Clinical trial results:
A Multicenter, Randomized, Flexible-dose, Double-blind Trial of Brexpiprazole Versus Placebo for the Treatment of Adults With Borderline Personality Disorder

Summary

EudraCT number	2019-002813-20
Trial protocol	DE ES
Global end of trial date	27 June 2021

Results information

Result version number	v1 (current)
This version publication date	13 July 2022
First version publication date	13 July 2022

Trial information

Trial identification

Sponsor protocol code	331-201-00242

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04100096
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	27 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of brexpiprazole versus placebo for 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 2019
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	Ukraine: 15
Country: Number of subjects enrolled	United States: 308
Country: Number of subjects enrolled	Spain: 9
Worldwide total number of subjects	332
EEA total number of subjects	9

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)	332
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled in the study at 62 study centres in the United States, Spain, and Ukraine from 17 October 2019 to 27 June 2021.

Pre-assignment

Screening details:

332 subjects were enrolled out of which 324 subjects were randomised to receive brexpiprazole or matching placebo in the treatment phase.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Brexpiprazole 2-3 Milligrams Per Day

Arm description:

Subjects received brexpiprazole, 2-3 milligrams per day (mg/day) tablets, orally, up to Week 12 during the treatment phase.

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, administered orally, 2-3 mg/day up to Week 12 during the treatment phase.

Arm title	Placebo

Arm description:

Subjects received brexpiprazole-matching placebo tablets, orally, up to Week 12 during the treatment phase.

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, administered orally, up to Week 12 during the treatment phase.

Number of subjects in period 1[1]	Brexpiprazole 2-3 Milligrams Per Day	Placebo
Started	159	165
Safety Population	157	165
Full Analysis Set for Enriched Subjects	110 [2]	110 [3]
Completed	112	127
Not completed	47	38
Non-Compliance With Study Drug	1	3
Adverse event	19	7
Lost to follow-up	13	11
Protocol deviation	1	1
Withdrawal by subject	13	15
Lack of efficacy	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline data is reported for the randomised population which include all subjects who were randomised to receive brexpiprazole or matching placebo in the treatment phase.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Safety population include subjects who received at least 1 dose of study drug (brexpiprazole or placebo). Full analysis set for enriched subjects is a subset of randomised population who met pre-defined criteria and who received at least 1 dose of double-blind investigational medicinal product (IMP) and had baseline value and at least 1 valid post-randomisation efficacy evaluation for ZAN-BPD total score.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Safety population include subjects who received at least 1 dose of study drug (brexpiprazole or placebo). Full analysis set for enriched subjects is a subset of randomised population who met pre-defined criteria and who received at least 1 dose of double-blind investigational medicinal product (IMP) and had baseline value and at least 1 valid post-randomisation efficacy evaluation for ZAN-BPD total score.

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole 2-3 Milligrams Per Day
Reporting group description:	
Subjects received brexpiprazole, 2-3 milligrams per day (mg/day) tablets, orally, up to Week 12 during the treatment phase.	
Reporting group title	Placebo
Reporting group description:	
Subjects received brexpiprazole-matching placebo tablets, orally, up to Week 12 during the treatment phase.	

Reporting group values	Brexpiprazole 2-3 Milligrams Per Day	Placebo	Total
Number of subjects	159	165	324
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	32.0	31.0	
standard deviation	± 10.6	± 10.9	-
Gender categorical Units: Subjects			
Female	129	137	266
Male	30	28	58
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	3	0	3
Asian	7	2	9
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	19	22	41
White	123	131	254
More than one race	0	0	0
Unknown or Not Reported	6	9	15
Ethnicity Units: Subjects			
Hispanic or Latino	31	33	64
Not Hispanic or Latino	127	131	258
Unknown	1	0	1
Other	0	1	1

End points

End points reporting groups

Reporting group title	Brexpiprazole 2-3 Milligrams Per Day
Reporting group description:	
Subjects received brexpiprazole, 2-3 milligrams per day (mg/day) tablets, orally, up to Week 12 during the treatment phase.	
Reporting group title	Placebo
Reporting group description:	
Subjects received brexpiprazole-matching placebo tablets, orally, up to Week 12 during the treatment phase.	

Primary: Change From Baseline in the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) Total Score

End point title	Change From Baseline in the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) Total Score
End point description:	
A clinician-administered scale with a total score range of 0 to 36. A higher score represents a higher severity of disease symptoms. Mixed model repeated measures=MMRM, antidepressant therapy=ADT. Full analysis set (FAS) for enriched subjects= subset of randomised population who met pre-defined criteria and who received at least 1 dose of double-blind investigational medicinal product (IMP) and had baseline value and at least 1 valid post-randomisation efficacy evaluation for ZAN-BPD total score.	
End point type	Primary
End point timeframe:	
Change from Baseline	

End point values	Brexpiprazole 2-3 Milligrams Per Day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: score on a scale				
least squares mean (standard error)	-7.27 (± 0.80)	-6.25 (± 0.76)		

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole 2-3 Milligrams Per Day v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.243 [1]
Method	MMRM
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-1.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	0.7

Notes:

[1] - Comparison was carried out using MMRM, with study centre (pooled), treatment group (TG), visit, ADT status, and TG by visit interaction (BVI), gender BVI, age BVI as factors and baseline BVI as covariate. An unstructured covariance was used.

Secondary: Change From Baseline in the Clinical Global Impression - Severity of Illness (CGI-S) Score

End point title	Change From Baseline in the Clinical Global Impression - Severity of Illness (CGI-S) Score

End point description:

The severity of illness for each subject was rated using the CGI-S. CGI-S is an observer-rated scale with a total score range of 0 to 7 where a higher score represented a worse outcome. The 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 subjects. FAS for enriched subjects is a subset of randomised population who met pre-defined criteria and who received at least 1 dose of double-blind IMP and had a baseline value and at least 1 valid post-randomisation efficacy evaluation for ZAN-BPD total score.

End point type	Secondary

End point timeframe:

Change from Baseline

End point values	Brexpiprazole 2-3 Milligrams Per Day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: score on a scale				
least squares mean (standard error)	-1.13 (± 0.14)	-1.09 (± 0.14)		

Statistical analyses

Statistical analysis title	Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole 2-3 Milligrams Per Day v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7759 [2]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.27

Notes:

[2] - Comparison was carried out using MMRM, with study centre (pooled), TG, visit, ADT status, and TG BVI, gender BVI, age BVI as factors and baseline BVI as covariate. An unstructured covariance was used.

Secondary: Clinical Global Impression - Improvement (CGI-I) Scale Score

End point title	Clinical Global Impression - Improvement (CGI-I) Scale Score

End point description:

Subject's condition was assessed using CGI-I scale. CGI-I is an observer-rated scale with a total score of 0 to 7 and a higher score represents a worse outcome. The score included the following response choices: 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 subjects. FAS for enriched subjects is a subset of randomised population who met pre-defined criteria and who received at least 1 dose of double-blind IMP and had a baseline value and at least 1 valid post-randomisation efficacy evaluation for ZAN-BPD total score. n = number of subjects with data available for analyses at the specified time point.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 6, 8, 10 and 12

End point values	Brexpiprazole 2-3 Milligrams Per Day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 2 (n=110, 109)	2.99 (± 0.96)	2.99 (± 0.97)		
Week 4 (n=110, 110)	2.89 (± 1.04)	3.00 (± 1.20)		
Week 6 (n=110, 110)	2.62 (± 1.05)	2.77 (± 1.21)		
Week 8 (n=110, 110)	2.39 (± 1.06)	2.79 (± 1.26)		
Week 10 (n=110, 110)	2.45 (± 1.18)	2.61 (± 1.20)		
Week 12 (n=110, 110)	2.37 (± 1.19)	2.65 (± 1.17)		

Statistical analyses

Statistical analysis title	Week 2: Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole 2-3 Milligrams Per Day v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6579 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.19

Notes:

[3] - Comparison between TGs was carried out using the Cochran-Mantel-Haenszel (CMH) Row Mean Score Differ Test controlling for trial site.

Statistical analysis title	Week 4: Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole 2-3 Milligrams Per Day v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3728 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.16

Notes:

[4] - Comparison between TGs was carried out using the CMH Row Mean Score Differ Test controlling for trial site.

Statistical analysis title	Week 6: Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole 2-3 Milligrams Per Day v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1684 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.09

Notes:

[5] - Comparison between TGs was carried out using the CMH Row Mean Score Differ Test controlling for trial site.

Statistical analysis title	Week 8: Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole 2-3 Milligrams Per Day v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0046 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	-0.13

Notes:

[6] - Comparison between TGs was carried out using the CMH Row Mean Score Differ Test controlling for trial site.

Statistical analysis title	Week 10: Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole 2-3 Milligrams Per Day v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2087 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.11

Notes:

[7] - Comparison between TGs was carried out using the CMH Row Mean Score Differ Test controlling for trial site.

Statistical analysis title	Week 12: Brexpiprazole vs Placebo
Comparison groups	Brexpiprazole 2-3 Milligrams Per Day v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0389 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	-0.02

Notes:

[8] - Comparison between TGs was carried out using the CMH Row Mean Score Differ Test controlling for trial site.

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. A TEAE is defined as an AE that started after start of study

treatment. Safety population (SP): Subjects who received at least 1 dose of study drug (brexpiprazole or placebo).

End point type	Secondary

End point timeframe:

From Baseline to 21 days after last dose (up to Week 15)

End point values	Brexpiprazole 2-3 Milligrams Per Day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	165		
Units: subjects with TEAEs	95	79		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline to 21 days after last dose (up to Week 15)

Adverse event reporting additional description:

Safety population included randomised subjects who received at least 1 dose of study drug (brexpiprazole or placebo).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Brexpiprazole 2-3 Milligrams Per Day

Reporting group description:

Subjects received brexpiprazole, 2-3 mg/day tablets, orally, up to Week 12 during the treatment phase.

Reporting group title	Placebo

Reporting group description:

Subjects received brexpiprazole-matching placebo tablets, orally, up to Week 12 during the treatment phase.

Serious adverse events	Brexpiprazole 2-3 Milligrams Per Day	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 157 (3.18%)	2 / 165 (1.21%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	1 / 157 (0.64%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Dissociation			

subjects affected / exposed	0 / 157 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major Depression			
subjects affected / exposed	1 / 157 (0.64%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic Attack			
subjects affected / exposed	1 / 157 (0.64%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	2 / 157 (1.27%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	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	Brexpiprazole 2-3 Milligrams Per Day	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 157 (43.95%)	45 / 165 (27.27%)	
Investigations			
Weight Increased			
subjects affected / exposed	10 / 157 (6.37%)	4 / 165 (2.42%)	
occurrences (all)	10	4	
Nervous system disorders			
Akathisia			
subjects affected / exposed	22 / 157 (14.01%)	2 / 165 (1.21%)	
occurrences (all)	27	3	
Headache			

subjects affected / exposed	8 / 157 (5.10%)	12 / 165 (7.27%)	
occurrences (all)	8	13	
Somnolence			
subjects affected / exposed	8 / 157 (5.10%)	5 / 165 (3.03%)	
occurrences (all)	9	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 157 (7.64%)	6 / 165 (3.64%)	
occurrences (all)	13	6	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	13 / 157 (8.28%)	9 / 165 (5.45%)	
occurrences (all)	16	9	
Insomnia			
subjects affected / exposed	15 / 157 (9.55%)	10 / 165 (6.06%)	
occurrences (all)	15	11	
Restlessness			
subjects affected / exposed	10 / 157 (6.37%)	2 / 165 (1.21%)	
occurrences (all)	10	2	
Metabolism and nutrition disorders			
Increased Appetite			
subjects affected / exposed	8 / 157 (5.10%)	4 / 165 (2.42%)	
occurrences (all)	8	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 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