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

Summary

EudraCT number	2013-000503-17
Trial protocol	GB FI SI BG
Global end of trial date	30 March 2017

Results information

Result version number	v1
This version publication date	14 June 2018
First version publication date	14 June 2018

Trial information

Trial identification

Sponsor protocol code	331-12-284

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01922258
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka
Sponsor organisation address	2440 Research Boulevard, Maryland, United States, 20850
Public contact	Laura Beth Duncan, Otsuka Pharmaceutical Development & Commercialization, Inc., 001 240780 4286, LauraBeth.Duncan@otsuka-us.com
Scientific contact	Laura Beth Duncan, Otsuka Pharmaceutical Development & Commercialization, Inc., 001 240780 4286, LauraBeth.Duncan@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	30 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2017
Global end of trial reached?	Yes
Global end of trial date	30 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of flexible dosing of brexpiprazole (dose range of 0.5 to 2 mg/day) with placebo in subjects with agitation associated with dementia of the Alzheimer's type, as assessed by the Cohen-Mansfield Agitation Inventory (CMAI) after 12 weeks of treatment.

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the Institutional Review Board or Independent Ethics Committee at each respective trial center

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 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	Russian Federation: 52
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Ukraine: 78
Country: Number of subjects enrolled	United States: 61
Country: Number of subjects enrolled	Bulgaria: 48
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Slovenia: 6
Worldwide total number of subjects	270
EEA total number of subjects	66

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)	43
From 65 to 84 years	195
85 years and over	32

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 62 sites in 9 countries: Bulgaria, Canada, Finland, France, Russia, Slovenia, Ukraine, the United Kingdom
(UK), and the United States (US) and 270 participants were randomized. The date of the first ICF signed by a participant in this trial was 28 October 2013 and the date of the last trial observation was 30 March 2017.

Pre-assignment

Screening details:

The screening period ranged from 2 to 42 days (with an option to extend with approval of the medical monitor). 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, Monitor, Data analyst, Assessor

Blinding implementation details:

During the trial, investigational medicinal product (IMP) was administered in a double-blind manner so that neither the investigator nor the subject had knowledge of the treatment assignment. Treatment assignments were based on a computer-generated randomization code provided by the Biometrics Department. Sponsor personnel, including those involved in monitoring, data management, and data analysis, did not have access to the treatment code during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Brexpiprazole

Arm description:

Titrate up from 0.25 mg/day brexpiprazole to 1 mg/day brexpiprazole.
After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability. Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 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:

Titrate up from 0.25 mg/day brexpiprazole to 1 mg/day brexpiprazole.
After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability. Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

Arm title	Placebo

Arm description:

Titrate up from 0.25 mg/day placebo to 1 mg/day placebo.
After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability. Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

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:

Titrate up from 0.25 mg/day placebo to 1 mg/day placebo. After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability. Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

Number of subjects in period 1	Brexpiprazole	Placebo
Started	133	137
Completed	117	121
Not completed	16	16
Withdrawn by the Investigator	1	4
Withdrawal by participant	5	5
Met withdrawal criteria	-	4
Adverse event	9	2
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole
Reporting group description:	
Titrate up from 0.25 mg/day brexpiprazole to 1 mg/day brexpiprazole. After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability. Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.	
Reporting group title	Placebo
Reporting group description:	
Titrate up from 0.25 mg/day placebo to 1 mg/day placebo. After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability. Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.	

Reporting group values	Brexpiprazole	Placebo	Total
Number of subjects	133	137	270
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
All participants who were randomized into this trial. Participants were considered randomized when they were assigned a treatment number by interactive voice response system (IVRS) at the end of screening period. A participant who received trial treatment outside of the IVRS was not considered randomized, but safety was reported.			
Units: years			
arithmetic mean	73.5	74.0	
standard deviation	± 8.5	± 7.8	-
Gender categorical			
All participants who were randomized into this trial. Participants were considered randomized when they were assigned a treatment number by interactive voice response system (IVRS) at the end of screening period. A participant who received trial treatment outside of the IVRS was not considered randomized, but safety was reported.			
Units: Subjects			
Female	82	88	170
Male	51	49	100

End points

End points reporting groups

Reporting group title	Brexpiprazole
Reporting group description:	
Titrate up from 0.25 mg/day brexpiprazole to 1 mg/day brexpiprazole. After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability. Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.	
Reporting group title	Placebo
Reporting group description:	
Titrate up from 0.25 mg/day placebo to 1 mg/day placebo. After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability. Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.	

Primary: Change From Baseline to Week 12/Early Termination in the Cohen-Mansfield Agitation Inventory (CMAI) Total Score

End point title	Change From Baseline to Week 12/Early Termination in the Cohen-Mansfield Agitation Inventory (CMAI) Total Score
End point description:	
The mean change from baseline (Day 0) to week 12 in the CMAI total score. Statistical comparison of interest was brexpiprazole flexible dose versus placebo, analyzed using an mixed-effect model repeated measure (MMRM) model. CMAI total score was based on adding responses (1= Never and 7= Several times in an hour) for each of the 29 agitated behaviors.	
End point type	Primary
End point timeframe:	
From screening to week 12/early termination.	

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	135		
Units: unit on a scale				
least squares mean (standard error)	-18.9 (± 1.17)	-16.5 (± 1.13)		

Statistical analyses

Statistical analysis title	CMAI Total Score
Comparison groups	Brexpiprazole v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1454
Method	Mixed-effect model repeated
Parameter estimate	treatment difference
Point estimate	-2.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.49
upper limit	0.82

Secondary: Change in the Clinical Global Impression Severity of Illness (CGI-S) Score, as Related to Symptoms of Agitation

End point title	Change in the Clinical Global Impression Severity of Illness (CGI-S) Score, as Related to Symptoms of Agitation

End point description:

The severity of agitation for each participant was rated using the CGI-S.
The investigator (or designee) answered the following question: "Considering your total clinical experience with this particular population, how mentally ill (as related to agitation) was the participant at the observation period?" Response choices 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. The score 0 (=not assessed) was set to missing. The CGI-S was therefore a 7-point scale (1-7). The primary
analysis used a mixed-effect model repeated measure (MMRM) approach.

End point type	Secondary

End point timeframe:

From screening to week 12/early termination.

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	135		
Units: units on a scale				
arithmetic mean (standard deviation)	4.54 (± 0.77)	4.51 (± 0.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores : Factor 1 (Aggressive Behavior)

End point title	Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores : Factor 1 (Aggressive Behavior)

End point description:

Mean change in factor scores from baseline for 3 distinct agitation syndromes of aggressive behavior based on the CMAI subscale scores
(aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior) were compared between brexpiprazole and placebo at Week 12 on a 1 to 7 scale with 1 being the "best" rating and 7 being the "worst" rating. Statistical comparison of interest was brexpiprazole flexible dose versus placebo, analyzed using an mixed-effect model repeated measure (MMRM) model.

End point type	Secondary

End point timeframe:

From screening to week 12/early termination.

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	135		
Units: units on a scale				
arithmetic mean (standard deviation)	23.84 (± 9.20)	22.22 (± 7.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores :Factor 2 (Physically Nonaggressive Behavior)

End point title	Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores :Factor 2 (Physically Nonaggressive Behavior)

End point description:

Mean change in factor scores from baseline for 3 distinct agitation syndromes of aggressive behavior based on the CMAI subscale scores (aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior) were compared between brexpiprazole and placebo at Week 12 on a 1 to 7 scale with 1 being the "best" rating and 7 being the "worst" rating. Statistical comparison of interest was brexpiprazole flexible dose versus placebo, analyzed using an mixed-effect model repeated measure (MMRM) model.

End point type	Secondary

End point timeframe:

From screening to week 12/early termination

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	135		
Units: units on a scale				
arithmetic mean (standard deviation)	20.65 (± 7.10)	19.72 (± 7.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores: Factor 3 (Verbally Agitated Behavior)

End point title	Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores: Factor 3 (Verbally Agitated Behavior)

End point description:

Mean change in factor scores from baseline for 3 distinct agitation syndromes of aggressive behavior based on the CMAI subscale scores
(aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior) were compared between brexpiprazole and placebo at Week 12 on a 1 to 7 scale with 1 being the "best" rating and 7 being the "worst" rating. Statistical comparison of interest was brexpiprazole flexible dose versus placebo, analyzed using an mixed-effect model repeated measure (MMRM) model.

End point type	Secondary

End point timeframe:

From screening to week 12/early termination

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	135		
Units: units on a scale				
arithmetic mean (standard deviation)	15.40 (± 4.85)	14.76 (± 5.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Summary of Mean Change From Baseline to Week 12 in Neuropsychiatric Inventory-Nursing Home (NPI-NH) 12-item

End point title	Secondary: Summary of Mean Change From Baseline to Week 12 in Neuropsychiatric Inventory-Nursing Home (NPI-NH) 12-item

End point description:

The NPI consisted of 12 items. For each item there was a screening question to determine if the behavioral change was present (rated 1) or absent (rated 0). For each item there were three scores: frequency, severity, and caregiver distress (NPI/NPI-NH) or occupational disruptiveness (NPI-NH). Frequency was rated on a 1 to 4 scale, severity was rated on a 1 to 3 scale and the caregiver distress was rated on a 0 to 5 scale. The individual item score was calculated as presence x frequency x severity and had a range from 0 to 12. If presence was zero, the individual item score and caregiver distress score were set to zero. For all items, low scores were 'better' than high scores.

End point type	Secondary

End point timeframe:

From screening to week 12/early termination.

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	135		
Units: units on a scale				
arithmetic mean (standard deviation)	37.18 (± 14.10)	34.70 (± 14.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Summary of Mean Change From Baseline to Week 12 in Neuropsychiatric Inventory-Nursing Home (NPI-NH) - Agitation/Aggression Score

End point title	Secondary: Summary of Mean Change From Baseline to Week 12 in Neuropsychiatric Inventory-Nursing Home (NPI-NH) - Agitation/Aggression Score

End point description:

The NPI consisted of 12 items. For each item there was a screening question to determine if the behavioral change was present (rated 1) or
absent (rated 0). For each item there are three scores: frequency, severity, and caregiver distress (NPI/NPI-NH) or occupational disruptiveness (NPI-NH). Frequency was rated on a 1 to 4 scale, severity was rated on a 1 to 3 scale and the caregiver distress was rated on a 0 to 5 scale. The individual item score was calculated as presence x frequency x severity and had a range from 0 to 12. If presence was zero, the individual item score and caregiver distress score were set to zero. For all items, low scores were
'better' than high scores.

End point type	Secondary

End point timeframe:

From screening to week 12/early termination

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	135		
Units: units on a scale				
arithmetic mean (standard deviation)	7.53 (± 1.89)	7.43 (± 1.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Summary of Mean Change From Baseline at Week 12 in Clinical Global Impression-Improvement (CGI-I) Scale

End point title	Secondary: Summary of Mean Change From Baseline at Week 12 in Clinical Global Impression-Improvement (CGI-I) Scale

End point description:

The efficacy of brexpiprazole in the treatment of agitation rated for each participant using the CGI-I. The investigator (or designee) rated the participant's total improvement (as related to agitation) whether or not it was due entirely to drug treatment. Response choices were 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The score 0 (=not assessed) was set to missing and that determined the sale was a 7-point scale, with 1 being very much improved and 7 being very much worse.

End point type	Secondary

End point timeframe:

From week 2 to week 12/early termination

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	137		
Units: units on a scale				
arithmetic mean (standard deviation)	2.56 (± 0.97)	2.94 (± 1.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Simpson-Angus Scale (SAS) Total Score

End point title	Summary of Mean Change From Baseline to Week 12 in Simpson-Angus Scale (SAS) Total Score

End point description:

The SAS consisted of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item rated on a 5-point scale, with a score of zero representing absence of symptoms and a score of 4 representing a severe condition. The SAS total score is the sum of the scores for all 10 items.

End point type	Secondary

End point timeframe:

From baseline to week 12/early termination

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	117		
Units: units on a scale				
arithmetic mean (standard deviation)	0.15 (± 1.67)	-0.28 (± 1.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Study Week 12 in Abnormal Involuntary Movement Scale (AIMS) Total Score

End point title	Summary of Mean Change From Baseline to Study Week 12 in Abnormal Involuntary Movement Scale (AIMS) Total Score

End point description:

The AIMS assessment consisted of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1-4), extremity movements (items 5-6), and trunk movements (item 7) observed unobtrusively while the participant was at rest and the investigator also made global judgments on the participant's dyskinesias (items 8-10). Each item was rated on a 5-point scale, with a score of zero representing absence of symptoms, and a score of 4, indicating a severe condition.

End point type	Secondary

End point timeframe:

From baseline to week 12/early termination

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	114		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.03 (± 0.31)	-0.04 (± 0.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Double Blind Treatment Period by Study Week in Barnes Akathisia Rating Scale (BARS)

End point title	Summary of Mean Change From Baseline to Double Blind Treatment Period by Study Week in Barnes Akathisia Rating Scale (BARS)

End point description:

The BARS consisted of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the paricipant, subjective distress due to akathisia, and global clinical assessment of akathisia. The global clinical evaluation was made on a 6-point scale, with zero representing absence of symptoms and a score of 5 representing severe akathisia.

End point type	Secondary

End point timeframe:

From baseline to week12/early termination

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	117		
Units: units on a scale				
arithmetic mean (standard deviation)	0.00 (± 0.23)	0.00 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Sheehan Suicidality Tracking Scale (Sheehan-STS) Score

End point title	Summary of Mean Change From Baseline to Week 12 in Sheehan Suicidality Tracking Scale (Sheehan-STS) Score

End point description:

Suicidality was monitored during the trial using the Sheehan-STS. The Sheehan-STS is a prospective scale that used to assess treatment emergent suicidal thoughts and behaviors. Each item of the Sheehan-STS was scored on a 5-point scale (0 = not at all; 1 = a little; 2 = moderate; 3 = very; and 4 = extremely).

End point type	Secondary

End point timeframe:

From screening to week12/early termination

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	123		
Units: units on a scale				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Mini-Mental State Examination Total Score

End point title	Summary of Mean Change From Baseline to Week 12 in Mini-Mental State Examination Total Score

End point description:

The MMSE was a brief practical test for assessing cognitive dysfunction. The test consisted of 5 sections (orientation, registration, attention and calculation, recall, and language) and had a total possible score of 30.

End point type	Secondary

End point timeframe:

From screening to week12/early termination

End point values	Brexpiprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	117		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.18 (± 2.02)	0.15 (± 2.30)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through the trial: From screening to Week 12 and 30(+2) days follow-up period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Brexpiprazole

Reporting group description:

Titrate up from 0.25 mg/day brexpiprazole to 1 mg/day brexpiprazole.
After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability.
Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

Reporting group title	Placebo

Reporting group description:

Titrate up from 0.25 mg/day placebo to 1 mg/day placebo.
After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability.
Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

Serious adverse events	Brexpiprazole	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 132 (5.30%)	6 / 137 (4.38%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consiousness			

subjects affected / exposed	1 / 132 (0.76%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 132 (0.76%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 132 (1.52%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 132 (0.00%)	1 / 137 (0.73%)	
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			
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 132 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea Exertional			
subjects affected / exposed	1 / 132 (0.76%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 132 (0.76%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hip Fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 132 (0.76%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 132 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 132 (0.00%)	1 / 137 (0.73%)	
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	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 132 (18.18%)	29 / 137 (21.17%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 132 (4.55%)	7 / 137 (5.11%)	
occurrences (all)	7	11	
Headache			
subjects affected / exposed	10 / 132 (7.58%)	17 / 137 (12.41%)	
occurrences (all)	10	21	
Somnolence			

subjects affected / exposed occurrences (all)	8 / 132 (6.06%) 10	5 / 137 (3.65%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2013	The amendment changes were made on the basis of adjustments to facilitate appropriate trial implementation and communication. 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 subjects who complete the 331-12-284 trial to enter the 331-13-211 observational trial.
07 July 2014	The changes were made to address the potential issue of missing data due to subjects terminating early. Noninstitutionalized subjects were allowed with revisions to criteria and assessments for subjects in this setting. The RUD scale and Mortality Assessment at Week 16 for subjects who discontinue the trial early were added.
10 September 2015	The changes reflect clarifications and changes to trial procedures intended to enhance subject 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. The power was increased from 80% to 85%, which resulted in an increase in the sample size from 230 to 260 subjects. Actigraphy was removed and eDiary was replaced with paper diaries. Revisions were made to the Schedule of Assessments to decrease subject burden. Administrative clarifications were made to enhance readability and consistency.

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: