



Clinical trial results:

A Phase 3, 12-week, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Flexible Dosing of Brexpiprazole (OPC-34712) in the Treatment of Subjects with Agitation Associated with Dementia of the Alzheimer's Type

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-000503-17 |
| Trial protocol | GB FI SI BG |
| Global end of trial date | 30 March 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 14 June 2018 |
| First version publication date | 14 June 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | 331-12-284 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01922258 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Otsuka |
| Sponsor organisation address | 2440 Research Boulevard, 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 | 30 March 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 March 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 March 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of flexible dosing of brexpiprazole (dose range of 0.5 to 2 mg/day) with placebo in subjects with agitation associated with dementia of the Alzheimer's type, as assessed by the Cohen-Mansfield Agitation Inventory (CMAI) after 12 weeks of treatment.

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent 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 | 28 October 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Russian Federation: 52 |
| Country: Number of subjects enrolled | Canada: 13 |
| Country: Number of subjects enrolled | Ukraine: 78 |
| Country: Number of subjects enrolled | United States: 61 |
| Country: Number of subjects enrolled | Bulgaria: 48 |
| Country: Number of subjects enrolled | Finland: 1 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | Slovenia: 6 |
| Worldwide total number of subjects | 270 |
| EEA total number of subjects | 66 |

Notes:

Subjects enrolled per age group

| | |
|----------|---|
| In utero | 0 |
|----------|---|

| | |
|---|-----|
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 43 |
| From 65 to 84 years | 195 |
| 85 years and over | 32 |

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 62 sites in 9 countries: Bulgaria, Canada, Finland, France, Russia, Slovenia, Ukraine, the United Kingdom (UK), and the United States (US) and 270 participants were randomized. The date of the first ICF signed by a participant in this trial was 28 October 2013 and the date of the last trial observation was 30 March 2017.

Pre-assignment

Screening details:

The screening period ranged from 2 to 42 days (with an option to extend with approval of the medical monitor). The screening period was to determine the participant's eligibility and to washout prohibited concomitant pharmacotherapy prior to randomization.

Period 1

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

Blinding implementation details:

During the trial, investigational medicinal product (IMP) was administered in a double-blind manner so that neither the investigator nor the subject had knowledge of the treatment assignment. Treatment assignments were based on a computer-generated randomization code provided by the Biometrics Department. Sponsor personnel, including those involved in monitoring, data management, and data analysis, did not have access to the treatment code during the trial.

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Brexpiprazole |

Arm description:

Titrate up from 0.25 mg/day brexpiprazole to 1 mg/day brexpiprazole.
After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability.
Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

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

Dosage and administration details:

Titrate up from 0.25 mg/day brexpiprazole to 1 mg/day brexpiprazole.
After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability.
Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Titrate up from 0.25 mg/day placebo to 1 mg/day placebo.
After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability.
Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|----------|
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Titrate up from 0.25 mg/day placebo to 1 mg/day placebo. After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability. Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

| Number of subjects in period 1 | Brexpiprazole | Placebo |
|---------------------------------------|---------------|---------|
| Started | 133 | 137 |
| Completed | 117 | 121 |
| Not completed | 16 | 16 |
| Withdrawn by the Investigator | 1 | 4 |
| Withdrawal by participant | 5 | 5 |
| Met withdrawal criteria | - | 4 |
| Adverse event | 9 | 2 |
| Lost to follow-up | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Brexpiprazole |
|-----------------------|---------------|

Reporting group description:

Titrate up from 0.25 mg/day brexpiprazole to 1 mg/day brexpiprazole.

After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability.

Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

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

Reporting group description:

Titrate up from 0.25 mg/day placebo to 1 mg/day placebo.

After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability.

Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

| Reporting group values | Brexpiprazole | Placebo | Total |
|---|---------------|---------|-------|
| Number of subjects | 133 | 137 | 270 |
| 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 | | | |
| All participants who were randomized into this trial. Participants were considered randomized when they were assigned a treatment number by interactive voice response system (IVRS) at the end of screening period. A participant who received trial treatment outside of the IVRS was not considered randomized, but safety was reported. | | | |
| Units: years | | | |
| arithmetic mean | 73.5 | 74.0 | |
| standard deviation | ± 8.5 | ± 7.8 | - |
| Gender categorical | | | |
| All participants who were randomized into this trial. Participants were considered randomized when they were assigned a treatment number by interactive voice response system (IVRS) at the end of screening period. A participant who received trial treatment outside of the IVRS was not considered randomized, but safety was reported. | | | |
| Units: Subjects | | | |
| Female | 82 | 88 | 170 |
| Male | 51 | 49 | 100 |

End points

End points reporting groups

| | |
|--|---------------|
| Reporting group title | Brexpiprazole |
| Reporting group description: Titrate up from 0.25 mg/day brexpiprazole to 1 mg/day brexpiprazole. After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability. Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day. | |
| Reporting group title | Placebo |
| Reporting group description: Titrate up from 0.25 mg/day placebo to 1 mg/day placebo. After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability. Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day. | |

Primary: Change From Baseline to Week 12/Early Termination in the Cohen-Mansfield Agitation Inventory (CMAI) Total Score

| | |
|---|---|
| End point title | Change From Baseline to Week 12/Early Termination in the Cohen-Mansfield Agitation Inventory (CMAI) Total Score |
| End point description: The mean change from baseline (Day 0) to week 12 in the CMAI total score. Statistical comparison of interest was brexpiprazole flexible dose versus placebo, analyzed using an mixed-effect model repeated measure (MMRM) model. CMAI total score was based on adding responses (1= Never and 7= Several times in an hour) for each of the 29 agitated behaviors. | |
| End point type | Primary |
| End point timeframe: From screening to week 12/early termination. | |

| End point values | Brexpiprazole | Placebo | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 135 | | |
| Units: unit on a scale | | | | |
| least squares mean (standard error) | -18.9 (± 1.17) | -16.5 (± 1.13) | | |

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | CMAI Total Score |
| Comparison groups | Brexpiprazole v Placebo |
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1454 |
| Method | Mixed-effect model repeated |
| Parameter estimate | treatment difference |
| Point estimate | -2.34 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.49 |
| upper limit | 0.82 |

Secondary: Change in the Clinical Global Impression Severity of Illness (CGI-S) Score, as Related to Symptoms of Agitation

| | |
|-----------------|---|
| End point title | Change in the Clinical Global Impression Severity of Illness (CGI-S) Score, as Related to Symptoms of Agitation |
|-----------------|---|

End point description:

The severity of agitation for each participant was rated using the CGI-S. The investigator (or designee) answered the following question: "Considering your total clinical experience with this particular population, how mentally ill (as related to agitation) was the participant at the observation period?" Response choices were 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants. The score 0 (=not assessed) was set to missing. The CGI-S was therefore a 7-point scale (1-7). The primary analysis used a mixed-effect model repeated measure (MMRM) approach.

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

End point timeframe:

From screening to week 12/early termination.

| End point values | Brexpiprazole | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 135 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 4.54 (± 0.77) | 4.51 (± 0.74) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores : Factor 1 (Aggressive Behavior)

| | |
|-----------------|--|
| End point title | Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores : Factor 1 (Aggressive Behavior) |
|-----------------|--|

End point description:

Mean change in factor scores from baseline for 3 distinct agitation syndromes of aggressive behavior based on the CMAI subscale scores (aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior) were compared between brexpiprazole and placebo at Week 12 on a 1 to 7 scale with 1 being the "best" rating and 7 being the "worst" rating. Statistical comparison of interest was brexpiprazole flexible dose versus placebo, analyzed using an mixed-effect model repeated measure (MMRM) model.

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

End point timeframe:

From screening to week 12/early termination.

| End point values | Brexipiprazole | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 135 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 23.84 (± 9.20) | 22.22 (± 7.69) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores :Factor 2 (Physically Nonaggressive Behavior)

| | |
|-----------------|---|
| End point title | Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores :Factor 2 (Physically Nonaggressive Behavior) |
|-----------------|---|

End point description:

Mean change in factor scores from baseline for 3 distinct agitation syndromes of aggressive behavior based on the CMAI subscale scores (aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior) were compared between brexpiprazole and placebo at Week 12 on a 1 to 7 scale with 1 being the "best" rating and 7 being the "worst" rating. Statistical comparison of interest was brexpiprazole flexible dose versus placebo, analyzed using an mixed-effect model repeated measure (MMRM) model.

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

End point timeframe:

From screening to week 12/early termination

| End point values | Brexipiprazole | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 135 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 20.65 (± 7.10) | 19.72 (± 7.15) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores: Factor 3 (Verbally Agitated Behavior)

| | |
|-----------------|--|
| End point title | Summary of Mean Change From Baseline to Week 12 in Cohen-Mansfield Agitation Inventory (CMAI) Subscale Scores: Factor 3 (Verbally Agitated Behavior) |
|-----------------|--|

End point description:

Mean change in factor scores from baseline for 3 distinct agitation syndromes of aggressive behavior based on the CMAI subscale scores (aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior) were compared between brexpiprazole and placebo at Week 12 on a 1 to 7 scale with 1 being the "best" rating and 7 being the "worst" rating. Statistical comparison of interest was brexpiprazole flexible dose versus placebo, analyzed using an mixed-effect model repeated measure (MMRM) model.

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

End point timeframe:

From screening to week 12/early termination

| End point values | Brexpiprazole | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 135 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 15.40 (± 4.85) | 14.76 (± 5.50) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Summary of Mean Change From Baseline to Week 12 in Neuropsychiatric Inventory-Nursing Home (NPI-NH) 12-item

| | |
|-----------------|--|
| End point title | Secondary: Summary of Mean Change From Baseline to Week 12 in Neuropsychiatric Inventory-Nursing Home (NPI-NH) 12-item |
|-----------------|--|

End point description:

The NPI consisted of 12 items. For each item there was a screening question to determine if the behavioral change was present (rated 1) or absent (rated 0). For each item there were three scores: frequency, severity, and caregiver distress (NPI/NPI-NH) or occupational disruptiveness (NPI-NH). Frequency was rated on a 1 to 4 scale, severity was rated on a 1 to 3 scale and the caregiver distress was rated on a 0 to 5 scale. The individual item score was calculated as presence x frequency x severity and had a range from 0 to 12. If presence was zero, the individual item score and caregiver distress score were set to zero. For all items, low scores were 'better' than high scores.

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

End point timeframe:

From screening to week 12/early termination.

| End point values | Brexpiprazole | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 135 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 37.18 (± 14.10) | 34.70 (± 14.82) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Summary of Mean Change From Baseline to Week 12 in Neuropsychiatric Inventory-Nursing Home (NPI-NH) - Agitation/Aggression Score

| | |
|-----------------|---|
| End point title | Secondary: Summary of Mean Change From Baseline to Week 12 in Neuropsychiatric Inventory-Nursing Home (NPI-NH) - Agitation/Aggression Score |
|-----------------|---|

End point description:

The NPI consisted of 12 items. For each item there was a screening question to determine if the behavioral change was present (rated 1) or absent (rated 0). For each item there are three scores: frequency, severity, and caregiver distress (NPI/NPI-NH) or occupational disruptiveness (NPI-NH). Frequency was rated on a 1 to 4 scale, severity was rated on a 1 to 3 scale and the caregiver distress was rated on a 0 to 5 scale. The individual item score was calculated as presence x frequency x severity and had a range from 0 to 12. If presence was zero, the individual item score and caregiver distress score were set to zero. For all items, low scores were 'better' than high scores.

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

End point timeframe:

From screening to week 12/early termination

| End point values | Brexpiprazole | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 135 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 7.53 (± 1.89) | 7.43 (± 1.82) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Summary of Mean Change From Baseline at Week 12 in Clinical Global Impression-Improvement (CGI-I) Scale

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|-----------------|--|
| End point title | Secondary: Summary of Mean Change From Baseline at Week 12 in Clinical Global Impression-Improvement (CGI-I) Scale |
|-----------------|--|

End point description:

The efficacy of brexpiprazole in the treatment of agitation rated for each participant using the CGI-I. The investigator (or designee) rated the participant's total improvement (as related to agitation) whether or not it was due entirely to drug treatment. Response choices 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. The score 0 (=not assessed) was set to missing and that determined the scale was a 7-point scale, with 1 being very much improved and 7 being very much worse.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From week 2 to week 12/early termination | |

| End point values | Brexipiprazole | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 132 | 137 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 2.56 (\pm 0.97) | 2.94 (\pm 1.19) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Simpson-Angus Scale (SAS) Total Score

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|-----------------|--|
| End point title | Summary of Mean Change From Baseline to Week 12 in Simpson-Angus Scale (SAS) Total Score |
|-----------------|--|

End point description:

The SAS consisted of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item rated on a 5-point scale, with a score of zero representing absence of symptoms and a score of 4 representing a severe condition. The SAS total score is the sum of the scores for all 10 items.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From baseline to week 12/early termination | |

| End point values | Brexipiprazole | Placebo | | |
|--------------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 117 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 0.15 (\pm 1.67) | -0.28 (\pm 1.19) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Study Week 12 in Abnormal Involuntary Movement Scale (AIMS) Total Score

| | |
|-----------------|---|
| End point title | Summary of Mean Change From Baseline to Study Week 12 in Abnormal Involuntary Movement Scale (AIMS) Total Score |
|-----------------|---|

End point description:

The AIMS assessment consisted of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1-4), extremity movements (items 5-6), and trunk movements (item 7) observed unobtrusively while the participant was at rest and the investigator also made global judgments on the participant's dyskinesias (items 8-10). Each item was rated on a 5-point scale, with a score of zero representing absence of symptoms, and a score of 4, indicating a severe condition.

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

End point timeframe:

From baseline to week 12/early termination

| End point values | Brexpiprazole | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 114 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.03 (± 0.31) | -0.04 (± 0.56) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Double Blind Treatment Period by Study Week in Barnes Akathisia Rating Scale (BARS)

| | |
|-----------------|---|
| End point title | Summary of Mean Change From Baseline to Double Blind Treatment Period by Study Week in Barnes Akathisia Rating Scale (BARS) |
|-----------------|---|

End point description:

The BARS consisted of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the participant, subjective distress due to akathisia, and global clinical assessment of akathisia. The global clinical evaluation was made on a 6-point scale, with zero representing absence of symptoms and a score of 5 representing severe akathisia.

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

End point timeframe:

From baseline to week12/early termination

| End point values | Brexpiprazole | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 114 | 117 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 0.00 (± 0.23) | 0.00 (± 0.13) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Sheehan Suicidality Tracking Scale (Sheehan-STS) Score

| | |
|--|---|
| End point title | Summary of Mean Change From Baseline to Week 12 in Sheehan Suicidality Tracking Scale (Sheehan-STS) Score |
| End point description: Suicidality was monitored during the trial using the Sheehan-STS. The Sheehan-STS is a prospective scale that used to assess treatment emergent suicidal thoughts and behaviors. Each item of the Sheehan-STS was scored on a 5-point scale (0 = not at all; 1 = a little; 2 = moderate; 3 = very; and 4 = extremely). | |
| End point type | Secondary |
| End point timeframe: From screening to week12/early termination | |

| End point values | Brexpiprazole | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 123 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 0 (± 0) | 0 (± 0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Mean Change From Baseline to Week 12 in Mini-Mental State Examination Total Score

| | |
|--|--|
| End point title | Summary of Mean Change From Baseline to Week 12 in Mini-Mental State Examination Total Score |
| End point description: The MMSE was a brief practical test for assessing cognitive dysfunction. The test consisted of 5 sections (orientation, registration, attention and calculation, recall, and language) and had a total possible score of 30. | |
| End point type | Secondary |
| End point timeframe: From screening to week12/early termination | |

| End point values | Brexpiprazole | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 117 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.18 (± 2.02) | 0.15 (± 2.30) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through the trial: From screening to Week 12 and 30(+2) days follow-up period.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Brexpiprazole |
|-----------------------|---------------|

Reporting group description:

Titrate up from 0.25 mg/day brexpiprazole to 1 mg/day brexpiprazole.

After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability.

Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

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

Reporting group description:

Titrate up from 0.25 mg/day placebo to 1 mg/day placebo.

After achieving 1 mg/day target, dose may be increased or decreased based on efficacy and tolerability.

Allowable flexible doses will be 0.5 mg/day, 1 mg/day, or 2 mg/day.

| Serious adverse events | Brexpiprazole | Placebo | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 132 (5.30%) | 6 / 137 (4.38%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Femur Fracture | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 137 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 137 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Loss of consciousness | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 137 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 137 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 2 / 132 (1.52%) | 0 / 137 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 137 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 137 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 137 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea Exertional | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 137 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 132 (0.76%) | 1 / 137 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hip Fracture | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 137 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 137 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 137 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 137 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Brexipiprazole | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 24 / 132 (18.18%) | 29 / 137 (21.17%) | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 132 (4.55%) | 7 / 137 (5.11%) | |
| occurrences (all) | 7 | 11 | |
| Headache | | | |
| subjects affected / exposed | 10 / 132 (7.58%) | 17 / 137 (12.41%) | |
| occurrences (all) | 10 | 21 | |
| Somnolence | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 8 / 132 (6.06%) | 5 / 137 (3.65%) | |
| occurrences (all) | 10 | 5 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 16 December 2013 | The amendment changes were made on the basis of adjustments to facilitate appropriate trial implementation and communication. Revised items included increasing the number of participating sites and recruitment period, clarification on consenting requirements, clarification of certain inclusion/exclusion criteria, and updates to the prohibited medication list. The amendment also added the option for subjects who complete the 331-12-284 trial to enter the 331-13-211 observational trial. |
| 07 July 2014 | The changes were made to address the potential issue of missing data due to subjects terminating early. Noninstitutionalized subjects were allowed with revisions to criteria and assessments for subjects in this setting. The RUD scale and Mortality Assessment at Week 16 for subjects who discontinue the trial early were added. |
| 10 September 2015 | The changes reflect clarifications and changes to trial procedures intended to enhance subject safety and accuracy of data as well as streamline the inclusion/exclusion criteria. The number of trial sites as well as participating countries was increased. The power was increased from 80% to 85%, which resulted in an increase in the sample size from 230 to 260 subjects. Actigraphy was removed and eDiary was replaced with paper diaries. Revisions were made to the Schedule of Assessments to decrease subject burden. Administrative clarifications were made to enhance readability and consistency. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes: