Clinical trial results:
A Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Subjects with Bipolar I Disorder

Summary

EudraCT number	2017-002225-38
Trial protocol	BG PL HR
Global end of trial date	31 July 2019

Results information

Result version number	v1 (current)
This version publication date	14 August 2020
First version publication date	14 August 2020

Trial information

Trial identification

Sponsor protocol code	331-201-00083

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03287869
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., +1 609 524-6788, clinicaltransparency@otsuka-us.com
Scientific contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 609 524-6788, 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	31 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the safety and tolerability of brexpiprazole in the treatment of participants with bipolar I disorder.

Protection of trial subjects:

This trial 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	24 October 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	Poland: 21
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Bulgaria: 47
Country: Number of subjects enrolled	Serbia: 28
Country: Number of subjects enrolled	Ukraine: 82
Country: Number of subjects enrolled	United States: 202
Worldwide total number of subjects	381
EEA total number of subjects	69

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)	379
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included participants who completed 3-week double-blind treatment in studies 331-201-00080 (NCT03259555)/331-201-00081 (NCT03257865) and, who in the investigator's judgment, could potentially benefit to receive brexpiprazole in this study. Data were summarized per treatment received in prior studies.

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:

Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received brexpiprazole in the double-blind treatment period in previous studies were included in this group.

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

Dosage and administration details:

Brexpiprazole 2 mg/day from Days 1 to 3, followed by titration to 3 mg/day on Day 4, dose was titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4.

Arm title	Prior Placebo

Arm description:

Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received placebo in the double-blind treatment period in previous studies were included in this group.

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

Dosage and administration details:

Brexpiprazole 2 mg/day from Days 1 to 3, followed by titration to 3 mg/day on Day 4, dose was titrated

(or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4.

Number of subjects in period 1	Prior Brexpiprazole	Prior Placebo
Started	188	193
Analyzed For Safety	184	184
Completed	105	100
Not completed	83	93
Consent withdrawn by subject	36	43
Physician decision	5	5
Reason no Specified	6	-
Adverse event, non-fatal	14	12
Progressive Disease	1	-
Non-Compliance With Study Drug	5	9
Lost to follow-up	13	19
Early Closure of the Site	-	1
Reason not Specified	-	3
Lack of efficacy	1	-
Protocol deviation	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study (overall period)

Reporting group description: -

Reporting group values	Overall Study (overall period)	Total	
Number of subjects	381	381	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	379	379	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	45.8		
standard deviation	± 11.2	-	
Gender categorical Units: Subjects			
Female	189	189	
Male	192	192	
Race Units: Subjects			
White	275	275	
Black or African American	99	99	
American Indian or Alaska Native	3	3	
Asian	2	2	
Native Hawaiian or Other Pacific Islander	0	0	
Other	2	2	
Ethnicity Units: Subjects			
Hispanic or Latino	45	45	
Not Hispanic or Latino	334	334	
Other	2	2	

End points

End points reporting groups

Reporting group title	Prior Brexpiprazole

Reporting group description:

Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received brexpiprazole in the double-blind treatment period in previous studies were included in this group.

Reporting group title	Prior Placebo

Reporting group description:

Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received placebo in the double-blind treatment period in previous studies were included in this group.

Primary: Number of Participants With at Least one Treatment Emergent Adverse Event (TEAE) by Severity

End point title	Number of Participants With at Least one Treatment Emergent Adverse Event (TEAE) by Severity[1]

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. AEs severity were graded on a 3-point scale as: 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. Safety Sample included all participants who received at least 1 dose of IMP (brexpiprazole).

End point type	Primary

End point timeframe:

From Day 1 (after dosing) through 29 weeks (26 weeks treatment, 3 weeks safety follow-up)

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: Inferential statistical analysis was not performed for the safety endpoint. Descriptive statistics are included (number of participants).

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	184		
Units: participants				
TEAE, Any grade	79	86		
TEAE, Mild	60	68		
TEAE, Moderate	31	29		
TEAE, Severe	8	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 26 plus 3 weeks (21 days) follow-up period (Up to 29 weeks)

Adverse event reporting additional description:

Safety Sample included all participants who received at least 1 dose of Investigational medicinal product (IMP-brexpiprazole).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Prior Brexpiprazole

Reporting group description:

Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received brexpiprazole in the double-blind treatment period in previous studies were included in this group.

Reporting group title	Prior Placebo

Reporting group description:

Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received placebo in the double-blind treatment period in previous studies were included in this group.

Serious adverse events	Prior Brexpiprazole	Prior Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 184 (5.98%)	8 / 184 (4.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 184 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			

subjects affected / exposed	0 / 184 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 184 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	0 / 184 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 184 (0.54%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar Disorder			
subjects affected / exposed	0 / 184 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	3 / 184 (1.63%)	2 / 184 (1.09%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	5 / 184 (2.72%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Behaviour			

subjects affected / exposed	1 / 184 (0.54%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	0 / 184 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 184 (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	13 / 184 (7.07%)	26 / 184 (14.13%)	
Nervous system disorders			
Akathisia			
subjects affected / exposed	8 / 184 (4.35%)	17 / 184 (9.24%)	
occurrences (all)	9	17	
Headache			
subjects affected / exposed	5 / 184 (2.72%)	10 / 184 (5.43%)	
occurrences (all)	5	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2017	The following updates were made as per Amendment 1 - •Added information on self-reported participants daily sleep diary. •Removed language indicating a confirmation of data download from the wearable device was performed. •Removed laboratory tests for adrenocorticotropic hormone and cortisol. •Allowed anticholinergics and propranolol with daily limits. •Updated the way pregnancy was reported in Section 5 "Reporting of Adverse Events". •Updated the Young-Mania Rating Scale (YMRS) version cited in the protocol. •Updated the version of the Clinical Global Impressions – Bipolar Scale in the appendix to alternate version and added clarifying details on administration of this assessment. •Updated the Simpson-Angus Scale (SAS)/ Abnormal Involuntary Movement Scale (AIMS)/ Barnes Akathisia Rating Scale (BARS) scales in the appendix to match the licensed versions.

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.

As predefined in the protocol, there were no primary or secondary efficacy endpoints in this trial.

Notes: