

**Clinical trial results:****A Multicenter, Randomized, Double-blind Trial of Brexpiprazole versus Placebo for the Acute Treatment Manic Episodes, With or Without Mixed Features, Associated With Bipolar I Disorder****Summary**

| | |
|--------------------------|-----------------|
| EudraCT number | 2017-002190-20 |
| Trial protocol | HR |
| Global end of trial date | 22 January 2019 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 29 February 2020 |
| First version publication date | 29 December 2019 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Update for alignment with revised clinicaltrials.gov results posting |

Trial information**Trial identification**

| | |
|-----------------------|---------------|
| Sponsor protocol code | 331-201-00081 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03257865 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Otsuka Pharmaceutical Development & Commercialization, Inc. |
| Sponsor organisation address | 2440 Research Boulevard, Rockville, MD, 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 | 10 September 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 22 January 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 January 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of brexpiprazole for the acute treatment of manic episodes, with or without mixed features, in participants with a diagnosis of 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 country or countries in which the trial was conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 19 September 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 | Croatia: 1 |
| Country: Number of subjects enrolled | Ukraine: 93 |
| Country: Number of subjects enrolled | United States: 239 |
| Worldwide total number of subjects | 333 |
| EEA total number of subjects | 1 |

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) | 333 |
| From 65 to 84 years | 0 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The trial population consisted of adult participants (18 to 65 years) diagnosed with bipolar I disorder displaying an acute manic episode with or without mixed features requiring hospitalization. One participant randomized to brexpiprazole was not treated and excluded from the safety analysis set.

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 | Investigator, Subject |

Blinding implementation details:

Treatment assignments were based on a computer-generated randomization code. 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:

Brexpiprazole was administered orally with flexible dosing from 2 to 4 milligram (mg)/day; titrated to a maximum of 4 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:

Starting dose of 2 mg/day; titrated to a maximum of 4 mg/day. Adjustments could be made to dosing. Treatment duration was 3 weeks.

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

Arm description:

Matching placebo was administered orally in the same way as brexpiprazole to maintain the blind.

| | |
|--|----------|
| 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:

Tablet taken daily for 3 weeks.

| Number of subjects in period 1 | Brexpiprazole | Placebo |
|--|---------------|---------|
| Started | 163 | 170 |
| Received at least 1 dose of study drug | 162 | 170 |
| Completed | 128 | 135 |
| Not completed | 35 | 35 |
| Consent withdrawn by subject | 23 | 17 |
| Physician decision | 3 | 1 |
| Adverse event, non-fatal | 4 | 8 |
| Other | - | 1 |
| Non-Compliance With Study Drug | - | 2 |
| Lost to follow-up | 4 | 4 |
| Lack of efficacy | 1 | 2 |

Baseline characteristics

Reporting groups

| | |
|---|---------------|
| Reporting group title | Brexpiprazole |
| Reporting group description: Brexpiprazole was administered orally with flexible dosing from 2 to 4 milligram (mg)/day; titrated to a maximum of 4 mg/day. | |
| Reporting group title | Placebo |
| Reporting group description: Matching placebo was administered orally in the same way as brexpiprazole to maintain the blind. | |

| Reporting group values | Brexpiprazole | Placebo | Total |
|---------------------------|---------------|---------|-------|
| Number of subjects | 163 | 170 | 333 |
| Age categorical Units: | | | |

| | | | |
|---|----------------|----------------|-----|
| Age continuous Units: Years arithmetic mean standard deviation | 44.6 ± 10.7 | 44.3 ± 12.0 | - |
| Gender categorical Units: Subjects | | | |
| Female | 85 | 82 | 167 |
| Male | 78 | 88 | 166 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 90 | 102 | 192 |
| Black or African American | 70 | 67 | 137 |
| American Indian or Alaska Native | 1 | 0 | 1 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Other Race | 2 | 1 | 3 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Hispanic or Latino | 22 | 17 | 39 |
| Not Hispanic or Latino | 140 | 153 | 293 |
| Other Ethnicity | 1 | 0 | 1 |

End points

End points reporting groups

| | |
|---|---------------|
| Reporting group title | Brexpiprazole |
| Reporting group description: | |
| Brexpiprazole was administered orally with flexible dosing from 2 to 4 milligram (mg)/day; titrated to a maximum of 4 mg/day. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo was administered orally in the same way as brexpiprazole to maintain the blind. | |

Primary: Change From Baseline In Young-Mania Rating Scale (YMRS) Score At Week 3

| | |
|--|---|
| End point title | Change From Baseline In Young-Mania Rating Scale (YMRS) Score At Week 3 |
| End point description: | |
| The YMRS was utilized to assess a participant's level of manic symptoms. It consists of 11 items: 1) elevated mood, 2) increased motor activity-energy, 3) sexual interest, 4) sleep, 5) irritability, 6) speech (rate and amount), 7) language-thought disorder, 8) content, 9) disruptive-aggressive behavior, 10) appearance, and 11) insight. Seven items are rated on a 0- to 4-scale, while four items (Items 5, 6, 8, and 9) are rated on a 0- to 8-scale with 0, 2, 4, 6, and 8 being the possible scores (twice the weight of the other items). For all items, 0 is the "best" rating and the highest score (4 or 8) is the 'worst' rating. The YMRS total score is the sum of ratings for all 11 items; therefore, possible total scores range from 0 to 60, with higher scores signifying more severe manic symptoms. Comparison between treatment groups was carried out using mixed-effect model repeated measure (MMRM). | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 3 | |

| End point values | Brexpiprazole | Placebo | | |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 ^[1] | 133 ^[2] | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -12.3 (± 0.73) | -10.7 (± 0.71) | | |

Notes:

[1] - Participants who had analyzable data at the specified timepoint.

[2] - Participants who had analyzable data at the specified timepoint.

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Treatment Difference in YMRS |
| Comparison groups | Brexpiprazole v Placebo |
| Number of subjects included in analysis | 261 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1011 |
| Method | mixed-effect model repeated measure |
| Parameter estimate | Treatment difference |
| Point estimate | -1.62 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.56 |
| upper limit | 0.32 |

Secondary: Change From Baseline In Clinical Global Impression-Bipolar (CGI-BP) Severity Score In Mania At Week 3

| | |
|-----------------|---|
| End point title | Change From Baseline In Clinical Global Impression-Bipolar (CGI-BP) Severity Score In Mania At Week 3 |
|-----------------|---|

End point description:

The CGI-BP scale refers to the global impression of the participant with respect to bipolar disorder. The scale rates the participant's severity of illness (CGI-BP severity of illness: mania, depression, and overall bipolar illness) based on a 7-point scale: 1 = normal, not at all ill, 2 = minimally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = very severely ill.

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

End point timeframe:

Baseline, Week 3

| End point values | Brexpiprazole | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 ^[3] | 133 ^[4] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -1.31 (± 1.22) | -1.06 (± 1.09) | | |

Notes:

[3] - Participants who had analyzable data at the specified timepoint.

[4] - Participants who had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 (after dosing) through 6 weeks (3 weeks treatment, 3 weeks safety follow-up).

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Brexpiprazole was administered orally with flexible dosing from 2 to 4 milligram (mg)/day; titrated to a maximum of 4 mg/day.

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

Reporting group description:

Matching placebo was administered orally in the same way as brexpiprazole to maintain the blind.

| Serious adverse events | Brexpiprazole | Placebo | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | 3 / 170 (1.76%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | 1 / 170 (0.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Mania | | | |
| subjects affected / exposed | 0 / 162 (0.00%) | 2 / 170 (1.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | Brexpiprazole | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 32 / 162 (19.75%) | 28 / 170 (16.47%) | |
| Nervous system disorders | | | |
| Akathisia | | | |
| subjects affected / exposed | 13 / 162 (8.02%) | 4 / 170 (2.35%) | |
| occurrences (all) | 14 | 4 | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 162 (3.09%) | 1 / 170 (0.59%) | |
| occurrences (all) | 5 | 1 | |
| Headache | | | |
| subjects affected / exposed | 10 / 162 (6.17%) | 18 / 170 (10.59%) | |
| occurrences (all) | 12 | 19 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 6 / 162 (3.70%) | 5 / 170 (2.94%) | |
| occurrences (all) | 6 | 5 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 162 (1.23%) | 7 / 170 (4.12%) | |
| occurrences (all) | 2 | 8 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 5 / 162 (3.09%) | 2 / 170 (1.18%) | |
| occurrences (all) | 6 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 21 December 2017 | <ul style="list-style-type: none">• Remove an incorrect exclusion criteria of $\geq 30\%$ decrease in YMRS between screening and baseline• Add clarifying details on administration of the Clinical Global Impressions – Bipolar Scale assessment• Add information on retesting participants with elevated lithium, valproate, or carbamazepine at screening• Add information on use of anticholinergics• Update the efficacy scales in the appendices to match the licensed versions currently available |

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.

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|------|
| None |
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Notes: