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	v2 (current)
This version publication date	20 November 2020
First version publication date	14 June 2018
Version creation reason	

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 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	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 study was conducted in accordance with International Conference 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	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	Bulgaria: 48
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Russian Federation: 52
Country: Number of subjects enrolled	Slovenia: 6
Country: Number of subjects enrolled	Ukraine: 78
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 61
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, Assessor, Data analyst

Blinding implementation details:

During the trial, investigational medicinal product 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 (flexible dose range 0.5 to 2 mg/day)

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 (flexible dose range 0.5 to 2 mg/day)

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 (flexible dose range 0.5 to 2 mg/day)	Placebo (flexible dose range 0.5 to 2 mg/day)
Started	133	137
Completed	117	121
Not completed	16	16
Withdrawal By Participant	5	5
Adverse event, non-fatal	9	2
Withdrawn By The Investigator	1	4
Lost to follow-up	1	1
Met Withdrawal Criteria	-	4

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole (flexible dose range 0.5 to 2 mg/day)
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 (flexible dose range 0.5 to 2 mg/day)
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 (flexible dose range 0.5 to 2 mg/day)	Placebo (flexible dose range 0.5 to 2 mg/day)	Total
Number of subjects	133	137	270
Age categorical Units: Subjects			
<65 years	24	19	43
>=65 <75 years	46	49	95
>=75 years	63	69	132
Gender categorical Units: Subjects			
Female	82	88	170
Male	51	49	100
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	3	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	5	9
White	128	129	257
More than one race	0	0	0
Unknown or Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	Brexpiprazole (flexible dose range 0.5 to 2 mg/day)

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 (flexible dose range 0.5 to 2 mg/day)

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 CMAI is widely used in clinical research for evaluation of agitation associated with Alzheimer's dementia, with reliability and validity in both institutionalized and noninstitutionalized participants. It consists of 29 items, all rated on a 1 to 7 scale (1=Never and 7=Several times in an hour), with 1 being the "best" rating and 7 being the "worst" rating. The total score is the sum of ratings for all 29 items. The possible total scores range from 29 to 203. The total score will be unevaluable if less than 24 of the 29 items are recorded. If 24 to 28 of the 29 items are recorded, the total score will be the mean of the recorded items multiplied by 29 and rounded to the first decimal place. The mean change from baseline (Day 0) to week 12 in the CMAI total score is reported. Statistical comparison of interest was brexpiprazole flexible dose versus placebo, analyzed using a mixed-effect model repeated measure approach. A decrease in score indicates improvement in symptoms.

End point type	Primary

End point timeframe:

From screening to week 12/early termination

End point values	Brexpiprazole (flexible dose range 0.5 to 2 mg/day)	Placebo (flexible dose range 0.5 to 2 mg/day)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	135		
Units: units on a scale				
least squares mean (standard error)	-18.9 (± 1.17)	-16.5 (± 1.13)		

Statistical analyses

Statistical analysis title	Brexpiprazole versus Placebo

Statistical analysis description:

Change from baseline in the CMAI Total Score after 12 weeks of brexpiprazole treatment (0.5 - 2 mg/day) compared to 12 weeks of placebo.

Comparison groups	Brexpiprazole (flexible dose range 0.5 to 2 mg/day) v Placebo (flexible dose range 0.5 to 2 mg/day)
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1454
Method	Mixed-effect model repeated measure
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 approach.

End point type	Secondary

End point timeframe:

From screening to week 12/early termination

End point values	Brexpiprazole (flexible dose range 0.5 to 2 mg/day)	Placebo (flexible dose range 0.5 to 2 mg/day)		
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

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.

Adverse event reporting additional description:

Only participants who received at least 1 dose of investigational medical product were analyzed for safety (Brexpiprazole N=132).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Brexpiprazole (flexible dose range 0.5 to 2 mg/day)

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 (flexible dose range 0.5 to 2 mg/day)

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 (flexible dose range 0.5 to 2 mg/day)	Placebo (flexible dose range 0.5 to 2 mg/day)	
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	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	
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	
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 consciousness			
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			
alternative dictionary used: MedDRA 19.0			
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 / 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 (flexible dose range 0.5 to 2 mg/day)	Placebo (flexible dose range 0.5 to 2 mg/day)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 132 (18.18%)	29 / 137 (21.17%)	
Nervous system disorders			
Somnolence			
alternative dictionary used: MedDRA 19.0			
subjects affected / exposed	8 / 132 (6.06%)	5 / 137 (3.65%)	
occurrences (all)	10	5	
Headache			

alternative assessment type: Systematic			
subjects affected / exposed	10 / 132 (7.58%)	17 / 137 (12.41%)	
occurrences (all)	10	21	
Dizziness			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 132 (4.55%)	7 / 137 (5.11%)	
occurrences (all)	7	11	

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 (2013-000503-17) trial to enter the 331-13-211 (2014-000424-23) 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

None reported