

**Clinical trial results:****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 | v2 (current) |
| This version publication date | 24 December 2020 |
| First version publication date | 14 June 2018 |
| Version creation reason | |

Trial information**Trial identification**

| | |
|-----------------------|------------|
| Sponsor protocol code | 331-12-283 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01862640 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Otsuka Pharmaceutical Development & Commercialization, Inc. |
| Sponsor organisation address | 2440 Research Boulevard, Rockville, Maryland, United States, 20850 |
| Public contact | Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., 1-609 524-6788, clinicaltransparency@otsuka-us.com |
| Scientific contact | Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., 1-609 524-6788, clinicaltransparency@otsuka-us.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 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 participants with agitation associated with Alzheimer's dementia, as assessed by the Cohen-Mansfield Agitation Inventory (CMAI) after 12 weeks of treatment.

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 11 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 | Spain: 19 |
| Country: Number of subjects enrolled | Ukraine: 64 |
| Country: Number of subjects enrolled | United States: 121 |
| 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:

Participants who met all the inclusion and none of the exclusion criteria were enrolled in this study. The study was conducted in 433 participants at 81 sites in 7 countries: Croatia, Germany, Serbia, Spain, Russia, Ukraine, and the United States.

Pre-assignment

Screening details:

Participants attended a screening period ranging from 2 to 42 days. The purpose of the screening period was to determine the participant's eligibility and to washout prohibited concomitant pharmacotherapy prior to randomization.

Period 1

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

Arms

| | |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Brexpiprazole 0.5 mg/day |

Arm description:

All randomized participants received orally brexpiprazole 0.25 milligrams (mg)/day as a starting dose, which was up titrated to 0.5 mg/day. The investigational medicinal product (IMP) was administered once daily in the form of a tablet.

| | |
|--|---------------|
| 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 participants received orally a brexpiprazole 0.5 mg/day tablet.

| | |
|------------------|------------------------|
| Arm title | Brexpiprazole 1 mg/day |
|------------------|------------------------|

Arm description:

All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 1 mg/day. The IMP was administered once daily in the form of a tablet.

| | |
|--|---------------|
| 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 participants received orally a brexpiprazole 1.0 mg/day tablet.

| | |
|------------------|------------------------|
| Arm title | Brexpiprazole 2 mg/day |
|------------------|------------------------|

Arm description:

All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 2 mg/day. The IMP was administered once daily in the form of a tablet.

| | |
|----------|--------------|
| 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 participants received orally a brexpiprazole 2.0 mg/day tablet. | |
| Arm title | Placebo |

Arm description:

All randomized participants received orally brexpiprazole-matching Placebo. The Placebo was administered once daily in the form of a tablet.

| | |
|--|----------|
| 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 participants received orally a brexpiprazole-matching placebo tablet.

| Number of subjects in period 1 | Brexpiprazole 0.5 mg/day | Brexpiprazole 1 mg/day | Brexpiprazole 2 mg/day |
|---------------------------------------|--------------------------|------------------------|------------------------|
| Started | 20 | 137 | 140 |
| Completed | 13 | 121 | 122 |
| Not completed | 7 | 16 | 18 |
| Consent withdrawn by subject | 2 | 4 | 8 |
| Participant Withdrawn By Investigator | - | 1 | 1 |
| Adverse event, non-fatal | 4 | 10 | 6 |
| Protocol Deviation | - | - | 1 |
| Participant Met Withdrawal Criteria | 1 | 1 | 2 |

| Number of subjects in period 1 | Placebo |
|---------------------------------------|---------|
| Started | 136 |
| Completed | 121 |
| Not completed | 15 |
| Consent withdrawn by subject | 5 |
| Participant Withdrawn By Investigator | 1 |
| Adverse event, non-fatal | 8 |
| Protocol Deviation | - |
| Participant Met Withdrawal Criteria | 1 |

Baseline characteristics

Reporting groups

| | |
|--|--------------------------|
| Reporting group title | Brexpiprazole 0.5 mg/day |
| Reporting group description: All randomized participants received orally brexpiprazole 0.25 milligrams (mg)/day as a starting dose, which was up titrated to 0.5 mg/day. The investigational medicinal product (IMP) was administered once daily in the form of a tablet. | |
| Reporting group title | Brexpiprazole 1 mg/day |
| Reporting group description: All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 1 mg/day. The IMP was administered once daily in the form of a tablet. | |
| Reporting group title | Brexpiprazole 2 mg/day |
| Reporting group description: All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 2 mg/day. The IMP was administered once daily in the form of a tablet. | |
| Reporting group title | Placebo |
| Reporting group description: All randomized participants received orally brexpiprazole-matching Placebo. The Placebo was administered once daily in the form of a tablet. | |

| Reporting group values | Brexpiprazole 0.5 mg/day | Brexpiprazole 1 mg/day | Brexpiprazole 2 mg/day |
|------------------------|--------------------------|------------------------|------------------------|
| Number of subjects | 20 | 137 | 140 |
| Age categorical | | | |
| Units: | | | |

| | | | |
|---|-------|-------|-------|
| 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 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 1 | 2 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 2 | 5 |
| White | 20 | 134 | 133 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |

| Reporting group values | Placebo | Total | |
|------------------------|---------|-------|--|
| Number of subjects | 136 | 433 | |
| Age categorical | | | |
| Units: | | | |

| | | | |
|---|---------------|-----|--|
| Age continuous Units: years arithmetic mean standard deviation | 74.1 ± 8.0 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 70 | 239 | |
| Male | 66 | 194 | |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 1 | 4 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 5 | 12 | |
| White | 130 | 417 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 0 | 0 | |

End points

End points reporting groups

| | |
|--|--------------------------|
| Reporting group title | Brexpiprazole 0.5 mg/day |
| Reporting group description: All randomized participants received orally brexpiprazole 0.25 milligrams (mg)/day as a starting dose, which was up titrated to 0.5 mg/day. The investigational medicinal product (IMP) was administered once daily in the form of a tablet. | |
| Reporting group title | Brexpiprazole 1 mg/day |
| Reporting group description: All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 1 mg/day. The IMP was administered once daily in the form of a tablet. | |
| Reporting group title | Brexpiprazole 2 mg/day |
| Reporting group description: All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 2 mg/day. The IMP was administered once daily in the form of a tablet. | |
| Reporting group title | Placebo |
| Reporting group description: All randomized participants received orally brexpiprazole-matching Placebo. The Placebo was administered once daily in the form of a tablet. | |

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: To compare the efficacy of 2 fixed doses (1 mg/day and 2 mg/day) of brexpiprazole with placebo in participants with agitation associated with dementia of the Alzheimer's type, by the assessment of CMAI after 12 weeks of treatment. The CMAI assesses the frequency of agitated behaviors in elderly persons, such as hitting, cursing, and restlessness. It consists of 29 items all rated on a 1 to 7 scale with 1 being the "best" rating and 7 being the "worst" rating. The minimum possible CMAI total score is 29, and the maximum possible CMAI total score is 203. A decrease in score indicates improvement in symptoms. To control the overall type I error at 0.05 level when making 2 comparisons of brexpiprazole doses versus placebo, statistical testing was carried out using a hierarchical testing procedure in the order of: 1) comparison of 2 mg/day brexpiprazole versus placebo, and 2) comparison of 1 mg/day brexpiprazole versus placebo. | |
| End point type | Primary |
| End point timeframe: Baseline, 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: Quantitative statistical analysis (for example, a p-value) was performed only for the Brexpiprazole 2 mg/Day, Brexpiprazole 1 mg/Day, and Placebo reporting groups.

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

Statistical analyses

| | |
|--|--------------------------------------|
| Statistical analysis title | Brexiprazole 2 mg/Day versus Placebo |
| Statistical analysis description: Change from baseline in the CMAI Total Score after 12 weeks of brexiprazole treatment (2 mg/day) compared to 12 weeks of placebo. | |
| Comparison groups | Brexiprazole 2 mg/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 | Least square (LS) mean difference |
| Point estimate | -3.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.38 |
| upper limit | -0.17 |

| | |
|--|--------------------------------------|
| Statistical analysis title | Brexiprazole 1 mg/Day versus Placebo |
| Statistical analysis description: Change from baseline in the CMAI Total Score after 12 weeks of brexiprazole treatment (1 mg/day) compared to 12 weeks of placebo. | |
| Comparison groups | Brexiprazole 1 mg/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 | LS mean difference |
| Point estimate | 0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 3.86 |

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 Brexiprazole 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:

To compare the efficacy of 2 fixed doses (1 mg/day and 2 mg/day) of brexpiprazole with placebo in participants with agitation associated with Alzheimer's dementia, by the assessment of CGI-S score after 12 weeks of treatment. 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 participants. A decrease in score indicates improvement in symptoms.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 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: Quantitative statistical analysis (for example, a p-value) was performed only for the Brexpiprazole 2 mg/Day, Brexpiprazole 1 mg/Day, and Placebo reporting groups.

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

Statistical analyses

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | Brexpiprazole 2 mg/Day versus Placebo |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

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

| | |
|---|-------------------------------------|
| Comparison groups | Brexpiprazole 2 mg/day v Placebo |
| 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 |

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | Brexpiprazole 1 mg/Day versus Placebo |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

Change from baseline in the CGI-S Score after 12 weeks of brexpiprazole treatment (1 mg/day) compared to 12 weeks of placebo.

| | |
|---|-------------------------------------|
| Comparison groups | Brexpiprazole 1 mg/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 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected throughout the study (Baseline to Week 12/ET).

Adverse event reporting additional description:

Only participants who received at least 1 dose of study drug were analyzed for safety (Placebo N=135).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Brexiprazole 0.5 mg/day |
|-----------------------|-------------------------|

Reporting group description:

All randomized participants received orally brexpiprazole 0.25 milligrams (mg)/day as a starting dose, which was up titrated to 0.5 mg/day. The investigational medicinal product (IMP) was administered once daily in the form of a tablet.

| | |
|-----------------------|-----------------------|
| Reporting group title | Brexiprazole 1 mg/day |
|-----------------------|-----------------------|

Reporting group description:

All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 1 mg/day. The IMP was administered once daily in the form of a tablet.

| | |
|-----------------------|-----------------------|
| Reporting group title | Brexiprazole 2 mg/day |
|-----------------------|-----------------------|

Reporting group description:

All randomized participants received orally brexpiprazole 0.25 mg/day as a starting dose, which was up titrated to 2 mg/day. The IMP was administered once daily in the form of a tablet.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

All randomized participants received orally brexpiprazole-matching Placebo. The Placebo was administered once daily in the form of a tablet.

| Serious adverse events | Brexiprazole 0.5 mg/day | Brexiprazole 1 mg/day | Brexiprazole 2 mg/day |
|---|-------------------------|-----------------------|-----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 20 (25.00%) | 11 / 137 (8.03%) | 13 / 140 (9.29%) |
| number of deaths (all causes) | 2 | 2 | 1 |
| number of deaths resulting from adverse events | 2 | 2 | 1 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 137 (0.00%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus Fracture | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 137 (0.00%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Patella Fracture | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 137 (0.00%) | 0 / 140 (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 / 20 (0.00%) | 0 / 137 (0.00%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular Accident | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dementia Alzheimer's Type | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage Intracranial | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 137 (0.00%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lacunar Infarction | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychomotor Hyperactivity | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 137 (0.00%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 137 (0.00%) | 0 / 140 (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 | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient Ischaemic Attack | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 137 (0.00%) | 0 / 140 (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 / 20 (0.00%) | 0 / 137 (0.00%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Microcytic Anaemia | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 137 (0.00%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Duodenal Ulcer Haemorrhage | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 137 (0.00%) | 0 / 140 (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 | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| 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 / 20 (5.00%) | 0 / 137 (0.00%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 137 (0.00%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstructive Airways Disorder | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pneumonia Aspiration | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pulmonary Oedema | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 137 (0.00%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Abnormal Behaviour | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Agitation | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 137 (0.73%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delusion | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intentional Self-Injury | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 137 (0.00%) | 0 / 140 (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 / 20 (0.00%) | 0 / 137 (0.00%) | 1 / 140 (0.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacterial Sepsis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 137 (0.00%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium Difficile Colitis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 137 (0.00%) | 0 / 140 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 137 (0.00%) | 0 / 140 (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 / 20 (0.00%) | 0 / 137 (0.00%) | 4 / 140 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 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 / 135 (5.19%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus Fracture | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Patella Fracture | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Venous Thrombosis Limb | | | |
| subjects affected / exposed | 0 / 135 (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 / 135 (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 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage Intracranial | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lacunar Infarction | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychomotor Hyperactivity | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient Ischaemic Attack | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 135 (0.74%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Microcytic Anaemia | | | |
| subjects affected / exposed | 0 / 135 (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 / 135 (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 / 135 (0.74%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 135 (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 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 135 (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 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia Aspiration | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary Oedema | | | |
| subjects affected / exposed | 0 / 135 (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 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Delusion | | | |
| subjects affected / exposed | 0 / 135 (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 / 135 (0.74%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychotic Disorder | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 135 (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 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 135 (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 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Brexiprazole 0.5 mg/day | Brexiprazole 1 mg/day | Brexiprazole 2 mg/day |
|---|-------------------------|-----------------------|-----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 20 (55.00%) | 27 / 137 (19.71%) | 43 / 140 (30.71%) |
| Investigations | | | |
| Activated Partial Thromboplastin Time Prolonged | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 137 (0.00%) | 1 / 140 (0.71%) |
| occurrences (all) | 1 | 0 | 1 |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Aspartate Aminotransferase Increased | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Blood Alkaline Phosphatase Increased | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Blood Creatine Phosphokinase Increased | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 1 / 137 (0.73%) | 1 / 140 (0.71%) |
| occurrences (all) | 2 | 1 | 1 |
| Blood Insulin Decreased | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 137 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood Lactate Dehydrogenase Increased | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Electrocardiogram QT Prolonged | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 3 / 137 (2.19%) | 2 / 140 (1.43%) |
| occurrences (all) | 1 | 4 | 2 |
| Gamma-Glutamyltransferase Increased | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 137 (0.00%) | 0 / 140 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Protein Total Decreased | | | |

| | | | |
|--|---------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 137 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 137 (0.00%) | 3 / 140 (2.14%) |
| occurrences (all) | 1 | 0 | 3 |
| Laceration | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 137 (0.73%) | 0 / 140 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Orthostatic Hypotension | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 137 (0.00%) | 1 / 140 (0.71%) |
| occurrences (all) | 1 | 0 | 1 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 137 (0.73%) | 8 / 140 (5.71%) |
| occurrences (all) | 0 | 1 | 10 |
| Headache | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 12 / 137 (8.76%) | 13 / 140 (9.29%) |
| occurrences (all) | 0 | 13 | 17 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 137 (0.73%) | 2 / 140 (1.43%) |
| occurrences (all) | 1 | 1 | 2 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 2 / 137 (1.46%) | 3 / 140 (2.14%) |
| occurrences (all) | 2 | 2 | 3 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 137 (0.73%) | 5 / 140 (3.57%) |
| occurrences (all) | 1 | 1 | 7 |
| Salivary Hypersecretion | | | |

| | | | |
|---|---------------------|-----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 137 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 137 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 137 (0.00%) 0 | 1 / 140 (0.71%) 1 |
| Skin and subcutaneous tissue disorders Dermatitis Allergic subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 137 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Ecchymosis subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 137 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Psychiatric disorders Agitation subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 137 (1.46%) 3 | 4 / 140 (2.86%) 4 |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 7 / 137 (5.11%) 10 | 8 / 140 (5.71%) 9 |
| Paranoia subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 137 (0.00%) 0 | 0 / 140 (0.00%) 0 |
| Infections and infestations Urinary Tract Infection subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 137 (1.46%) 2 | 3 / 140 (2.14%) 3 |
| Metabolism and nutrition disorders Vitamin B12 Deficiency subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 137 (0.00%) 0 | 0 / 140 (0.00%) 0 |

| | | | |
|---|---------|--|--|
| Non-serious adverse events | Placebo | | |
| Total subjects affected by non-serious adverse events | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 29 / 135 (21.48%) | | |
| Investigations | | | |
| Activated Partial Thromboplastin Time Prolonged | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences (all) | 0 | | |
| Aspartate Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood Alkaline Phosphatase Increased | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood Creatine Phosphokinase Increased | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood Insulin Decreased | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood Lactate Dehydrogenase Increased | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences (all) | 0 | | |
| Electrocardiogram QT Prolonged | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | | |
| occurrences (all) | 1 | | |
| Gamma-Glutamyltransferase Increased | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences (all) | 0 | | |
| Protein Total Decreased | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|------------------------|--|--|
| Fall subjects affected / exposed occurrences (all) | 2 / 135 (1.48%) 2 | | |
| Laceration subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 3 / 135 (2.22%) 3 | | |
| Orthostatic Hypotension subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 4 / 135 (2.96%) 6 | | |
| Headache subjects affected / exposed occurrences (all) | 11 / 135 (8.15%) 16 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 3 / 135 (2.22%) 3 | | |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | | |
| Salivary Hypersecretion subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|----------------------|--|--|
| Cough subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | | |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | | |
| Skin and subcutaneous tissue disorders Dermatitis Allergic subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | | |
| Ecchymosis subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | | |
| Psychiatric disorders Agitation subjects affected / exposed occurrences (all) | 4 / 135 (2.96%) 4 | | |
| Insomnia subjects affected / exposed occurrences (all) | 6 / 135 (4.44%) 7 | | |
| Paranoia subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | | |
| Infections and infestations Urinary Tract Infection subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | | |
| Metabolism and nutrition disorders Vitamin B12 Deficiency subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | | |

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 | 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 participant 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 participants who completed the 331-12-283 (2013-000503-17) trial to enter the 331-13-211 (2014-000424-23) safety trial. |
| 07 July 2014 | Amendment number 3: The changes were made to address the potential issue of missing data due to participants terminating early, as well as on the basis of adjustments considered important to ensure the safety of the participants 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 participants randomized. Noninstitutionalized participants were included with revisions to criteria and assessments for participants in this setting. The RUD scale and Mortality Assessment at Week 16 for participants 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 participant 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 participant burden. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: