



Clinical trial results:

A Multicenter, Open-label Trial to Evaluate the Safety and Tolerability of Brexpiprazole in the Treatment of Subjects with Bipolar I Disorder

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-002225-38 |
| Trial protocol | BG PL HR |
| Global end of trial date | 31 July 2019 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 14 August 2020 |
| First version publication date | 14 August 2020 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | 331-201-00083 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03287869 |
| 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 | 31 July 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 31 July 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the safety and tolerability of brexpiprazole in the treatment of participants with bipolar I disorder.

Protection of trial subjects:

This trial 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 countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 24 October 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 21 |
| Country: Number of subjects enrolled | Croatia: 1 |
| Country: Number of subjects enrolled | Bulgaria: 47 |
| Country: Number of subjects enrolled | Serbia: 28 |
| Country: Number of subjects enrolled | Ukraine: 82 |
| Country: Number of subjects enrolled | United States: 202 |
| Worldwide total number of subjects | 381 |
| 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) | 379 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included participants who completed 3-week double-blind treatment in studies 331-201-00080 (NCT03259555)/331-201-00081 (NCT03257865) and, who in the investigator's judgment, could potentially benefit to receive brexpiprazole in this study. Data were summarized per treatment received in prior studies.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

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

Arm description:

Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received brexpiprazole in the double-blind treatment period in previous studies were included in this group.

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

Dosage and administration details:

Brexpiprazole 2 mg/day from Days 1 to 3, followed by titration to 3 mg/day on Day 4, dose was titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4.

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

Arm description:

Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received placebo in the double-blind treatment period in previous studies were included in this group.

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

Dosage and administration details:

Brexpiprazole 2 mg/day from Days 1 to 3, followed by titration to 3 mg/day on Day 4, dose was titrated

(or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4.

| Number of subjects in period 1 | Prior Brexpiprazole | Prior Placebo |
|---------------------------------------|---------------------|---------------|
| Started | 188 | 193 |
| Analyzed For Safety | 184 | 184 |
| Completed | 105 | 100 |
| Not completed | 83 | 93 |
| Consent withdrawn by subject | 36 | 43 |
| Physician decision | 5 | 5 |
| Reason no Specified | 6 | - |
| Adverse event, non-fatal | 14 | 12 |
| Progressive Disease | 1 | - |
| Non-Compliance With Study Drug | 5 | 9 |
| Lost to follow-up | 13 | 19 |
| Early Closure of the Site | - | 1 |
| Reason not Specified | - | 3 |
| Lack of efficacy | 1 | - |
| Protocol deviation | 2 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Overall Study (overall period) |
|-----------------------|--------------------------------|

Reporting group description: -

| Reporting group values | Overall Study (overall period) | Total | |
|---|-----------------------------------|-------|--|
| Number of subjects | 381 | 381 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 379 | 379 | |
| From 65-84 years | 2 | 2 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 45.8 | | |
| standard deviation | ± 11.2 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 189 | 189 | |
| Male | 192 | 192 | |
| Race | | | |
| Units: Subjects | | | |
| White | 275 | 275 | |
| Black or African American | 99 | 99 | |
| American Indian or Alaska Native | 3 | 3 | |
| Asian | 2 | 2 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Other | 2 | 2 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 45 | 45 | |
| Not Hispanic or Latino | 334 | 334 | |
| Other | 2 | 2 | |

End points

End points reporting groups

| | |
|---|---------------------|
| Reporting group title | Prior Brexpiprazole |
| Reporting group description: | |
| Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received brexpiprazole in the double-blind treatment period in previous studies were included in this group. | |
| Reporting group title | Prior Placebo |
| Reporting group description: | |
| Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received placebo in the double-blind treatment period in previous studies were included in this group. | |

Primary: Number of Participants With at Least one Treatment Emergent Adverse Event (TEAE) by Severity

| | |
|--|---|
| End point title | Number of Participants With at Least one Treatment Emergent Adverse Event (TEAE) by Severity ^[1] |
| End point description: | |
| An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. AEs severity were graded on a 3-point scale as: 1 = mild; discomfort noticed, but no disruption to daily activity, 2 = moderate; discomfort sufficient to reduce or affect normal daily activity, and 3 = severe; inability to work or perform normal daily activity. Safety Sample included all participants who received at least 1 dose of IMP (brexpiprazole). | |
| End point type | Primary |
| End point timeframe: | |
| From Day 1 (after dosing) through 29 weeks (26 weeks treatment, 3 weeks safety follow-up) | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Inferential statistical analysis was not performed for the safety endpoint. Descriptive statistics are included (number of participants).

| End point values | Prior Brexpiprazole | Prior Placebo | | |
|-----------------------------|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 184 | 184 | | |
| Units: participants | | | | |
| TEAE, Any grade | 79 | 86 | | |
| TEAE, Mild | 60 | 68 | | |
| TEAE, Moderate | 31 | 29 | | |
| TEAE, Severe | 8 | 5 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 26 plus 3 weeks (21 days) follow-up period (Up to 29 weeks)

Adverse event reporting additional description:

Safety Sample included all participants who received at least 1 dose of Investigational medicinal product (IMP-brexpiprazole).

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received brexpiprazole in the double-blind treatment period in previous studies were included in this group.

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

Reporting group description:

Brexpiprazole was administered in participants orally with flexible dosing from 2 mg/day from Days 1 to 3 regardless of treatment assignment in the previous double-blind trial, followed by titration to 3 mg/day on Day 4. Participants may have been titrated (or re-titrated) to a higher dose of brexpiprazole, up to a maximum of 4 mg/day, based on treatment response and at the investigator's discretion anytime at Day 7 or thereafter. Participants who were unable to tolerate their current dose could have been titrated down to a minimum of 2 mg/day any time after Day 4. Participants who received placebo in the double-blind treatment period in previous studies were included in this group.

| Serious adverse events | Prior Brexpiprazole | Prior Placebo | |
|---|---------------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 184 (5.98%) | 8 / 184 (4.35%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 0 / 184 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Migraine | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 184 (0.00%) | 1 / 184 (0.54%) | |
| 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 | | | |
| Chest Pain | | | |
| subjects affected / exposed | 0 / 184 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo Positional | | | |
| subjects affected / exposed | 0 / 184 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Upper Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 1 / 184 (0.54%) | 0 / 184 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Bipolar Disorder | | | |
| subjects affected / exposed | 0 / 184 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 3 / 184 (1.63%) | 2 / 184 (1.09%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mania | | | |
| subjects affected / exposed | 5 / 184 (2.72%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal Behaviour | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 184 (0.54%) | 0 / 184 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal Ideation | | | |
| subjects affected / exposed | 0 / 184 (0.00%) | 1 / 184 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 184 (0.54%) | 0 / 184 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Prior Brexpiprazole | Prior Placebo | |
|---|---------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 184 (7.07%) | 26 / 184 (14.13%) | |
| Nervous system disorders | | | |
| Akathisia | | | |
| subjects affected / exposed | 8 / 184 (4.35%) | 17 / 184 (9.24%) | |
| occurrences (all) | 9 | 17 | |
| Headache | | | |
| subjects affected / exposed | 5 / 184 (2.72%) | 10 / 184 (5.43%) | |
| occurrences (all) | 5 | 12 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 20 October 2017 | The following updates were made as per Amendment 1 - <ul style="list-style-type: none">•Added information on self-reported participants daily sleep diary.•Removed language indicating a confirmation of data download from the wearable device was performed.•Removed laboratory tests for adrenocorticotrophic hormone and cortisol.•Allowed anticholinergics and propranolol with daily limits.•Updated the way pregnancy was reported in Section 5 "Reporting of Adverse Events".•Updated the Young-Mania Rating Scale (YMRS) version cited in the protocol.•Updated the version of the Clinical Global Impressions – Bipolar Scale in the appendix to alternate version and added clarifying details on administration of this assessment.•Updated the Simpson-Angus Scale (SAS)/ Abnormal Involuntary Movement Scale (AIMS)/ Barnes Akathisia Rating Scale (BARS) scales in the appendix to match the licensed versions. |

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.

As predefined in the protocol, there were no primary or secondary efficacy endpoints in this trial.

Notes: