Clinical trial results:
A Phase 3, 12-week, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of 2 Fixed Doses of Brexpiprazole (OPC-34712) in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type

Summary

EudraCT number	2013-000504-41
Trial protocol	DE ES HR
Global end of trial date	15 March 2017

Results information

Result version number	v2 (current)
This version publication date	24 December 2020
First version publication date	14 June 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	331-12-283

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01862640
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	15 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2017
Global end of trial reached?	Yes
Global end of trial date	15 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of 2 fixed doses (1 mg/day and 2 mg/day) of brexpiprazole with placebo in participants with agitation associated with Alzheimer's dementia, as assessed by the Cohen-Mansfield Agitation Inventory (CMAI) after 12 weeks of treatment.

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 country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 July 2013
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	Croatia: 37
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Russian Federation: 126
Country: Number of subjects enrolled	Serbia: 53
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Ukraine: 64
Country: Number of subjects enrolled	United States: 121
Worldwide total number of subjects	433
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)	72
From 65 to 84 years	321
85 years and over	40

Subject disposition

Recruitment

Recruitment details:

Participants who met all the inclusion and none of the exclusion criteria were enrolled in this study. The study was conducted in 433 participants at 81 sites in 7 countries: Croatia, Germany, Serbia, Spain, Russia, Ukraine, and the United States.

Pre-assignment

Screening details:

Participants attended a screening period ranging from 2 to 42 days. The purpose of the screening period was to determine the participant's eligibility and to washout prohibited concomitant pharmacotherapy prior to randomization.

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 0.5 mg/day

Arm description:

All randomized participants received orally brexpiprazole 0.25 milligrams (mg)/day as a starting dose, which was up titrated to 0.5 mg/day. The investigational medicinal product (IMP) was administered once daily in the form of a tablet.

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:

All randomized participants received orally a brexpiprazole 0.5 mg/day tablet.

Arm title	Brexpiprazole 1 mg/day

Arm description:

All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 1 mg/day. The IMP was administered once daily in the form of a tablet.

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:

All randomized participants received orally a brexpiprazole 1.0 mg/day tablet.

Arm title	Brexpiprazole 2 mg/day

Arm description:

All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 2 mg/day. The IMP was administered once daily in the form of a tablet.

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:

All randomized participants received orally a brexpiprazole 2.0 mg/day tablet.

Arm title	Placebo

Arm description:

All randomized participants received orally brexpiprazole-matching Placebo. The Placebo was administered once daily in the form of a tablet.

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:

All randomized participants received orally a brexpiprazole-matching placebo tablet.

Number of subjects in period 1	Brexpiprazole 0.5 mg/day	Brexpiprazole 1 mg/day	Brexpiprazole 2 mg/day
Started	20	137	140
Completed	13	121	122
Not completed	7	16	18
Consent withdrawn by subject	2	4	8
Participant Withdrawn By Investigator	-	1	1
Adverse event, non-fatal	4	10	6
Protocol Deviation	-	-	1
Participant Met Withdrawal Criteria	1	1	2

Number of subjects in period 1	Placebo
Started	136
Completed	121
Not completed	15
Consent withdrawn by subject	5
Participant Withdrawn By Investigator	1
Adverse event, non-fatal	8
Protocol Deviation	-
Participant Met Withdrawal Criteria	1

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole 0.5 mg/day
Reporting group description:	
All randomized participants received orally brexpiprazole 0.25 milligrams (mg)/day as a starting dose, which was up titrated to 0.5 mg/day. The investigational medicinal product (IMP) was administered once daily in the form of a tablet.	
Reporting group title	Brexpiprazole 1 mg/day
Reporting group description:	
All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 1 mg/day. The IMP was administered once daily in the form of a tablet.	
Reporting group title	Brexpiprazole 2 mg/day
Reporting group description:	
All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 2 mg/day. The IMP was administered once daily in the form of a tablet.	
Reporting group title	Placebo
Reporting group description:	
All randomized participants received orally brexpiprazole-matching Placebo. The Placebo was administered once daily in the form of a tablet.	

Reporting group values	Brexpiprazole 0.5 mg/day	Brexpiprazole 1 mg/day	Brexpiprazole 2 mg/day
Number of subjects	20	137	140
Age categorical			
Units:			
Age continuous			
Units: years			
arithmetic mean	73.9	73.8	73.7
standard deviation	± 9.1	± 8.8	± 8.1
Gender categorical			
Units: Subjects			
Female	12	78	79
Male	8	59	61
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	5
White	20	134	133
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Placebo	Total	
Number of subjects	136	433	
Age categorical			
Units:			

Age continuous Units: years			
arithmetic mean	74.1		
standard deviation	± 8.0	-	
Gender categorical Units: Subjects			
Female	70	239	
Male	66	194	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	4	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	5	12	
White	130	417	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Brexpiprazole 0.5 mg/day

Reporting group description:

All randomized participants received orally brexpiprazole 0.25 milligrams (mg)/day as a starting dose, which was up titrated to 0.5 mg/day. The investigational medicinal product (IMP) was administered once daily in the form of a tablet.

Reporting group title	Brexpiprazole 1 mg/day

Reporting group description:

All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 1 mg/day. The IMP was administered once daily in the form of a tablet.

Reporting group title	Brexpiprazole 2 mg/day

Reporting group description:

All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 2 mg/day. The IMP was administered once daily in the form of a tablet.

Reporting group title	Placebo

Reporting group description:

All randomized participants received orally brexpiprazole-matching Placebo. The Placebo was administered once daily in the form of a tablet.

Primary: Change From Baseline In The Cohen-Mansfield Agitation Inventory (CMAI) Total Score After 12 Weeks Of Brexpiprazole Treatment

End point title	Change From Baseline In The Cohen-Mansfield Agitation Inventory (CMAI) Total Score After 12 Weeks Of Brexpiprazole Treatment[1]

End point description:

To compare the efficacy of 2 fixed doses (1 mg/day and 2 mg/day) of brexpiprazole with placebo in participants with agitation associated with dementia of the Alzheimer's type, by the assessment of CMAI after 12 weeks of treatment. The CMAI assesses the frequency of agitated behaviors in elderly persons, such as hitting, cursing, and restlessness. It consists of 29 items all rated on a 1 to 7 scale with 1 being the "best" rating and 7 being the "worst" rating. The minimum possible CMAI total score is 29, and the maximum possible CMAI total score is 203. A decrease in score indicates improvement in symptoms. To control the overall type I error at 0.05 level when making 2 comparisons of brexpiprazole doses versus placebo, statistical testing was carried out using a hierarchical testing procedure in the order of: 1) comparison of 2 mg/day brexpiprazole versus placebo, and 2) comparison of 1 mg/day brexpiprazole versus placebo.

End point type	Primary

End point timeframe:

Baseline, Week 12/Early Termination (ET)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Quantitative statistical analysis (for example, a p-value) was performed only for the Brexpiprazole 2 mg/Day, Brexpiprazole 1 mg/Day, and Placebo reporting groups.

End point values	Brexpiprazole 1 mg/day	Brexpiprazole 2 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	138	131	
Units: units on a scale				
least squares mean (standard error)	-17.6 (± 1.33)	-21.6 (± 1.32)	-17.8 (± 1.34)	

Statistical analyses

Statistical analysis title	Brexpiprazole 2 mg/Day versus Placebo
Statistical analysis description:	
Change from baseline in the CMAI Total Score after 12 weeks of brexpiprazole treatment (2 mg/day) compared to 12 weeks of placebo.	
Comparison groups	Brexpiprazole 2 mg/day v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0404
Method	Mixed-effect model repeated measure
Parameter estimate	Least square (LS) mean difference
Point estimate	-3.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.38
upper limit	-0.17

Statistical analysis title	Brexpiprazole 1 mg/Day versus Placebo
Statistical analysis description:	
Change from baseline in the CMAI Total Score after 12 weeks of brexpiprazole treatment (1 mg/day) compared to 12 weeks of placebo.	
Comparison groups	Brexpiprazole 1 mg/day v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9015
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	3.86

Secondary: Change From Baseline In The Clinical Global Impression-Severity Of Illness (CGI-S) Score, As Related To Symptoms Of Agitation After 12 Weeks Of Brexpiprazole Treatment

End point title	Change From Baseline In The Clinical Global Impression-Severity Of Illness (CGI-S) Score, As Related To Symptoms Of Agitation After 12 Weeks Of Brexpiprazole Treatment[2]

End point description:

To compare the efficacy of 2 fixed doses (1 mg/day and 2 mg/day) of brexpiprazole with placebo in participants with agitation associated with Alzheimer's dementia, by the assessment of CGI-S score after 12 weeks of treatment. The CGI-S was used to rate the severity of agitation. Scores were: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants. A decrease in score indicates improvement in symptoms.

End point type	Secondary

End point timeframe:

Baseline, Week 12/ET

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Quantitative statistical analysis (for example, a p-value) was performed only for the Brexpiprazole 2 mg/Day, Brexpiprazole 1 mg/Day, and Placebo reporting groups.

End point values	Brexpiprazole 1 mg/day	Brexpiprazole 2 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	138	131	
Units: units on a scale				
arithmetic mean (standard deviation)	-1.04 (± 1.12)	-1.29 (± 1.05)	-1.08 (± 0.89)	

Statistical analyses

Statistical analysis title	Brexpiprazole 2 mg/Day versus Placebo

Statistical analysis description:

Change from baseline in the CGI-S Score after 12 weeks of brexpiprazole treatment (2 mg/day) compared to 12 weeks of placebo.

Comparison groups	Brexpiprazole 2 mg/day v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1566
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.06

Statistical analysis title	Brexpiprazole 1 mg/Day versus Placebo

Statistical analysis description:

Change from baseline in the CGI-S Score after 12 weeks of brexpiprazole treatment (1 mg/day) compared to 12 weeks of placebo.

Comparison groups	Brexpiprazole 1 mg/day v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.444
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.32

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events (AEs) were collected throughout the study (Baseline to Week 12/ET).	
Adverse event reporting additional description:	
Only participants who received at least 1 dose of study drug were analyzed for safety (Placebo N=135).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Brexpiprazole 0.5 mg/day
Reporting group description:	
All randomized participants received orally brexpiprazole 0.25 milligrams (mg)/day as a starting dose, which was up titrated to 0.5 mg/day. The investigational medicinal product (IMP) was administered once daily in the form of a tablet.	
Reporting group title	Brexpiprazole 1 mg/day
Reporting group description:	
All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 1 mg/day. The IMP was administered once daily in the form of a tablet.	
Reporting group title	Brexpiprazole 2 mg/day
Reporting group description:	
All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 2 mg/day. The IMP was administered once daily in the form of a tablet.	
Reporting group title	Placebo
Reporting group description:	
All randomized participants received orally brexpiprazole-matching Placebo. The Placebo was administered once daily in the form of a tablet.	

Serious adverse events	Brexpiprazole 0.5 mg/day	Brexpiprazole 1 mg/day	Brexpiprazole 2 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 20 (25.00%)	11 / 137 (8.03%)	13 / 140 (9.29%)
number of deaths (all causes)	2	2	1
number of deaths resulting from adverse events	2	2	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			

subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella Fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Venous Thrombosis Limb			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia Alzheimer’s Type			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Epilepsy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage Intracranial			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lacunar Infarction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychomotor Hyperactivity			

subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microcytic Anaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pancreatitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive Airways Disorder			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia Aspiration			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary Oedema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Abnormal Behaviour			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			

subjects affected / exposed	1 / 20 (5.00%)	1 / 137 (0.73%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Self-Injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic Disorder			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial Sepsis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 137 (0.00%)	4 / 140 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 135 (5.19%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus Fracture			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Patella Fracture			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous Thrombosis Limb			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular Accident			

subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dementia Alzheimer’s Type				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage Intracranial				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lacunar Infarction				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychomotor Hyperactivity				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient Ischaemic Attack				

subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Microcytic Anaemia			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			

subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstructive Airways Disorder				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia Aspiration				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary Oedema				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Abnormal Behaviour				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Agitation				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Delusion				
subjects affected / exposed	0 / 135 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intentional Self-Injury				
subjects affected / exposed	1 / 135 (0.74%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychotic Disorder				

subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacterial Sepsis			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Brexpiprazole 0.5 mg/day	Brexpiprazole 1 mg/day	Brexpiprazole 2 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 20 (55.00%)	27 / 137 (19.71%)	43 / 140 (30.71%)
Investigations			
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences (all)	1	0	1
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences (all)	2	1	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences (all)	2	1	0
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences (all)	1	1	0
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	2 / 20 (10.00%)	1 / 137 (0.73%)	1 / 140 (0.71%)
occurrences (all)	2	1	1
Blood Insulin Decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences (all)	1	1	0
Electrocardiogram QT Prolonged			
subjects affected / exposed	1 / 20 (5.00%)	3 / 137 (2.19%)	2 / 140 (1.43%)
occurrences (all)	1	4	2
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Protein Total Decreased			

subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	3 / 140 (2.14%)
occurrences (all)	1	0	3
Laceration			
subjects affected / exposed	1 / 20 (5.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences (all)	1	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)	1 / 137 (0.73%)	0 / 140 (0.00%)
occurrences (all)	1	1	0
Orthostatic Hypotension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences (all)	1	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 137 (0.73%)	8 / 140 (5.71%)
occurrences (all)	0	1	10
Headache			
subjects affected / exposed	0 / 20 (0.00%)	12 / 137 (8.76%)	13 / 140 (9.29%)
occurrences (all)	0	13	17
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 137 (0.73%)	2 / 140 (1.43%)
occurrences (all)	1	1	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 137 (1.46%)	3 / 140 (2.14%)
occurrences (all)	2	2	3
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 20 (5.00%)	1 / 137 (0.73%)	5 / 140 (3.57%)
occurrences (all)	1	1	7
Salivary Hypersecretion			

subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	1 / 140 (0.71%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Ecchymosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 20 (5.00%)	2 / 137 (1.46%)	4 / 140 (2.86%)
occurrences (all)	1	3	4
Insomnia			
subjects affected / exposed	0 / 20 (0.00%)	7 / 137 (5.11%)	8 / 140 (5.71%)
occurrences (all)	0	10	9
Paranoia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	1 / 20 (5.00%)	2 / 137 (1.46%)	3 / 140 (2.14%)
occurrences (all)	1	2	3
Metabolism and nutrition disorders			
Vitamin B12 Deficiency			
subjects affected / exposed	1 / 20 (5.00%)	0 / 137 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	29 / 135 (21.48%)		
Investigations			
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Blood Insulin Decreased			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Electrocardiogram QT Prolonged			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Protein Total Decreased			
subjects affected / exposed	0 / 135 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all) Laceration subjects affected / exposed occurrences (all)	 2 / 135 (1.48%) 2 0 / 135 (0.00%) 0		
Vascular disorders Hypertension subjects affected / exposed occurrences (all) Orthostatic Hypotension subjects affected / exposed occurrences (all)	 3 / 135 (2.22%) 3 0 / 135 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 4 / 135 (2.96%) 6 11 / 135 (8.15%) 16		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 0 / 135 (0.00%) 0		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	 3 / 135 (2.22%) 3		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Salivary Hypersecretion subjects affected / exposed occurrences (all)	 1 / 135 (0.74%) 1 0 / 135 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1 0 / 135 (0.00%) 0		
Skin and subcutaneous tissue disorders Dermatitis Allergic subjects affected / exposed occurrences (all) Ecchymosis subjects affected / exposed occurrences (all)	0 / 135 (0.00%) 0 0 / 135 (0.00%) 0		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Paranoia subjects affected / exposed occurrences (all)	4 / 135 (2.96%) 4 6 / 135 (4.44%) 7 0 / 135 (0.00%) 0		
Infections and infestations Urinary Tract Infection subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Metabolism and nutrition disorders Vitamin B12 Deficiency subjects affected / exposed occurrences (all)	0 / 135 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2013	Amendment number 1: Based on FDA feedback, the randomization ratio was changed from 1:2:2:2 to 1:1:1:1 (brexpiprazole 0.5 mg/day, brexpiprazole 1 mg/day, brexpiprazole 2 mg/day, placebo, respectively). Actigraphy and eDiary assessments were added to the protocol along with description of the use of day passes in this trial.
16 December 2013	Amendment number 2: The second amendment changes were made on the basis of adjustments to facilitate appropriate trial implementation and communication. It served to reflect clarifications and additions to study procedures intended to enhance participant safety and accuracy of data. Revised items included increasing the number of participating sites and recruitment period, clarification on consenting requirements, clarification of certain inclusion/exclusion criteria, and updates to the prohibited medication list. The amendment also added the option for participants who completed the 331-12-283 (2013-000503-17) trial to enter the 331-13-211 (2014-000424-23) safety trial.
07 July 2014	Amendment number 3: The changes were made to address the potential issue of missing data due to participants terminating early, as well as on the basis of adjustments considered important to ensure the safety of the participants enrolled and to facilitate appropriate study implementation and communication. The 0.5-mg arm was removed, which resulted in a reduction to the number of participants randomized. Noninstitutionalized participants were included with revisions to criteria and assessments for participants in this setting. The RUD scale and Mortality Assessment at Week 16 for participants who discontinued the trial early were added.
10 September 2015	Amendment number 4: The changes reflect clarifications and changes to trial procedures intended to enhance participant safety and accuracy of data as well as streamline the inclusion/exclusion criteria. The number of trial sites, as well as participating countries, was increased. Actigraphy was removed and eDiary was replaced with paper diaries. Revisions were made to the Schedule of Assessments to decrease participant burden.

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 reported

Notes: