Clinical trial results:
A 12-week, Multicenter, Active-treatment Extension Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type

Summary

EudraCT number	2018-002783-88
Trial protocol	BG ES HU SK
Global end of trial date	19 September 2022

Results information

Result version number	v2 (current)
This version publication date	19 May 2024
First version publication date	05 October 2023
Version creation reason	• Correction of full data set Based on PRS QC comments, EudraCT record requires updating

Trial information

Trial identification

Sponsor protocol code	331-201-00182

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03594123
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	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc, clinicaltransparency@otsuka-us.com
Scientific contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc, 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	19 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety and tolerability of oral brexpiprazole as treatment in adult subjects with agitation associated with dementia of Alzheimer's type (AAD).

Protection of trial subjects:

Informed consent was obtained from all subjects participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 October 2018
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	Slovakia: 8
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Bulgaria: 26
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Serbia: 17
Country: Number of subjects enrolled	United States: 109
Country: Number of subjects enrolled	Ukraine: 86
Worldwide total number of subjects	259
EEA total number of subjects	47

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)	29
From 65 to 84 years	208
85 years and over	22

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 66 sites from 11 October 2018 to 19 September 2022 in the following countries: Bulgaria, Hungary, Serbia, Slovakia, Spain, Ukraine, and the United States.

Pre-assignment

Screening details:

Of the 259 participants, 163 received brexpiprazole and 96 received placebo in the parent study 331-14-213. All participants received brexpiprazole in this study. As prespecified in the SAP, data was analyzed based on the treatments in the parent study. Data for this study was analyzed and reported in a combined way for brexpiprazole 2 and 3 mg.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

Although this was an active-treatment extension trial, dose assignment was handled in a blinded fashion to maintain blinding of subjects' previous treatment in Trial 331-14-213 (2017-003940-19).

Arms

Are arms mutually exclusive?	Yes
Arm title	Prior Brexpiprazole

Arm description:

Subjects who received brexpiprazole in a previous double-blind phase 3 study (Trial 331-14-213 {2017-003940-19}), received the same dose of brexpiprazole [2 or 3 milligrams (mg)] once daily (QD), orally, as they received during the previous study, for up to 12 weeks with dose adjustment.

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

Dosage and administration details:

Brexpiprazole tablets, administered orally, 2-3 mg QD up to Week 12 during the treatment phase. Adjustments could be made to dosing.

Arm title	Prior Placebo

Arm description:

Subjects who received placebo in a previous double-blind phase 3 study (Trial 331-14-213 {2017-003940-19}), received brexpiprazole following a titration schedule, to gradually increase their dose from 0.5 mg QD, in the starting to 2 or 3 mg QD, orally, for up to 12 weeks with dose adjustment.

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

Dosage and administration details:

Brexpiprazole tablets, administered orally, in a titration manner starting from 0.5 mg up to 2-3 mg QD, up to Week 12 during the treatment phase. Adjustments could be made to dosing.

Number of subjects in period 1	Prior Brexpiprazole	Prior Placebo
Started	163	96
Completed	142	87
Not completed	21	9
Lack of Efficacy	1	-
Adverse Event	8	5
Not Related to COVID-19	1	1
Site Terminated by Sponsor	4	1
Lost to follow-up	-	1
Subject Withdrew Consent to Participate	7	1

Baseline characteristics

Reporting groups	
Reporting group title	Prior Brexpiprazole
Reporting group description:	
Subjects who received brexpiprazole in a previous double-blind phase 3 study (Trial 331-14-213 {2017-003940-19}), received the same dose of brexpiprazole [2 or 3 milligrams (mg)] once daily (QD), orally, as they received during the previous study, for up to 12 weeks with dose adjustment.	
Reporting group title	Prior Placebo
Reporting group description:	
Subjects who received placebo in a previous double-blind phase 3 study (Trial 331-14-213 {2017-003940-19}), received brexpiprazole following a titration schedule, to gradually increase their dose from 0.5 mg QD, in the starting to 2 or 3 mg QD, orally, for up to 12 weeks with dose adjustment.	

Reporting group values	Prior Brexpiprazole	Prior Placebo	Total
Number of subjects	163	96	259
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	74.8	73.4	
standard deviation	± 7.9	± 73.0	-
Gender categorical Units: Subjects			
Female	99	46	145
Male	64	50	114
Ethnicity Units: Subjects			
Hispanic or Latino	52	30	82
Not Hispanic or Latino	111	66	177
Race Units: Subjects			
Asian	2	1	3
Black or African American	7	1	8
White	154	94	248
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Unknown or Not Reported	0	0	0
More than one race	0	0	0

End points

End points reporting groups

Reporting group title	Prior Brexpiprazole

Reporting group description:

Subjects who received brexpiprazole in a previous double-blind phase 3 study (Trial 331-14-213 {2017-003940-19}), received the same dose of brexpiprazole [2 or 3 milligrams (mg)] once daily (QD), orally, as they received during the previous study, for up to 12 weeks with dose adjustment.

Reporting group title	Prior Placebo

Reporting group description:

Subjects who received placebo in a previous double-blind phase 3 study (Trial 331-14-213 {2017-003940-19}), received brexpiprazole following a titration schedule, to gradually increase their dose from 0.5 mg QD, in the starting to 2 or 3 mg QD, orally, for up to 12 weeks with dose adjustment.

Primary: Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs) by Severity

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs) by Severity[1]

End point description:

An AE was defined as any untoward medical occurrence in a subject administered a medicinal product,which does not necessarily have a causal relationship with treatment.TEAEs were defined as AEs with an onset date on or after the first dose of brexpiprazole.They started after start of brexpiprazole;continuous from baseline and worsening,serious,study drug-related,or resulted in death,discontinuation,interruption,or reduction of study therapy.AEs were graded on a 3-point scale:1=Mild:Discomfort noticed,but no disruption to daily activity,2=Moderate: Discomfort sufficient to reduce or affect normal daily activity,3=Severe:Inability to work or perform normal daily activity.Safety Sample comprised of those subjects who signed an informed consent form(ICF)and received at least one dose of brexpiprazole in Trial 331-201-00182. As prespecified in the SAP,data was analyzed based on the treatments in the parent study.Data for this study was reported in a combined way for brexpiprazole 2 or 3mg.

End point type	Primary

End point timeframe:

From first dose through 30 days after last dose of study drug (Up to approximately Week 16)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Inferential statistical analysis was not performed for the safety endpoint. Descriptive statistics are included (percentage of participants).

End point values	Prior Brexpiprazole	Prior Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	96		
Units: percentage of subjects				
number (not applicable)				
Mild	20.9	13.5		
Moderate	9.2	19.8		
Severe	3.1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose through 30 days after last dose of study drug (Up to approximately Week 16)

Adverse event reporting additional description:

Safety Sample comprised of subjects who signed an ICF for the trial and received at least one dose of brexpiprazole in Trial 331-201-00182.As prespecified in SAP,data was analyzed based on treatments received in parent study 331-14-213.Adverse events were analyzed and reported irrespective of the dose,in a combined way for brexpiprazole 2 and 3 mg.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Prior Brexpiprazole

Reporting group description:

Subjects who received brexpiprazole in a previous double-blind phase 3 study (Trial 331-14-213 {2017-003940-19}), received the same dose of brexpiprazole [2 or 3 mg], QD, orally, as they received during the previous study, for up to 12 weeks with dose adjustment.

Reporting group title	Prior Placebo

Reporting group description:

Subjects who received placebo in a previous double-blind phase 3 study (Trial 331-14-213 {2017-003940-19}), received brexpiprazole following a titration schedule, to gradually increase their dose from 0.5 mg QD, in the starting to 2 or 3 mg QD, orally, for up to 12 weeks with dose adjustment.

Serious adverse events	Prior Brexpiprazole	Prior Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 163 (3.68%)	0 / 96 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 163 (0.61%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 163 (1.84%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	1 / 163 (0.61%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 163 (0.61%)	0 / 96 (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			
Syncope			
subjects affected / exposed	1 / 163 (0.61%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood Loss Anaemia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	1 / 163 (0.61%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Prior Brexpiprazole	Prior Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 163 (0.00%)	5 / 96 (5.21%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 163 (0.00%)	5 / 96 (5.21%)	
occurrences (all)	0	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2020	•Addendum for any protocol-specified activities that are not able to be performed or cannot be performed due to COVID-19 considerations. •Added that subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial. •The changes from amendment 1 of protocol 331-201-00182 did not go into effect and the amendment was not distributed to sites or Institutional review boards.
06 August 2020	• Deleted language stating that subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial.
22 September 2020	• Added that subjects who are early terminated from Trial 331-14-213, if the trial is terminated due to overwhelming efficacy from the interim analysis, may be offered entry into this trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported