Clinical trial results:
A 2-month, Observational, Rollover Trial to Evaluate the Safety of Subjects with Agitation Associated with Dementia of the Alzheimer's Type who were Previously Treated with Brexpiprazole (OPC-34712) or Placebo in a Phase 3, Double-blind Trial

Summary

EudraCT number	2014-000424-23
Trial protocol	ES DE SI FR GB HR BG
Global end of trial date	30 May 2017

Results information

Result version number	v1 (current)
This version publication date	02 April 2021
First version publication date	02 April 2021

Trial information

Trial identification

Sponsor protocol code	331-13-211

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02192554
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, MD 20850
Public contact	Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp
Scientific contact	Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp

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 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 May 2017
Global end of trial reached?	Yes
Global end of trial date	30 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of subjects with agitation associated with dementia of the Alzheimer's type who were previously treated with brexpiprazole (0.5, 1, or 2 mg/day) or placebo during Trial 331-12-283 or Trial 331-12-284.

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 had been obtained from them. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the institutional review board or ethics committee at each respective trial center. During the phase 3 trials, subjects were treated for a period of 12 weeks with a 30-day safety follow-up period. Trial 331-13-211 was designed to extend the duration of the safety follow-up period for the aforementioned Phase 3 trials from 30 days to 3 months (ie, 30 days from the previous phase 3 trials [331-12-283 or 331-12-284] plus 2 months from Trial 331-13-211).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 July 2014
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	Slovenia: 4
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Croatia: 16
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Russian Federation: 108
Country: Number of subjects enrolled	Serbia: 37
Country: Number of subjects enrolled	Ukraine: 92
Country: Number of subjects enrolled	United States: 111
Country: Number of subjects enrolled	Bulgaria: 42
Worldwide total number of subjects	450
EEA total number of subjects	95

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)	66
From 65 to 84 years	339
85 years and over	45

Subject disposition

Recruitment

Recruitment details:

This trial was conducted at 87 sites in 12 countries: Bulgaria, Canada, Croatia, France, Germany, Great Britain, Russia, Serbia, Slovenia, Spain, Ukraine, and United States. Subjects with agitation associated with dementia of the Alzheimer's type were involved in this study.

Pre-assignment

Screening details:

This was an observational trial without study drug to characterize the long-term safety of subjects after the investigational trials (Trials 331-12-283 & Trial 331-12-284). Subjects were allowed to take any medications to treat agitation or other symptoms of illness without limitation. Informed consent signed, eligibility criteria checked.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Prior Brexpiprazole

Arm description:

This arm comprised of subjects with agitation associated with dementia of the Alzheimer's type who previously received brexpiprazole (0.5, 1, or 2 mg/day) during a phase 3 brexpiprazole trial (Trial 331-12-283 and Trial 331-12-284). This study comprised of 2 months of continued observation following a subject's completion of participation in the previous phase 3 brexpiprazole trials and included 3 visits: at baseline, Month 1 (± 5 days), and Month 2 (±5 days)/ Early termination (ET). No Investigational medicinal product (IMP) was provided during this 2-month observational rollover trial.

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

Dosage and administration details:

Brexpiprazole (0.5, 1, or 2 mg/day) was administered during a phase 3 brexpiprazole trial (Trial 331-12-283 and Trial 331-12-284).

Arm title	Prior Placebo

Arm description:

This arm comprised of subjects with agitation associated with dementia of the Alzheimer's type, who previously received brexpiprazole matching placebo during a phase 3 brexpiprazole trial (Trial 331-12-283 and Trial 331-12-284). In this rollover study no placebo was administered.

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:

Brexpiprazole matching placebo was administered during a phase 3 brexpiprazole trial (Trial 331-12-283 and Trial 331-12-284).

Number of subjects in period 1	Prior Brexpiprazole	Prior Placebo
Started	262	188
Completed	259	188
Not completed	3	0
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Prior Brexpiprazole

Reporting group description:

This arm comprised of subjects with agitation associated with dementia of the Alzheimer's type who previously received brexpiprazole (0.5, 1, or 2 mg/day) during a phase 3 brexpiprazole trial (Trial 331-12-283 and Trial 331-12-284). This study comprised of 2 months of continued observation following a subject's completion of participation in the previous phase 3 brexpiprazole trials and included 3 visits: at baseline, Month 1 (± 5 days), and Month 2 (±5 days)/ Early termination (ET). No Investigational medicinal product (IMP) was provided during this 2-month observational rollover trial.

Reporting group title	Prior Placebo

Reporting group description:

This arm comprised of subjects with agitation associated with dementia of the Alzheimer's type, who previously received brexpiprazole matching placebo during a phase 3 brexpiprazole trial (Trial 331-12-283 and Trial 331-12-284). In this rollover study no placebo was administered.

Reporting group values	Prior Brexpiprazole	Prior Placebo	Total
Number of subjects	262	188	450
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	40	26	66
From 65-84 years	193	146	339
85 years and over	29	16	45
Age continuous Units: years			
arithmetic mean	74.1	74.0	
standard deviation	± 8.3	± 7.8	-
Gender categorical Units: Subjects			
Female	155	102	257
Male	107	86	193

End points

End points reporting groups

Reporting group title	Prior Brexpiprazole

Reporting group description:

This arm comprised of subjects with agitation associated with dementia of the Alzheimer's type who previously received brexpiprazole (0.5, 1, or 2 mg/day) during a phase 3 brexpiprazole trial (Trial 331-12-283 and Trial 331-12-284). This study comprised of 2 months of continued observation following a subject's completion of participation in the previous phase 3 brexpiprazole trials and included 3 visits: at baseline, Month 1 (± 5 days), and Month 2 (±5 days)/ Early termination (ET). No Investigational medicinal product (IMP) was provided during this 2-month observational rollover trial.

Reporting group title	Prior Placebo

Reporting group description:

This arm comprised of subjects with agitation associated with dementia of the Alzheimer's type, who previously received brexpiprazole matching placebo during a phase 3 brexpiprazole trial (Trial 331-12-283 and Trial 331-12-284). In this rollover study no placebo was administered.

Primary: Number of participants with Adverse Events (AEs)

End point title	Number of participants with Adverse Events (AEs)[1]

End point description:

An AE was defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A SAE included any event that resulted in death, life-threatening event, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, in-patient hospitalization or prolonged hospitalization, congenital anomaly/birth defect, and other medically significant events that, based upon appropriate medical judgment, jeopardized the subject and required medical or surgical intervention. Safety endpoints related to AEs that were evaluated during this trial were: frequency and severity of AEs, SAEs, and discontinuations from the trial due to AEs, frequency and severity of AEs related to the worsening of agitation and cognition associated with Alzheimer's disease. Subjects had no limitations to take any medication to treat agitation or other symptoms during this study.

End point type	Primary

End point timeframe:

From baseline to Month 2/ET

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Safety results were summarized and presented and no formal statistical analysis was performed.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	188		
Units: Participants				
number (not applicable)				
Participants with adverse events	57	37		
Participants with serious adverse events	1	1		
Participants with nonserious adverse events	57	36		
Participants with severe adverse events	1	0		
Death	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change in Mini-Mental State Examination (MMSE) Score

End point title	Mean Change in Mini-Mental State Examination (MMSE)

End point description:

The MMSE was a brief practical test used 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. Higher scores indicate better cognitive functioning.
MMSE safety scale was used as one of the safety variable. The MMSE was performed at the Month 2/ET visit.

End point type	Primary

End point timeframe:

From baseline to Month 2/ET

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a non-comparative, observational study. The mean change in the MMSE score from baseline to Month 2/ET was summarized by descriptive statistics, eg, mean and standard deviation.

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260	187		
Units: Unit on scale				
arithmetic mean (standard deviation)				
Month 2	-0.34 (± 2.12)	-0.46 (± 2.17)		
Last visit	-0.34 (± 2.12)	-0.46 (± 2.17)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to Month 2/ET

Adverse event reporting additional description:

An AE was defined as any untoward medical occurrence associated with the use of a drug in human. An serious adverse event (SAE) included events that resulted in death, life threatening event, persistent incapacity of the ability to conduct normal life functions, in-patient hospitalization, congenital anomaly, and other medically events.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Prior Brexpiprazole

Reporting group description:

This arm comprised of subjects with agitation associated with dementia of the Alzheimer's type who previously received brexpiprazole (0.5, 1, or 2 mg/day)during a phase 3 brexpiprazole trial (Trial 331-12-283 and Trial 331-12-284). This study comprised of 2 months of continued observation following a participant's completion of participation in the previous phase 3 brexpiprazole trials and included 3 visits: at baseline, Month 1 (± 5 days), and Month 2 (± 5 days)/ Early termination (ET). No Investigational medicinal product (IMP) was provided during this 2-month observational rollover trial.months of continued observation following a subject's completion of participation in the previous phase 3 brexpiprazole trials and included 3 visits: at baseline, Month 1 (± 5 days), and Month 2 (± 5 days)/ Early termination (ET). No Investigational medicinal product (IMP) was provided during this 2-month observational rollover trial.

Reporting group title	Prior Placebo

Reporting group description:

This arm comprised of subjects with agitation associated with dementia of the Alzheimer's type, who previously received brexpiprazole matching placebo during a phase 3 brexpiprazole trial (Trial 331-12-283 and Trial 331-12-284). In this rollover study no placebo was administered.

Serious adverse events	Prior Brexpiprazole	Prior Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 262 (0.38%)	1 / 188 (0.53%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 262 (0.38%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	1 / 262 (0.38%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 262 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Prior Brexpiprazole	Prior Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 262 (5.34%)	9 / 188 (4.79%)	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 262 (5.34%)	9 / 188 (4.79%)	
occurrences (all)	14	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2014	This first amendment served to reflect clarifications and additions to study procedures intended to enhance participant safety and accuracy of data. In addition, administrative clarifications were made, including changes to text to enhance readability and consistency and to correct typographical, punctuation, and formatting errors. These changes were minor and did not change the design or content of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported