



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 | v2 (current) |
| This version publication date | 20 November 2020 |
| First version publication date | 14 June 2018 |
| Version creation reason | |

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 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., 609 524-6788, clinicaltransparency@otsuka-us.com |
| Scientific contact | Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., 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 | 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 study was conducted in accordance with International Conference 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 | 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 | Bulgaria: 48 |
| Country: Number of subjects enrolled | Canada: 13 |
| Country: Number of subjects enrolled | Finland: 1 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Russian Federation: 52 |
| Country: Number of subjects enrolled | Slovenia: 6 |
| Country: Number of subjects enrolled | Ukraine: 78 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | United States: 61 |
| 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 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 (flexible dose range 0.5 to 2 mg/day) |

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 (flexible dose range 0.5 to 2 mg/day) |
|------------------|---|

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 (flexible dose range 0.5 to 2 mg/day) | Placebo (flexible dose range 0.5 to 2 mg/day) |
|---------------------------------------|---|---|
| Started | 133 | 137 |
| Completed | 117 | 121 |
| Not completed | 16 | 16 |
| Withdrawal By Participant | 5 | 5 |
| Adverse event, non-fatal | 9 | 2 |
| Withdrawn By The Investigator | 1 | 4 |
| Lost to follow-up | 1 | 1 |
| Met Withdrawal Criteria | - | 4 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Brexpiprazole (flexible dose range 0.5 to 2 mg/day) |
|-----------------------|---|

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 (flexible dose range 0.5 to 2 mg/day) |
|-----------------------|---|

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 (flexible dose range 0.5 to 2 mg/day) | Placebo (flexible dose range 0.5 to 2 mg/day) | Total |
|--|---|---|-------|
| Number of subjects | 133 | 137 | 270 |
| Age categorical | | | |
| Units: Subjects | | | |
| <65 years | 24 | 19 | 43 |
| >=65 <75 years | 46 | 49 | 95 |
| >=75 years | 63 | 69 | 132 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 82 | 88 | 170 |
| Male | 51 | 49 | 100 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 3 | 3 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 4 | 5 | 9 |
| White | 128 | 129 | 257 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 1 | 0 | 1 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Brexpiprazole (flexible dose range 0.5 to 2 mg/day) |
| 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 (flexible dose range 0.5 to 2 mg/day) |
| 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 CMAI is widely used in clinical research for evaluation of agitation associated with Alzheimer's dementia, with reliability and validity in both institutionalized and noninstitutionalized participants. It consists of 29 items, all rated on a 1 to 7 scale (1=Never and 7=Several times in an hour), with 1 being the "best" rating and 7 being the "worst" rating. The total score is the sum of ratings for all 29 items. The possible total scores range from 29 to 203. The total score will be unevaluable if less than 24 of the 29 items are recorded. If 24 to 28 of the 29 items are recorded, the total score will be the mean of the recorded items multiplied by 29 and rounded to the first decimal place. The mean change from baseline (Day 0) to week 12 in the CMAI total score is reported. Statistical comparison of interest was brexpiprazole flexible dose versus placebo, analyzed using a mixed-effect model repeated measure approach. A decrease in score indicates improvement in symptoms. | |
| End point type | Primary |
| End point timeframe: From screening to week 12/early termination | |

| End point values | Brexpiprazole (flexible dose range 0.5 to 2 mg/day) | Placebo (flexible dose range 0.5 to 2 mg/day) | | |
|-------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 135 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -18.9 (± 1.17) | -16.5 (± 1.13) | | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Brexpiprazole versus Placebo |
| Statistical analysis description: Change from baseline in the CMAI Total Score after 12 weeks of brexpiprazole treatment (0.5 - 2 mg/day) compared to 12 weeks of placebo. | |

| | |
|---|---|
| Comparison groups | Brexpiprazole (flexible dose range 0.5 to 2 mg/day) v Placebo (flexible dose range 0.5 to 2 mg/day) |
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1454 |
| Method | Mixed-effect model repeated measure |
| 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 approach.

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

End point timeframe:

From screening to week 12/early termination

| End point values | Brexpiprazole (flexible dose range 0.5 to 2 mg/day) | Placebo (flexible dose range 0.5 to 2 mg/day) | | |
|--------------------------------------|---|---|--|--|
| 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

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.

Adverse event reporting additional description:

Only participants who received at least 1 dose of investigational medical product were analyzed for safety (Brexpiprazole N=132).

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Brexpiprazole (flexible dose range 0.5 to 2 mg/day) |
|-----------------------|---|

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 (flexible dose range 0.5 to 2 mg/day) |
|-----------------------|---|

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 (flexible dose range 0.5 to 2 mg/day) | Placebo (flexible dose range 0.5 to 2 mg/day) | |
|---|---|---|--|
| 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 | 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 | |
| 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 | |
| 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 | | | |
| alternative dictionary used: MedDRA 19.0 | | | |
| 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 / 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 (flexible dose range 0.5 to 2 mg/day) | Placebo (flexible dose range 0.5 to 2 mg/day) | |
|---|--|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 24 / 132 (18.18%) | 29 / 137 (21.17%) | |
| Nervous system disorders | | | |
| Somnolence | | | |
| alternative dictionary used: MedDRA 19.0 | | | |
| subjects affected / exposed | 8 / 132 (6.06%) | 5 / 137 (3.65%) | |
| occurrences (all) | 10 | 5 | |
| Headache | | | |

| | | | |
|--|------------------|-------------------|--|
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 10 / 132 (7.58%) | 17 / 137 (12.41%) | |
| occurrences (all) | 10 | 21 | |
| Dizziness | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 6 / 132 (4.55%) | 7 / 137 (5.11%) | |
| occurrences (all) | 7 | 11 | |

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 (2013-000503-17) trial to enter the 331-13-211 (2014-000424-23) 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

None reported