorder (BPD), who completed the previous double-blind trial (2019-002813-20) were screened, out of which 201 subjects were enrolled in this study. Of enrolled subjects, 90 received 2 to 3 mg/day brexpiprazole and 111 received brexpiprazole matching placebo in previous double-blind trial.

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 2-3 Milligrams Per Day

Arm description:

Subjects who received blinded brexpiprazole 2 to 3 milligrams per day (mg/day) in the previous double-blind trial (2019-002813-20), received open-label brexpiprazole 2 to 3 mg/day tablets, orally for up to 12 weeks.

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

Dosage and administration details:

Brexpiprazole tablets, 1 or 2 or 3 mg/day administered orally up to Week 12.

Arm title	Prior Placebo

Arm description:

Subjects who received blinded brexpiprazole matching placebo in the previous double-blind trial (2019-002813-20), received open-label brexpiprazole 2 to 3 mg/day tablets, orally for up to 12 weeks.

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

Dosage and administration details:

Brexpiprazole tablets, 1 or 2 or 3 mg/day administered orally up to Week 12.

Number of subjects in period 1	Prior Brexpiprazole 2-3 Milligrams Per Day	Prior Placebo
Started	90	111
Safety Sample	88	111
Completed	71	92
Not completed	19	19
Physician decision	1	-
Adverse event	1	8
Lost to follow-up	7	3
Other: Not related to Covid-19	3	-
Withdrawal by subject	7	8

Baseline characteristics

Reporting groups	
Reporting group title	Prior Brexpiprazole 2-3 Milligrams Per Day
Reporting group description:	
Subjects who received blinded brexpiprazole 2 to 3 milligrams per day (mg/day) in the previous double-blind trial (2019-002813-20), received open-label brexpiprazole 2 to 3 mg/day tablets, orally for up to 12 weeks.	
Reporting group title	Prior Placebo
Reporting group description:	
Subjects who received blinded brexpiprazole matching placebo in the previous double-blind trial (2019-002813-20), received open-label brexpiprazole 2 to 3 mg/day tablets, orally for up to 12 weeks.	

Reporting group values	Prior Brexpiprazole 2-3 Milligrams Per Day	Prior Placebo	Total
Number of subjects	90	111	201
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	33.6	32.0	
standard deviation	± 10.5	± 10.6	-
Gender categorical Units: Subjects			
Female	71	92	163
Male	19	19	38
Race Units: Subjects			
White	72	89	161
Black or African American	7	19	26
American Indian or Alaska Native	2	0	2
Asian	4	0	4
Native Hawaiian or Other Pacific Islander	0	1	1
Other	5	2	7
Ethnicity Units: Subjects			
Hispanic or Latino	15	17	32
Not Hispanic or Latino	75	93	168
Other	0	1	1

End points

End points reporting groups

Reporting group title	Prior Brexpiprazole 2-3 Milligrams Per Day

Reporting group description:

Subjects who received blinded brexpiprazole 2 to 3 milligrams per day (mg/day) in the previous double-blind trial (2019-002813-20), received open-label brexpiprazole 2 to 3 mg/day tablets, orally for up to 12 weeks.

Reporting group title	Prior Placebo

Reporting group description:

Subjects who received blinded brexpiprazole matching placebo in the previous double-blind trial (2019-002813-20), received open-label brexpiprazole 2 to 3 mg/day tablets, orally for up to 12 weeks.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and as per Severity

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and as per Severity[1]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial subject administered an investigational medicinal product (IMP) and which does not necessarily have a causal relationship with this treatment. TEAEs are defined as AEs with an onset date on or after the start of open-label treatment. Safety sample included all subjects who received at least 1 dose of IMP. The severity of AEs was graded on a 3-point scale: 1=Mild (Discomfort noticed, but no disruption to daily activity), 2=Moderate (Discomfort sufficient to reduce or affect normal daily activity), and 3=Severe (Inability to work or perform normal daily activity).

End point type	Primary

End point timeframe:

Signing of ICF up to 30 days post last dose of study drug (up to approximately 16 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: Only descriptive statistical analysis was planned to be reported for this endpoint.

End point values	Prior Brexpiprazole 2-3 Milligrams Per Day	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	111		
Units: subjects				
Subjects with TEAEs	30	56		
Subjects with Mild TEAEs	14	37		
Subjects with Moderate TEAEs	19	30		
Subjects with Severe TEAEs	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant

Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects With Potentially Clinically Significant Electrocardiogram (ECG) Abnormalities

End point description:

Potentially clinically significant ECG abnormalities included rate: Bradycardia (vent <=50 beats per minute [bpm] and decrease >=15 bpm); Rhythm: Sinus bradycardia (<=50 bpm and decrease >=15 bpm), absence during baseline and presence of ventricular premature beat post baseline; ST/T morphology: Absence at baseline and presence of symmetrical T-wave inversion post baseline. Safety sample included all subjects who received at least 1 dose of IMP. 'Number analysed (n)' signifies number of subjects with available data for the specified measurement.

End point type	Secondary

End point timeframe:

Screening up to Week 12

End point values	Prior Brexpiprazole 2-3 Milligrams Per Day	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	111		
Units: subjects				
Bradycardia (n=75, 98)	0	1		
Sinus Bradycardia (n=75, 98)	0	1		
Ventricular Premature Beat (n=75, 99)	0	1		
Symmetrical T-Wave Inversion (n=75, 99)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant Vital Sign Abnormalities

End point title	Number of Subjects With Potentially Clinically Significant Vital Sign Abnormalities

End point description:

Potentially clinically significant vital sign abnormalities included: Heart rate standing in bpm (<50 bpm and decrease >=15 bpm, >120 bpm and increase >=15 bpm); Weight in kilograms (kgs) (decrease >=7%, increase >=7%). Safety sample included all subjects who received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

Screening up to Week 12

End point values	Prior Brexpiprazole 2-3 Milligrams Per Day	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	111		
Units: subjects				
Heart Rate Standing	3	1		
Weight Decreased	7	4		
Weight Increased	9	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities

End point title	Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities

End point description:

Potentially clinically significant laboratory abnormalities included serum chemistry: Prolactin >upper limit of normal (ULN) (nanograms per millilitre [ng/ml] in males and females), fasting glucose ≥100 (milligrams per decilitre [mg/dl]), fasting high-density lipoprotein (HDL) cholesterol <40 (men)/ <50 (women) (mg/dl), fasting low-density lipoprotein (LDL) cholesterol ≥160 (mg/dl), fasting cholesterol ≥240 (mg/dl), fasting triglycerides ≥150 (mg/dl); Creatine phosphokinase (CPK)/renal: Creatine kinase >3xULN (units per litre [U/l]), creatinine ≥2.0 (mg/dl), urea nitrogen ≥30 (mg/dl). Safety sample included all subjects who received at least 1 dose of IMP. 'Number analysed (n)' signifies number of subjects with available data for the specified measurement.

End point type	Secondary

End point timeframe:

Screening up to Week 12

End point values	Prior Brexpiprazole 2-3 Milligrams Per Day	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	111		
Units: subjects				
Prolactin (ng/ml)-Males (n=17,17)	1	0		
Glucose, Fasting (mg/dL) (n=57, 72)	13	11		
HDL Cholesterol, Fasting (mg/dL) (n=54, 71)	22	19		
LDL Cholesterol, Fasting (mg/dL) (n=54, 71)	2	3		
Cholesterol, Fasting (mg/dL) (n=55, 72)	2	7		
Triglycerides, Fasting (mg/dL) (n=54, 71)	13	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Simpson-Angus Scale (SAS) Total Score

End point title	Change From Baseline in Simpson-Angus Scale (SAS) Total Score

End point description:

The SAS scale is used to evaluate extrapyramidal symptoms (EPS) and 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 is rated on a 5-point scale, with a score range of 0 (absence of symptoms) to 4 (severe condition). The SAS total score is the sum of the scores for all 10 items, possible total score is 0 to 40. Negative change from baseline indicates less symptoms. Safety sample included all subjects who received at least 1 dose of IMP. Number of subjects analysed is the number of subjects with data available for analyses. 'Number analysed (n)' signifies number of subjects with available data for this outcome measure at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Prior Brexpiprazole 2-3 Milligrams Per Day	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	111		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	0.2 (± 0.9)	0.1 (± 0.6)		
Change From Baseline at Week 12 (n=70, 82)	-0.1 (± 0.7)	0.0 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Abnormal Involuntary Movement Scale (AIMS) Total Score

End point title	Change From Baseline in Abnormal Involuntary Movement Scale (AIMS) Total Score

End point description:

The AIMS scale consists of 10 items describing symptoms of dyskinesia: Facial and oral movements (items 1-4), extremity movements (items 5 and 6), and trunk movements (item 7), dyskinesias (items 8-10). Each item is rated on a 5-point scale, with a score range of 0 (absence of symptoms) (for item 10, no awareness) to 4 (severe condition) (for item 10, awareness, severe distress). AIMS total score is the sum of the ratings for the first seven items with the possible total scores of 0 to 28. Negative change from baseline indicates less symptoms. Safety sample included all subjects who received at least 1 dose of IMP. Number of subjects analysed is the number of subjects with data available for analyses. 'Number analysed (n)' signifies number of subjects with available data for this outcome measure at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Prior Brexpiprazole 2-3 Milligrams Per Day	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	111		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	0.0 (± 0.1)	0.1 (± 0.8)		
Change From Baseline at Week 12 (n=70, 83)	0.0 (± 0.2)	-0.1 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Barnes Akathisia Rating Scale (BARS): Global Clinical Assessment of Akathisia Score

End point title	Change From Baseline in Barnes Akathisia Rating Scale (BARS): Global Clinical Assessment of Akathisia Score

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 fourth item, global clinical evaluation was rated on a 6-point scale, with a score range of 0 (absence of symptoms) to 5 (severe akathisia). Lower scores indicate less symptoms and negative change from baseline indicate less symptoms. Safety sample included all subjects who received at least 1 dose of IMP. Number of subjects analysed is the number of subjects with data available for analyses. 'Number analysed (n)' signifies number of subjects with available data for this outcome measure at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Prior Brexpiprazole 2-3 Milligrams Per Day	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	111		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	0.1 (± 0.3)	0.1 (± 0.3)		
Change From Baseline at Week 12 (n=70, 83)	-0.1 (± 0.3)	-0.0 (± 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Suicidal Ideation and Behavior as Assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Number of Subjects With Suicidal Ideation and Behavior as Assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)

End point description:

C-SSRS was used to assess the suicidality of subjects during the study. The assessment included "yes" or "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) and suicidal behavior (preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt, suicide). Numeric ratings were provided for suicidal ideation: Score range of 1 (wish to be dead) to 5 (active suicidal ideation with specific plan and intent), higher total scores indicate more suicidal ideation; Suicidal behavior: Score range of 0 (no suicidal behavior) to 4 (actual suicide attempt), higher total scores indicate more suicidal behavior. Safety sample included all subjects who received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

Baseline up to Week 12

End point values	Prior Brexpiprazole 2-3 Milligrams Per Day	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	111		
Units: subjects				
Suicidal Ideation	28	28		
Suicidal Behavior	0	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Signing of ICF up to 30 days post last dose of study drug (up to approximately 16 weeks)

Adverse event reporting additional description:

All-cause mortality: Enrolled sample included all subjects who signed an ICF and were enrolled into the trial (N=90, 111);
Adverse events: Safety sample included all subjects who received at least 1 dose of IMP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Prior Brexpiprazole 2-3 Milligrams Per Day

Reporting group description:

Subjects who received blinded brexpiprazole 2 to 3 mg/day in the previous double-blind trial (2019-002813-20), received open-label brexpiprazole 2 to 3 mg/day tablets, orally for up to 12 weeks.

Reporting group title	Prior Placebo

Reporting group description:

Subjects who received blinded brexpiprazole matching placebo in the previous double-blind trial (2019-002813-20), received open-label brexpiprazole 2 to 3 mg/day tablets, orally for up to 12 weeks.

Serious adverse events	Prior Brexpiprazole 2-3 Milligrams Per Day	Prior Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 88 (1.14%)	2 / 111 (1.80%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 88 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal Ideation			
subjects affected / exposed	1 / 88 (1.14%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
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 2-3 Milligrams Per Day	Prior Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 88 (9.09%)	31 / 111 (27.93%)	
Investigations			
Weight increased			
subjects affected / exposed	0 / 88 (0.00%)	6 / 111 (5.41%)	
occurrences (all)	0	6	
Nervous system disorders			
Akathisia			
subjects affected / exposed	1 / 88 (1.14%)	9 / 111 (8.11%)	
occurrences (all)	1	9	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 88 (1.14%)	7 / 111 (6.31%)	
occurrences (all)	1	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 88 (5.68%)	6 / 111 (5.41%)	
occurrences (all)	5	7	
Restlessness			
subjects affected / exposed	1 / 88 (1.14%)	7 / 111 (6.31%)	
occurrences (all)	1	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2020	The purpose of this protocol amendment was to introduce a COVID-19 Addendum for any protocol-specified activities that were not able to be performed per protocol or could not be performed due to COVID-19 considerations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported