Clinical trial results:
Country-specific protocol amendment for Germany entitled: 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	v1
This version publication date	14 June 2018
First version publication date	14 June 2018

Trial information

Trial identification

Sponsor protocol code	331-12-283

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	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	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 subjects with agitation associated with Alzhemier's dementia, 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 the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) 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	06 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	Ukraine: 64
Country: Number of subjects enrolled	United States: 121
Country: Number of subjects enrolled	Spain: 19
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:

The study was conducted in 433 subjects at 81 sites in 7 countries: Croatia, Germany, Serbia, Spain, Russia, Ukraine, and the United States (US)

Pre-assignment

Screening details:

Subjects attended screening period ranging from 2 to 42 days. The purpose of the screening period was to determine the subject'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(Brex) 0.5mg/Day

Arm description:

All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 0.5 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:

All randomized subjects received orally brexpiprazole 0.5 mg/day tablet.

Arm title	Brexpiprazole(Brex) 1mg/Day

Arm description:

All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 1 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:

All randomized subjects received orally brexpiprazole 1 mg/day tablet.

Arm title	Brexpiprazole(Brex) 2mg/Day

Arm description:

All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 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:

All randomized subjects received orally brexpiprazole 2 mg/day tablet.

Arm title	Placebo

Arm description:

All randomized subjects received orally brexpiprazole matching Placebo tablet once daily in form of tablets.

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 subjects received orally brexpiprazole matching Placebo tablet.

Number of subjects in period 1	Brexpiprazole(Brex) 0.5mg/Day	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day
Started	20	137	140
Completed	13	121	122
Not completed	7	16	18
Consent withdrawn by subject	2	4	8
Adverse Event	4	10	6
Subject met withdrawal criteria	1	1	2
Subject withdrawn by Investigator	-	1	1
Protocol deviation	-	-	1

Number of subjects in period 1	Placebo
Started	136
Completed	121
Not completed	15
Consent withdrawn by subject	5
Adverse Event	8
Subject met withdrawal criteria	1
Subject withdrawn by Investigator	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Brexpiprazole(Brex) 0.5mg/Day
Reporting group description:	
All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 0.5 mg/day.	
Reporting group title	Brexpiprazole(Brex) 1mg/Day
Reporting group description:	
All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 1 mg/day.	
Reporting group title	Brexpiprazole(Brex) 2mg/Day
Reporting group description:	
All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 2 mg/day.	
Reporting group title	Placebo
Reporting group description:	
All randomized subjects received orally brexpiprazole matching Placebo tablet once daily in form of tablets.	

Reporting group values	Brexpiprazole(Brex) 0.5mg/Day	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day
Number of subjects	20	137	140
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
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

Reporting group values	Placebo	Total	
Number of subjects	136	433	
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			
Units: years			
arithmetic mean	74.1		
standard deviation	± 8.0	-	
Gender categorical			
Units: Subjects			
Female	70	239	
Male	66	194	

End points

End points reporting groups

Reporting group title	Brexpiprazole(Brex) 0.5mg/Day
Reporting group description:	
All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 0.5 mg/day.	
Reporting group title	Brexpiprazole(Brex) 1mg/Day
Reporting group description:	
All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 1 mg/day.	
Reporting group title	Brexpiprazole(Brex) 2mg/Day
Reporting group description:	
All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 2 mg/day.	
Reporting group title	Placebo
Reporting group description:	
All randomized subjects received orally brexpiprazole matching Placebo tablet once daily in form of tablets.	

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:	
The CMAI assess the frequency of agitated behaviors in elderly persons. It consisted of 29 agitated behaviors that are further categorized into distinct agitation syndromes or CMAI factors of agitation. These distinct agitation syndromes include aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior.	
End point type	Primary
End point timeframe:	
From baseline to 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

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

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 1mg/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	Least square (LS) mean difference
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	3.86

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 2mg/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	LS mean difference
Point estimate	-3.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.38
upper limit	-0.17

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:

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 subjects.

End point type	Secondary

End point timeframe:

From baseline to 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

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

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 1mg/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

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo
Comparison groups	Placebo v Brexpiprazole(Brex) 2mg/Day
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

Secondary: Change From Baseline in the CMAI Subscale Scores (Aggressive Behavior) After 12 Weeks of Brexpiprazole Treatment.

End point title	Change From Baseline in the CMAI Subscale Scores (Aggressive Behavior) After 12 Weeks of Brexpiprazole Treatment.[3]

End point description:

The CMAI was developed to assess the frequency of agitated behaviors in elderly persons and consists of 29 agitated behaviors that are further categorized into distinct agitation syndromes or CMAI factors of agitation. These distinct agitation syndromes include aggressive
behavior, physically nonaggressive behavior, and verbally agitated behavior. This endpoint provides an overview for aggressive behavior.

End point type	Secondary

End point timeframe:

From baseline to Week 12/ET

Notes:

[3] - 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

End point values	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	138	131	
Units: Participants				
arithmetic mean (standard deviation)	-5.69 (± 8.43)	-7.42 (± 7.63)	-6.53 (± 7.62)	

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 1mg/Day v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.9814
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	1.34

Notes:

[4] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported.

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 2mg/Day v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.1477
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.29
upper limit	0.35

Notes:

[5] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported.

Secondary: Change From Baseline in the CMAI Subscale Scores (Physically Nonaggressive Behavior) After 12 Weeks of Brexpiprazole Treatment

End point title	Change From Baseline in the CMAI Subscale Scores (Physically Nonaggressive Behavior) After 12 Weeks of Brexpiprazole Treatment[6]

End point description:

The CMAI was developed to assess the frequency of agitated behaviors in elderly persons and consists of 29 agitated behaviors that are further categorized into distinct agitation syndromes or CMAI factors of agitation. These distinct agitation syndromes include aggressive
behavior, physically nonaggressive behavior, and verbally agitated behavior. This endpoint provides an overview for physically non aggressive behavior.

End point type	Secondary

End point timeframe:

From baseline to Week 12/ET

Notes:

[6] - 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

End point values	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	138	131	
Units: Participants				
arithmetic mean (standard deviation)	-5.40 (± 6.69)	-6.75 (± 6.12)	-5.42 (± 5.39)	

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 1mg/Day v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.5506
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	1.81

Notes:

[7] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported.

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Placebo v Brexpiprazole(Brex) 2mg/Day
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.0945
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.57
upper limit	0.2

Notes:

[8] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported.

Secondary: Change From Baseline in the CMAI Subscale Scores (Verbally Agitated Behavior) After 12 Weeks of Brexpiprazole Treatment

End point title	Change From Baseline in the CMAI Subscale Scores (Verbally Agitated Behavior) After 12 Weeks of Brexpiprazole Treatment[9]

End point description:

The CMAI was developed to assess the frequency of agitated behaviors in elderly persons and consists of 29 agitated behaviors that are further categorized into distinct agitation syndromes or CMAI factors of agitation. These distinct agitation syndromes include aggressive
behavior, physically nonaggressive behavior, and verbally agitated behavior. This endpoint provides an overview for verbally agitated behavior.

End point type	Secondary

End point timeframe:

From baseline to Week 12/ET

Notes:

[9] - 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

End point values	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	138	131	
Units: Participants				
arithmetic mean (standard deviation)	-3.02 (± 4.84)	-4.35 (± 4.59)	-3.35 (± 4.34)	

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 1mg/Day v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.598
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.75

Notes:

[10] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported.

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 2mg/Day v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0153
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	-1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.29
upper limit	-0.24

Notes:

[11] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported.

Secondary: Change From Baseline in the Neuropsychiatric Inventory-Nursing Home Rating Scale (NPI-NH) 12- Item Total Score After 12 Weeks of Brexpiprazole Treatment

End point title	Change From Baseline in the Neuropsychiatric Inventory-Nursing Home Rating Scale (NPI-NH) 12- Item Total Score After 12 Weeks of Brexpiprazole Treatment[12]

End point description:

The NPI-NH questionnaire was used to interview the identified caregiver about the institutionalized subject's possible neuropsychiatric symptoms (ie, delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, aberrant motor behavior, nighttime behaviors, and appetite/eating behaviors). For each of the 12 separate behavioral domains, the NPI-NH evaluates the frequency (scale = 1 to 4), severity (scale = 1 to 3), and occupational disruption (scale = 0 to 5). A total NPI-NH score was calculated by adding the first 10 domain total scores (frequency x severity scores) together.

End point type	Secondary

End point timeframe:

From baseline to Week 12/ET

Notes:

[12] - 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

End point values	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	138	130	
Units: Participants				
arithmetic mean (standard deviation)	-15.9 (± 15.77)	-17.4 (± 14.78)	-15.9 (± 14.22)	

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 1mg/Day v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.8802
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.48
upper limit	2.98

Notes:

[13] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported.

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo

Statistical analysis description:

The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 2mg/Day v Placebo
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.281
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	-1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.99
upper limit	1.45

Notes:

[14] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported.

Secondary: Change From Baseline in the NPI-NH Agitation/Aggression Score After 12 Weeks of Brexpiprazole Treatment

End point title	Change From Baseline in the NPI-NH Agitation/Aggression Score After 12 Weeks of Brexpiprazole Treatment[15]

End point description:

The NPI-NH questionnaire was used to interview the identified caregiver about the institutionalized subject's possible neuropsychiatric symptoms (ie, delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria,
apathy/indifference, disinhibition, irritability, aberrant motor behavior, nighttime behaviors, and appetite/eating behaviors). For each of the 12 separate behavioral domains, the NPI-NH evaluates the frequency (scale = 1 to 4), severity (scale = 1 to 3), and occupational disruption (scale = 0 to 5). For each behavioral domain, 4 scores were calculated based on frequency, severity, total (frequency x severity), and occupational disruptiveness.

End point type	Secondary

End point timeframe:

From baseline to Week 12/ET

Notes:

[15] - 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

End point values	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	138	131	
Units: Participants				
arithmetic mean (standard deviation)	-3.43 (± 3.33)	-3.97 (± 3.16)	-3.60 (± 2.95)	

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 1mg/Day v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.7823
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.6

Notes:

[16] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported.

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 2mg/Day v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.1222
Method	Mixed-effect model repeated measure
Parameter estimate	LS mean difference
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	0.15

Notes:

[17] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported

Secondary: Change From Baseline in Clinical Global Impression-Improvement (CGI-I) Score, as Related to Agitation After 12 Weeks of Brexpiprazole Treatment

End point title	Change From Baseline in Clinical Global Impression-Improvement (CGI-I) Score, as Related to Agitation After 12 Weeks of Brexpiprazole Treatment[18]

End point description:

The CGI-I was used to rate the total improvement (as related to agitation) for each subject whether or not it was due entirely to drug treatment. Scores 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.

End point type	Secondary

End point timeframe:

From Week 2 to Week 12/ET

Notes:

[18] - 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

End point values	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	138	131	
Units: Participants				
arithmetic mean (standard deviation)	2.88 (± 1.26)	2.58 (± 1.17)	2.81 (± 1.11)	

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 1mg/Day v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.7499
Method	Cochran-Mantel-Haenszel
Parameter estimate	LS mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.33

Notes:

[19] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo

Statistical analysis description:

The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

Comparison groups	Brexpiprazole(Brex) 2mg/Day v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.1311
Method	Cochran-Mantel-Haenszel
Parameter estimate	LS mean difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.06

Notes:

[20] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported

Other pre-specified: Change From Baseline in Assessments of Extrapyramidal Symptoms (EPS) Using Simpson Angus Scale (SAS) After 12 Weeks of Brexpiprazole Treatment.

End point title	Change From Baseline in Assessments of Extrapyramidal Symptoms (EPS) Using Simpson Angus Scale (SAS) After 12 Weeks of Brexpiprazole Treatment.[21]

End point description:

The EPS was evaluated as a variable of safety assessment of 2 fixed doses of brexpiprazole (1 mg/day and 2 mg/day) compared with placebo using SAS, which consisted of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item was rated on a 5-point scale, with a score of 0 representing absence of symptoms and a score of 4 representing a severe condition. The SAS total score was the sum of the scores for all 10 items.

End point type	Other pre-specified

End point timeframe:

From baseline to Week 12/ET

Notes:

[21] - 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

End point values	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	139	132	
Units: Participants				
arithmetic mean (standard deviation)	-0.13 (± 0.96)	0.37 (± 2.82)	-0.13 (± 1.10)	

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo

Statistical analysis description:

Safety set consisted of all subjects who were administered at least 1 dose of IMP.

Comparison groups	Brexpiprazole(Brex) 1mg/Day v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.8453
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.44

Notes:

[22] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo

Statistical analysis description:

Safety set consisted of all subjects who were administered at least 1 dose of IMP.

Comparison groups	Brexpiprazole(Brex) 2mg/Day v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.013
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.9

Notes:

[23] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported

Other pre-specified: Change From Baseline in Assessments of EPS Using the Abnormal Involuntary Movement Scale (AIMS) After 12 Weeks of Brexpiprazole Treatment

End point title	Change From Baseline in Assessments of EPS Using the Abnormal Involuntary Movement Scale (AIMS) After 12 Weeks of Brexpiprazole Treatment[24]

End point description:

The EPS was evaluated using AIMS, which consisted of 10 items describing symptoms of dyskinesia. Each item was rated on a 5-point scale, with a score of 0 representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness, severe distress).

End point type	Other pre-specified

End point timeframe:

From baseline to Week 12/Early Termination

Notes:

[24] - 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

End point values	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	137	132	
Units: Participants				
arithmetic mean (standard deviation)	-0.01 (± 0.51)	-0.05 (± 0.47)	-0.05 (± 0.49)	

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo
Statistical analysis description:	
Safety set consisted of all subjects who were administered at least 1 dose of IMP.	
Comparison groups	Brexpiprazole(Brex) 1mg/Day v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.7228
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.12

Notes:

[25] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo
Statistical analysis description:	
Safety set consisted of all subjects who were administered at least 1 dose of IMP.	
Comparison groups	Brexpiprazole(Brex) 2mg/Day v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.8804
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.09

Notes:

[26] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported

Other pre-specified: Change From Baseline in Assessments of EPS Using the Barnes

Akathisia Rating Scale (BARS) After 12 Weeks of Brexpiprazole Treatment	
End point title	Change From Baseline in Assessments of EPS Using the Barnes Akathisia Rating Scale (BARS) After 12 Weeks of Brexpiprazole Treatment[27]

End point description:

The EPS was evaluated using BARS, consisted of items related to akathisia. The first 3 items were rated on a 4-point scale, with a score of 0 representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation was made on a 6-point scale, with 0 representing absence of symptoms and a score of 5 representing severe akathisia.

End point type	Other pre-specified

End point timeframe:

From baseline to Week 12/ET

Notes:

[27] - 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

End point values	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	139	132	
Units: Participants				
arithmetic mean (standard deviation)	-0.05 (± 0.33)	-0.01 (± 0.28)	-0.04 (± 0.26)	

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo

Statistical analysis description:

Safety set consisted of all subjects who were administered at least 1 dose of IMP.

Comparison groups	Brexpiprazole(Brex) 1mg/Day v Placebo
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.8891
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.05

Notes:

[28] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo

Statistical analysis description:

Safety set consisted of all subjects who were administered at least 1 dose of IMP.

Comparison groups	Brexpiprazole(Brex) 2mg/Day v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.4465
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.08

Notes:

[29] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported

Other pre-specified: Change From Baseline in Assessment of Suicidality Using Sheehan Suicidality Tracking Scale (Sheehan-STS) After 12 Weeks of Brexpiprazole Treatment

End point title	Change From Baseline in Assessment of Suicidality Using Sheehan Suicidality Tracking Scale (Sheehan-STS) After 12 Weeks of Brexpiprazole Treatment[30]

End point description:

The EPS was evaluated using Sheehan-STS, which was a prospective scale that assesses treatment-emergent suicidal thoughts and behaviors. Each item of the Sheehan-STS was scored on a 5-point Likert scale (0 = not at all; 1 = a little; 2 = moderate; 3 = very; and 4 = extremely).

End point type	Other pre-specified

End point timeframe:

From baseline to Week 12/ET

Notes:

[30] - 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

End point values	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	139	132	
Units: Participants				
arithmetic mean (standard deviation)	0.00 (± 0.40)	0.00 (± 0.20)	0.10 (± 0.50)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Assessment of Cognitive Function Using the Mini-mental State Examination (MMSE) After 12 Weeks of Brexpiprazole Treatment

End point title	Change From Baseline in Assessment of Cognitive Function Using the Mini-mental State Examination (MMSE) After 12 Weeks of Brexpiprazole Treatment[31]

End point description:

The safety of 2 fixed doses of brexpiprazole (1 mg/day and 2 mg/day) compared with placebo was evaluated using MMSE, which was a brief practical test for assessing cognitive dysfunction. The test consisted of 5 sections (orientation, registration, attention and calculation, recall, and language) and has a total possible score of 30.

End point type	Other pre-specified

End point timeframe:

From baseline to Week 12/ET

Notes:

[31] - 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: The analysis population consisted of modified ITT population. The modified ITT population consisted of all subjects in the randomized sample who took at least 1 dose of IMP (excluding 20 subjects randomized to Brexpiprazole 0.5 mg/day) and had a baseline and at least one post baseline evaluation for the CMAI total score.

End point values	Brexpiprazole(Brex) 1mg/Day	Brexpiprazole(Brex) 2mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	133	127	
Units: Participants				
arithmetic mean (standard deviation)	0.15 (± 1.98)	0.15 (± 2.35)	-0.14 (± 2.03)	

Statistical analyses

Statistical analysis title	Stat. comparison between Brex1mg/day and Placebo

Statistical analysis description:

Safety set consisted of all subjects who were administered at least 1 dose of IMP.

Comparison groups	Brexpiprazole(Brex) 1mg/Day v Placebo
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.7932
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.6

Notes:

[32] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported

Statistical analysis title	Stat. comparison between Brex2mg/day and Placebo
Statistical analysis description:	
Safety set consisted of all subjects who were administered at least 1 dose of IMP.	
Comparison groups	Brexpiprazole(Brex) 2mg/Day v Placebo
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.279
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.79

Notes:

[33] - No alternative hypotheses was pre-specified and only nominal exploratory comparisons are reported

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected throughout the study (Baseline to Week 12/ET)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Brexpiprazole≤1mg/Day
Reporting group description:	
All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 1 mg/day.	
Reporting group title	Brexpiprazole 2mg/Day
Reporting group description:	
All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 2 mg/day.	
Reporting group title	All Brexpiprazole
Reporting group description:	
All randomized subjects received orally brexpiprazole tablet 0.25 mg/day as a starting dose, which was up titrated to 1 to 2mg/day.	
Reporting group title	Placebo
Reporting group description:	
All randomized subjects received orally matching Placebo tablet oncedaily.	

Serious adverse events	Brexpiprazole≤1mg/Day	Brexpiprazole 2mg/Day	All Brexpiprazole
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 157 (10.19%)	13 / 140 (9.29%)	29 / 297 (9.76%)
number of deaths (all causes)	4	1	5
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella Fracture			

subjects affected / exposed	0 / 157 (0.00%)	0 / 140 (0.00%)	0 / 297 (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 / 157 (0.00%)	1 / 140 (0.71%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia Alzheimer's Type			
subjects affected / exposed	1 / 157 (0.64%)	1 / 140 (0.71%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Epilepsy			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage Intracranial			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Lacunar Infarction			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 157 (0.00%)	1 / 140 (0.71%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	0 / 157 (0.00%)	0 / 140 (0.00%)	0 / 297 (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	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	0 / 157 (0.00%)	0 / 140 (0.00%)	0 / 297 (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 / 157 (0.00%)	1 / 140 (0.71%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microcytic Anaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 140 (0.71%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	0 / 140 (0.00%)	0 / 297 (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	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
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 / 157 (0.64%)	1 / 140 (0.71%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 140 (0.71%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive Airways Disorder			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pneumonia Aspiration			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pulmonary Oedema			
subjects affected / exposed	0 / 157 (0.00%)	1 / 140 (0.71%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Abnormal Behaviour			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	2 / 157 (1.27%)	1 / 140 (0.71%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	2 / 2	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			

subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Self-Injury			
subjects affected / exposed	0 / 157 (0.00%)	0 / 140 (0.00%)	0 / 297 (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 / 157 (0.00%)	1 / 140 (0.71%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial Sepsis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 140 (0.00%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pneumonia			
subjects affected / exposed	0 / 157 (0.00%)	0 / 140 (0.00%)	0 / 297 (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 / 157 (0.00%)	4 / 140 (2.86%)	4 / 297 (1.35%)
occurrences causally related to treatment / all	0 / 0	4 / 4	4 / 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 / 136 (5.15%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus Fracture			
subjects affected / exposed	0 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Patella Fracture			
subjects affected / exposed	1 / 136 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous Thrombosis Limb			
subjects affected / exposed	0 / 136 (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 / 136 (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 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	0 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage Intracranial			
subjects affected / exposed	0 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lacunar Infarction			
subjects affected / exposed	0 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 136 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 136 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient Ischaemic Attack			
subjects affected / exposed	1 / 136 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 136 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Microcytic Anaemia				
subjects affected / exposed	0 / 136 (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 / 136 (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 / 136 (0.74%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 136 (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 / 136 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 136 (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 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia Aspiration			
subjects affected / exposed	0 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Oedema			
subjects affected / exposed	0 / 136 (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 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Agitation			
subjects affected / exposed	0 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Delusion			
subjects affected / exposed	0 / 136 (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 / 136 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic Disorder			
subjects affected / exposed	0 / 136 (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 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 136 (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 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	0 / 136 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 136 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	1 / 136 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Brexpiprazole≤1mg/Day	Brexpiprazole 2mg/Day	All Brexpiprazole
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 157 (12.74%)	29 / 140 (20.71%)	49 / 297 (16.50%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 157 (0.64%)	8 / 140 (5.71%)	9 / 297 (3.03%)
occurrences (all)	1	10	11

Headache			
subjects affected / exposed	12 / 157 (7.64%)	13 / 140 (9.29%)	25 / 297 (8.42%)
occurrences (all)	13	17	30
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 157 (4.46%)	8 / 140 (5.71%)	15 / 297 (5.05%)
occurrences (all)	10	9	19

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 136 (15.44%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 136 (2.94%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	11 / 136 (8.09%)		
occurrences (all)	16		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 136 (4.41%)		
occurrences (all)	7		

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	Protocol 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 subject 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 subjects who completed the 331-12-283 trial to enter the 331-13-211 safety trial.
07 July 2014	Protocol amendment number 3: The changes were made to address the potential issue of missing data due to subjects terminating early, as well as on the basis of adjustments considered important to ensure the safety of the subjects 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 subjects randomized. Noninstitutionalized subjects were included with revisions to criteria and assessments for subjects in this setting. The RUD scale and Mortality Assessment at Week 16 for subjects 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 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. Actigraphy was removed and eDiary was replaced with paper diaries. Revisions were made to the Schedule of Assessments to decrease subject burden.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported