Clinical trial results:
A Multicenter, Randomized, Double-blind Trial of Brexpiprazole versus Placebo for the Acute Treatment of Manic Episodes, With or Without Mixed Features, Associated With Bipolar I Disorder

Summary

EudraCT number	2017-002222-20
Trial protocol	BG PL
Global end of trial date	02 January 2019

Results information

Result version number	v1
This version publication date	29 December 2019
First version publication date	29 December 2019

Trial information

Trial identification

Sponsor protocol code	331-201-00080

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03259555
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, Maryland, United States, 20850
Public contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., 609 524-6788, clinicaltransparency@otsuka-us.com
Scientific contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., 609 524-6788, 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	10 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 January 2019
Global end of trial reached?	Yes
Global end of trial date	02 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of brexpiprazole for the acute treatment of manic episodes, with or without mixed features, in participants with a diagnosis of bipolar I disorder.

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 2017
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	Bulgaria: 54
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Serbia: 32
Country: Number of subjects enrolled	United States: 212
Worldwide total number of subjects	322
EEA total number of subjects	78

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)	321
From 65 to 84 years	1

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The trial population consisted of adult participants (18 to 65 years) diagnosed with bipolar I disorder displaying an acute manic episode with or without mixed features requiring hospitalization.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Brexpiprazole

Arm description:

Brexpiprazole was administered orally with flexible dosing from 2 to 4 milligrams (mg)/day; titrated to a maximum of 4 mg/day.

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

Dosage and administration details:

Starting dose of 2 mg/day; titrated to a maximum of 4 mg/day. Adjustments could be made to dosing. Treatment duration was 3 weeks.

Arm title	Placebo

Arm description:

Matching placebo was administered orally in the same way as brexpiprazole to maintain the blind.

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:

Tablet taken daily for 3 weeks.

Number of subjects in period 1	Brexpiprazole	Placebo
Started	158	164
Received At Least 1 Dose of Study Drug	158	163
Completed	124	134
Not completed	34	30
Consent withdrawn by subject	19	16
Physician decision	1	2
Adverse event, non-fatal	6	4
Other	1	-
Progressive Disease	-	2
Non-Compliance With Study Drug	1	-
Lost to follow-up	-	2
Lack of efficacy	6	4

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole
Reporting group description:	
Brexpiprazole was administered orally with flexible dosing from 2 to 4 milligrams (mg)/day; titrated to a maximum of 4 mg/day.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered orally in the same way as brexpiprazole to maintain the blind.	

Reporting group values	Brexpiprazole	Placebo	Total
Number of subjects	158	164	322
Age categorical			
Units:			
Age continuous			
Units: Years			
arithmetic mean	43.4	44.5	
standard deviation	± 11.7	± 11.2	-
Gender categorical			
Units: Subjects			
Female	80	83	163
Male	78	81	159
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	16	22	38
Not Hispanic or Latino	141	141	282
Unknown	0	1	1
Ethnicity - Other	1	0	1
Race/Ethnicity, Customized			
Units: Subjects			
White	95	113	208
Black or African American	54	51	105
American Indian or Alaska Native	2	0	2
Asian	3	0	3
Native Hawaiian or Other Pacific Islander	2	0	2
Race - Other	2	0	2

End points

End points reporting groups

Reporting group title	Brexpiprazole
Reporting group description:	
Brexpiprazole was administered orally with flexible dosing from 2 to 4 milligrams (mg)/day; titrated to a maximum of 4 mg/day.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered orally in the same way as brexpiprazole to maintain the blind.	

Primary: Change From Baseline In Young-Mania Rating Scale (YMRS) Score At Week 3

End point title	Change From Baseline In Young-Mania Rating Scale (YMRS) Score At Week 3
End point description:	
The YMRS was utilized to assess a participant's level of manic symptoms. It consists of 11 items: 1) elevated mood, 2) increased motor activity-energy, 3) sexual interest, 4) sleep, 5) irritability, 6) speech (rate and amount), 7) language-thought disorder, 8) content, 9) disruptive-aggressive behavior, 10) appearance, and 11) insight. Seven items are rated on a 0- to 4-scale, while four items (Items 5, 6, 8, and 9) are rated on a 0- to 8-scale with 0, 2, 4, 6, and 8 being the possible scores (twice the weight of the other items). For all items, 0 is the "best" rating and the highest score (4 or 8) is the 'worst' rating. The YMRS total score is the sum of ratings for all 11 items; therefore, possible total scores range from 0 to 60. Comparison between treatment groups was carried out using mixed-effect model repeated measure, with study center, treatment group, visit, and treatment group-by-visit interaction as factors and baseline-by-visit interaction as a covariate.	
End point type	Primary
End point timeframe:	
Baseline, Week 3	

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	161		
Units: units on a scale				
least squares mean (standard error)	-10.6 (± 0.72)	-10.8 (± 0.70)		

Statistical analyses

Statistical analysis title	Treatment Difference in YMRS
Comparison groups	Brexpiprazole v Placebo

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8797
Method	Mixed-effect Model Repeated Measure
Parameter estimate	Treatment difference
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.74
upper limit	2.03

Secondary: Change From Baseline In Clinical Global Impression-Bipolar (CGI-BP) Severity Of Illness Score In Mania At Week 3

End point title	Change From Baseline In Clinical Global Impression-Bipolar (CGI-BP) Severity Of Illness Score In Mania At Week 3

End point description:

The CGI-BP scale refers to the global impression of the participant with respect to bipolar disorder. The scale rates the participant's severity of illness (CGI-BP severity of illness: mania, depression, and overall bipolar illness) based on a 7-point scale and rates the participant's change from baseline (CGI-BP change from baseline: mania, depression, and overall bipolar illness) based on a 7-point scale. CGI-BP severity of illness items are: 1 = normal, not at all ill, 2 = minimally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = very severely ill. CGI-BP change from baseline items are: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

End point type	Secondary

End point timeframe:

Baseline, Week 3

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	161		
Units: units on a scale				
arithmetic mean (standard deviation)	4.56 (± 0.64)	4.60 (± 0.58)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Day 1 (after dosing) through 6 weeks (3 weeks treatment, 3 weeks safety follow-up).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered orally in the same way as brexpiprazole to maintain the blind.	
Reporting group title	Brexpiprazole
Reporting group description:	
Brexpiprazole was administered orally with flexible dosing from 2 to 4 milligrams (mg)/day; titrated to a maximum of 4 mg/day.	

Serious adverse events	Placebo	Brexpiprazole	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 163 (0.61%)	4 / 158 (2.53%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dystonia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mania			

subjects affected / exposed	1 / 163 (0.61%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Varicella			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	
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: 3 %

Non-serious adverse events	Placebo	Brexpiprazole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 163 (14.72%)	20 / 158 (12.66%)	
Nervous system disorders			
Akathisia			
subjects affected / exposed	2 / 163 (1.23%)	8 / 158 (5.06%)	
occurrences (all)	2	8	
Headache			
subjects affected / exposed	11 / 163 (6.75%)	6 / 158 (3.80%)	
occurrences (all)	11	8	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 163 (3.68%)	2 / 158 (1.27%)	
occurrences (all)	6	2	
Nausea			
subjects affected / exposed	5 / 163 (3.07%)	4 / 158 (2.53%)	
occurrences (all)	6	4	
Psychiatric disorders			
Agitation			
subjects affected / exposed	5 / 163 (3.07%)	1 / 158 (0.63%)	
occurrences (all)	5	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2017	• Removed an incorrect exclusion criteria of ≥ 30% decrease in YMRS between screening and baseline. • Added clarifying details on administration of the Clinical Global Impressions – Bipolar Scale assessment. • Added information on retesting participants with elevated lithium, valproate, or carbamazepine at screening. • Added information on use of anticholinergics. • Updated the efficacy scales in the appendices to match the licensed versions currently available.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: