# EU Clinical Trials Register

## Clinical trial results:
## A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Three Fixed Doses of OPC-34712 in the Treatment of Adults With Acute Schizophrenia

### Summary

| | |
|---|---|
| EudraCT number | 2011-002538-38 |
| Trial protocol | LV PL |
| Global end of trial date | 05 December 2013 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 02 July 2016 |
| First version publication date | 02 July 2016 |

### Trial information

#### Trial identification

| | |
|---|---|
| Sponsor protocol code | 331-10-231 |

#### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01396421 |
| 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 | Mary Hobart, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 240-683-3194, Mary.Hobart@otsuka-us.com |
| Scientific contact | Mary Hobart, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 240-683-3194, Mary.Hobart@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 | 16 May 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 December 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 December 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To compare the efficacy, safety and tolerability of each of three fixed doses of OPC-34712 with placebo in the treatment of acute schizophrenia in adults.

Protection of trial subjects:

This trial was conducted in compliance with the protocol, International Conference on Harmonization (ICH) Good Clinical Practice (GCP), and applicable local laws and regulatory requirements of the countries in which the trial was conducted, copies of the protocol, amendments, and informed consent form (ICF) were reviewed and approved by the governing institutional review board (IRB) or independent ethics committee (IEC) for each investigational site or country, as appropriate, prior to trial start or prior to implementation of the amendment at that site or country.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 August 2011 |
| 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 | Canada: 7 |
| Country: Number of subjects enrolled | Japan: 19 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 15 |
| Country: Number of subjects enrolled | Latvia: 31 |
| Country: Number of subjects enrolled | Malaysia: 21 |
| Country: Number of subjects enrolled | Poland: 16 |
| Country: Number of subjects enrolled | Romania: 109 |
| Country: Number of subjects enrolled | Serbia: 75 |
| Country: Number of subjects enrolled | Ukraine: 115 |
| Country: Number of subjects enrolled | United States: 228 |
| Worldwide total number of subjects | 636 |
| EEA total number of subjects | 156 |

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) | 634 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

# Subject disposition

## Recruitment

Recruitment details:

The trial was conducted in 636 participants from 65 trial sites in 10 countries.

## Pre-assignment

Screening details:

Participants entered a pre-treatment screening phase of up to 14 days before enrollment to assess eligibility criteria and to washout from prior antipsychotic medications and other prohibited concomitant medications, followed by a 6-week double blinded treatment phase.

## Period 1

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

Blinding implementation details:

Sponsor personnel, including those involved in monitoring, data management, and data analysis, did not have access to the treatment code during the trial. Access to the treatment codes was to have been restricted to personnel charged with generating and maintaining randomization files, packaging study medication, operating the interactive voice response system (IVRS)/ interactive web response system (IWRS), and reporting serious treatment-emergent adverse event (TEAEs) to regulatory agencies.

## Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | Brexpiprazole 4 mg |

Arm description:

Brexpiprazole 4 milligram (mg) tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 1-week period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose the day after the Week 1 visit (ie, the beginning of Week 2).

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

Dosage and administration details:

Brexpiprazole 4mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 1-week period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose the day after the Week 1 visit (ie, the beginning of Week 2).

| **Arm title** | Brexpiprazole 2mg |
|---|---|

Arm description:

Brexpiprazole 2mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 5 day period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose by Day 5.

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

Dosage and administration details:

Brexpiprazole 2mg tablet once daily for 6 weeks. Participants were titrated to the target dose of

brexpiprazole over a 5 day period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose by Day 5.

| Arm title | Brexpiprazole 0.25mg |
|---|---|
| Arm description: | |
| Brexpiprazole 0.25mg tablet once daily for 6 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | Brexpiprazole |
| Investigational medicinal product code | OPC-34712 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Brexpiprazole 0.25mg tablet once daily for 6 weeks. | |
| Arm title | Placebo |
| Arm description: | |
| Placebo tablet once daily for 6 weeks. | |
| 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: | |
| Placebo tablet once daily for 6 weeks. | |

| Number of subjects in period 1 | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg |
|---|---|---|---|
| Started | 180 | 182 | 90 |
| Completed | 121 | 124 | 56 |
| Not completed | 59 | 58 | 34 |
| Physician decision | 1 | 1 | - |
| Consent withdrawn by subject | 31 | 24 | 13 |
| Adverse event | 17 | 15 | 12 |
| Lost to follow-up | - | - | - |
| Participant met withdrawal criteria | 1 | - | 1 |
| Protocol deviation | 2 | 1 | 1 |
| Lack of efficacy | 7 | 17 | 7 |

| Number of subjects in period 1 | Placebo |
|---|---|
| Started | 184 |
| Completed | 109 |
| Not completed | 75 |

| | |
|---|---|
| Physician decision | 3 |
| Consent withdrawn by subject | 21 |
| Adverse event | 32 |
| Lost to follow-up | 1 |
| Participant met withdrawal criteria | - |
| Protocol deviation | - |
| Lack of efficacy | 18 |

## Baseline characteristics

### Reporting groups

| | |
|---|---|
| Reporting group title | Brexpiprazole 4 mg |
| Reporting group description: | |

Brexpiprazole 4 milligram (mg) tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 1-week period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose the day after the Week 1 visit (ie, the beginning of Week 2).

| | |
|---|---|
| Reporting group title | Brexpiprazole 2mg |
| Reporting group description: | |

Brexpiprazole 2mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 5 day period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose by Day 5.

| | |
|---|---|
| Reporting group title | Brexpiprazole 0.25mg |
| Reporting group description: | |

Brexpiprazole 0.25mg tablet once daily for 6 weeks.

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |

Placebo tablet once daily for 6 weeks.

| Reporting group values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg |
|---|---|---|---|
| Number of subjects | 180 | 182 | 90 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 180 | 181 | 89 |
| From 65-84 years | 0 | 1 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 40.8 | 39.6 | 40.5 |
| standard deviation | ± 11 | ± 10.2 | ± 11.4 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 69 | 71 | 29 |
| Male | 111 | 111 | 61 |

| Reporting group values | Placebo | Total | |
|---|---|---|---|
| Number of subjects | 184 | 636 | |
| 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) | 184 | 634 | |
| From 65-84 years | 0 | 2 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 39.7 | | |
| standard deviation | ± 10.8 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 66 | 235 | |
| Male | 118 | 401 | |

# End points

## End points reporting groups

| Reporting group title | Brexpiprazole 4 mg |
|---|---|

Reporting group description:

Brexpiprazole 4 milligram (mg) tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 1-week period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose the day after the Week 1 visit (ie, the beginning of Week 2).

| Reporting group title | Brexpiprazole 2mg |
|---|---|

Reporting group description:

Brexpiprazole 2mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 5 day period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose by Day 5.

| Reporting group title | Brexpiprazole 0.25mg |
|---|---|

Reporting group description:

Brexpiprazole 0.25mg tablet once daily for 6 weeks.

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

Reporting group description:

Placebo tablet once daily for 6 weeks.

## Primary: Mean change from Baseline to Week 6 Positive and Negative Syndrome Scale (PANSS) total score.

| End point title | Mean change from Baseline to Week 6 Positive and Negative Syndrome Scale (PANSS) total score. |
|---|---|

End point description:

The PANSS consists of 3 subscales (positive subscale, negative subscale and general psychopathology subscale) containing a total of 30 symptom constructs and was administered using the Structured Clinical Interview (SCI)-PANSS. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The PANSS total score ranged from 30 (best possible outcome) to 210 (worst possible outcome). Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline to Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 180 | 87 | 178 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -19.65 (± 1.54) | -20.73 (± 1.55) | -14.9 (± 2.23) | -12.01 (± 1.6) |

## Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 at Week 6 |
|---|---|

Statistical analysis description:

Difference between the average effect of brexpiprazole 2 and 4 mg/day and placebo was tested first at alpha level of 0.05. If statistically significant, then comparisons for each group (brexpiprazole 2 and 4 mg/day) versus placebo were performed at a significance level of 0.05. With fixed effect of treatment, (pooled) clinical center, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariates.

| Comparison groups | Brexpiprazole 4 mg v Brexpiprazole 2mg v Placebo |
|---|---|
| Number of subjects included in analysis | 536 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -8.18 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -12 |
|     upper limit | -4.4 |

| **Statistical analysis title** | Statistical analysis 2 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The primary efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 4 mg |
|---|---|
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0006 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -7.64 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -12 |
|     upper limit | -3.3 |

| **Statistical analysis title** | Statistical analysis 3 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The primary efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 2mg |
|---|---|
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate |  Treatment difference |
| Point estimate | -8.72 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -13.1 |
|     upper limit | -4.37 |

| **Statistical analysis title** | Statistical analysis 4 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The primary efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 0.25mg |
|---|---|
| Number of subjects included in analysis | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.291 |
| Method | Mixed models analysis |
| Parameter estimate |  Treatment difference |
| Point estimate | -2.89 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -8.27 |
|     upper limit | 2.49 |

## Secondary: Mean change from Baseline to Week 6 in Clinical Global Impression - Severity of Illness scale (CGI-S) score.

| End point title | Mean change from Baseline to Week 6 in Clinical Global Impression - Severity of Illness scale (CGI-S) score. |
|---|---|

End point description:

This is the key secondary endpoint. The severity of illness was rated using the CGI-S. To perform this assessment, the rater or study physician answered the following question: "Considering your total clinical experience with this particular population, how mentally ill is the participant at this time?" Response choices included: 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 participant. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 124, 56 and 109 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

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

End point timeframe:

Baseline to Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 181 | 89 | 178 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -1.2 (± 0.08) | -1.15 (± 0.08) | -0.85 (± 0.12) | -0.82 (± 0.09) |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 6 |
|---|---|

Statistical analysis description:

The analysis of the key secondary endpoint was conducted if both comparisons of brexpiprazole 2 mg/day versus placebo and brexpiprazole 4 mg/day versus placebo of the primary endpoint were statistically significant under the procedure described for the primary efficacy analysis. With fixed effect of treatment, (pooled) clinical center, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariates.

| Comparison groups | Brexpiprazole 4 mg v Brexpiprazole 2mg v Placebo |
|---|---|
| Number of subjects included in analysis | 537 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0006 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.36 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -0.56 |
|     upper limit | -0.15 |

| Statistical analysis title | Statistical analysis 2 at Week 6 |
|---|---|

Statistical analysis description:

The analysis of the key secondary endpoint was conducted if both comparisons of brexpiprazole 2 mg/day versus placebo and brexpiprazole 4 mg/day versus placebo of the primary endpoint were statistically significant under the procedure described for the primary efficacy analysis. With fixed effect of treatment, (pooled) clinical center, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariates.

| Comparison groups | Brexpiprazole 4 mg v Placebo |
|---|---|

| Number of subjects included in analysis | 356 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0012 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.38 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -0.61 |
|     upper limit | -0.15 |

| **Statistical analysis title** | Statistical analysis 3 at Week 6 |
|---|---|

Statistical analysis description:

The analysis of the key secondary endpoint was conducted if both comparisons of brexpiprazole 2 mg/day versus placebo and brexpiprazole 4 mg/day versus placebo of the primary endpoint were statistically significant under the procedure described for the primary efficacy analysis. With fixed effect of treatment, (pooled) clinical center, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariates.

| Comparison groups | Placebo v Brexpiprazole 2mg |
|---|---|
| Number of subjects included in analysis | 359 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0056 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.33 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -0.56 |
|     upper limit | -0.1 |

| **Statistical analysis title** | Statistical analysis 4 at Week 6 |
|---|---|

Statistical analysis description:

The analysis of the key secondary endpoint was conducted if both comparisons of brexpiprazole 2 mg/day versus placebo and brexpiprazole 4 mg/day versus placebo of the primary endpoint were statistically significant under the procedure described for the primary efficacy analysis. With fixed effect of treatment, (pooled) clinical center, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariates.

| Comparison groups | Placebo v Brexpiprazole 0.25mg |
|---|---|
| Number of subjects included in analysis | 267 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8491 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.03 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.31 |
| upper limit | 0.26 |

## Secondary: Mean change from Baseline to Week 6 in Personal and Social Performance Scale (PSP)

| End point title | Mean change from Baseline to Week 6 in Personal and Social Performance Scale (PSP) |
|---|---|

End point description:

The PSP is a clinician-rated scale that measures personal and social functioning in 4 domains: socially useful activities (eg, work and study), personal and social relationships, self-care, and disturbing and aggressive behaviors. Impairment in each of these domains was rated as absent, mild, manifest, marked, severe, or very severe. These ratings were then converted to a total score based on a 100-point scale using algorithms to identify the appropriate 10-point interval, and the rater's judgment to determine the total score within the 10-point interval. Participants with a PSP total score of 71 to 100 were considered to have mild functional difficulty. Scores of 31 to 70 represented manifest disabilities of various degrees and ratings of 1 to 30 indicated minimal functioning that required intense support and/or supervision. Efficacy: consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation.

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

End point timeframe:

Baseline to Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 168 | 173 | 86 | 170 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 12.72 (± 0.93) | 13.15 (± 0.93) | 11.84 (± 1.33) | 10.26 (± 0.98) |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Brexpiprazole 4 mg v Placebo |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 338 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0557 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | 2.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.06 |
| upper limit | 4.98 |

| | |
|---|---|
| **Statistical analysis title** | Statistical analysis 2 at Week 6 |

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| | |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2mg |
| Number of subjects included in analysis | 343 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.025 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | 2.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 5.42 |

| | |
|---|---|
| **Statistical analysis title** | Statistical analysis 3 at Week 6 |

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| | |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 0.25mg |
| Number of subjects included in analysis | 256 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3264 [1] |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | 1.58 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.58 |
| upper limit | 4.74 |

Notes:

[1] - With fixed effect of treatment, (pooled) clinical center, visit, treatment visit interaction, baseline value, baseline visit interaction as covariates.

## Secondary: Mean change from Baseline to Week 6 in PANSS Positive Subscale score

| End point title | Mean change from Baseline to Week 6 in PANSS Positive Subscale score |
|---|---|

End point description:

For each symptom construct of the PANSS Positive Subscale, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The symptom constructs were as follows: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. The PANSS total score ranged from 30 (best possible outcome) to 210 (worst possible outcome). Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

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

End point timeframe:

Baseline to Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 180 | 87 | 180 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -6.78 (± 0.51) | -6.57 (± 0.52) | -5.46 (± 0.74) | -4.35 (± 0.54) |

## Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Brexpiprazole 4 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -2.44 |

| Confidence interval | |
| --- | --- |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.88 |
| upper limit | -0.99 |

| **Statistical analysis title** | Statistical analysis 2 at Week 6 |
| --- | --- |

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 2mg |
| --- | --- |
| Number of subjects included in analysis | 360 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0029 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -2.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.67 |
| upper limit | -0.77 |

| **Statistical analysis title** | Statistical analysis 3 at Week 6 |
| --- | --- |

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 0.25mg |
| --- | --- |
| Number of subjects included in analysis | 267 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2227 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.9 |
| upper limit | -0.68 |

## Secondary: Mean change from Baseline to Week 6 in PANSS Negative Subscale score

| End point title | Mean change from Baseline to Week 6 in PANSS Negative Subscale score |
|---|---|

End point description:

For each symptom construct of the PANSS Negative Subscale, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The symptom constructs were as follows: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. The PANSS total score ranged from 30 (best possible outcome) to 210 (worst possible outcome). Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

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

End point timeframe:

Baseline to Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 180 | 87 | 178 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -3.65 (± 0.36) | -4.02 (± 0.36) | -3.31 (± 0.53) | -2.24 (± 0.38) |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Brexpiprazole 4 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0069 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.41 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -2.44 |
|     upper limit | 0.39 |

| Statistical analysis title | Statistical analysis 2 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Brexpiprazole 2mg v Placebo |
|---|---|
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0007 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.81 |
| upper limit | -0.76 |

| Statistical analysis title | Statistical analysis 3 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 0.25mg |
|---|---|
| Number of subjects included in analysis | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0996 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.33 |
| upper limit | 0.2 |

## Secondary: Clinical Global Impression- Improvement scale (CGI-I) score at Week 6

| End point title | Clinical Global Impression- Improvement scale (CGI-I) score at Week 6 |
|---|---|

End point description:

The participant's overall improvement was rated using the CGI-I. The rater or study physician rated the participant's total improvement whether or not it was due entirely to drug treatment. All responses were compared with the participant's condition at screening/baseline. 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. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation.

| End point type | Secondary |
|---|---|
| End point timeframe: | |
| Week 6 | |

| **End point values** | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 181 | 89 | 178 |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 2.94 (± 1.29) | 2.94 (± 1.34) | 3.37 (± 1.46) | 3.48 (± 1.47) |

## Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 at Week 6 |
|---|---|
| Statistical analysis description: | |
| The same analysis model as described for the primary analysis was applied. | |
| Comparison groups | Brexpiprazole 4 mg v Placebo |
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0004 [2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.77 |
| upper limit | -0.22 |

Notes:

[2] - The CMH row mean scores differ test controlling for trial center was applied to CGI-I score.

| **Statistical analysis title** | Statistical analysis 2 at Week 6 |
|---|---|
| Statistical analysis description: | |
| The same analysis model as described for the primary analysis was applied. | |
| Comparison groups | Placebo v Brexpiprazole 2mg |

| | |
|---|---|
| Number of subjects included in analysis | 359 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0004 [3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment difference |
| Point estimate | -0.54 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -0.82 |
|     upper limit | -0.26 |

Notes:

[3] - The CMH row mean scores differ test controlling for trial center was applied to CGI-I score.

| | |
|---|---|
| **Statistical analysis title** | Statistical analysis 3 at Week 6 |

Statistical analysis description:

The same analysis model as described for the primary analysis was applied.

| | |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 0.25mg |
| Number of subjects included in analysis | 267 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4505 [4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment difference |
| Point estimate | -0.14 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -0.5 |
|     upper limit | 0.22 |

Notes:

[4] - The CMH row mean scores differ test controlling for trial center was applied to CGI-I score.

## Secondary: Response rate at Week 6

| | |
|---|---|
| End point title | Response rate at Week 6 |

End point description:

Response rate was defined as improvement in mean change of ≥30% from baseline in PANSS Total Score at Week 6 or CGI-I score of 1 (very much improved) or 2 (much improved) at Week 6. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation.

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

End point timeframe:

Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 180 | 87 | 178 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 46.07 | 47.78 | 39.08 | 30.34 |

### Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 4 mg |
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0032 [5] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Point estimate | 1.48 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 1.14 |
|     upper limit | 1.91 |

Notes:

[5] - CMH general association test controlling for trial was applied to the analysis of response rate.

| Statistical analysis title | Statistical analysis 2 at Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2mg |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0004 [6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Point estimate | 1.59 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 1.23 |
|     upper limit | 2.05 |

Notes:

[6] - CMH general association test controlling for trial was applied to the analysis of response rate.

| Statistical analysis title | Statistical analysis 3 at Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 0.25mg |

| | |
|---|---|
| Number of subjects included in analysis | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1576 [7] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Point estimate | 1.27 |
| Confidence interval | |
|    level | 95 % |
|    sides | 2-sided |
|    lower limit | 0.92 |
|    upper limit | 1.76 |

Notes:

[7] - CMH general association test controlling for trial was applied to the analysis of response rate.

## Secondary: Mean change from Baseline to Week 6 in PANSS Excited Component (PEC) score

| | |
|---|---|
| End point title | Mean change from Baseline to Week 6 in PANSS Excited Component (PEC) score |

End point description:

The PEC consists of 5 PANSS items (excitement [P4], hostility [P7], tension [G4], uncooperativeness [G8], and poor impulse control [G14]). Each rated on a scale of 1 (absent) to 7 (extreme). The PEC for participants was calculated as the sum of the rating assigned to each of the 5 items, and ranged from 5 to 35 with a higher score indicating greater severity of symptoms. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

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

End point timeframe:

Baseline to Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 180 | 87 | 178 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -2.75 (± 0.34) | -2.87 (± 0.34) | -1.99 (± 0.49) | -1.64 (± 0.36) |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| | |
|---|---|
| Comparison groups | Brexpiprazole 0.25mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5706 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.34 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -1.53 |
|     upper limit | 0.85 |

| | |
|---|---|
| **Statistical analysis title** | Statistical analysis 2 at Week 6 |

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| | |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2mg |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0131 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.22 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -2.19 |
|     upper limit | -0.26 |

| | |
|---|---|
| **Statistical analysis title** | Statistical analysis 3 at Week 6 |

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| | |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 4 mg |
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0246 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.1 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.06 |
| upper limit | -0.14 |

## Secondary: Discontinuation rate for lack of efficacy at Week 6

| End point title | Discontinuation rate for lack of efficacy at Week 6 |
|---|---|

End point description:

Discontinuation rate for lack of efficacy during the trial at Week 6 is reported below. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation.

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

End point timeframe:

Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 180 | 87 | 178 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 3.93 | 9.44 | 8.05 | 10.11 |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 6 |
|---|---|
| Comparison groups | Brexpiprazole 4 mg v Placebo |
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0143 [8] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.18 |
| upper limit | 0.85 |

Notes:

[8] - CMH general association test controlling for trial center was applied to the analysis of discontinuation rate.

| Statistical analysis title | Statistical analysis 2 at Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2mg |

| Number of subjects included in analysis | 358 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6606 [9] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Point estimate | 0.87 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 0.46 |
|     upper limit | 1.65 |

Notes:

[9] - CMH general association test controlling for trial center was applied to the analysis of discontinuation rate.

| Statistical analysis title | Statistical analysis 3 at Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 0.25mg |
| Number of subjects included in analysis | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5115 [10] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Point estimate | 0.77 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 0.35 |
|     upper limit | 1.68 |

Notes:

[10] - CMH general association test controlling for trial center was applied to the analysis of discontinuation rate.

**Secondary: Change from Baseline to Week 6 in PANSS Marder Factor score - Positive Symptoms Score**

| End point title | Change from Baseline to Week 6 in PANSS Marder Factor score - Positive Symptoms Score |
|---|---|

End point description:

The PANSS Marder Factor score - Positive Symptoms Score consists of 8 PANSS items (delusions [P1], hallucinatory behaviour [P3], grandiosity [P5], suspiciousness [P6], stereotyped thinking [N7], somatic concern [G1], unusual thought content [G9], lack of judgment and insight [G10]. Each was rated on a scale of 1 (absent) to 7 (extreme). The PANSS Marder Factor score - Positive Symptoms Score for participants was calculated as the sum of the rating assigned to each of the 8 items, and ranged from 8 to 42 with a higher score indicating greater severity of symptoms. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

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

End point timeframe:

Baseline to Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 180 | 87 | 178 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -7.23 (± 0.51) | -7.37 (± 0.51) | -5.78 (± 0.73) | -4.89 (± 0.53) |

**Statistical analyses**

| Statistical analysis title | Statistical analysis 1 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Brexpiprazole 4 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0014 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -2.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.77 |
| upper limit | -0.91 |

| Statistical analysis title | Statistical analysis 2 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 2mg |
|---|---|
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0008 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -2.47 |

| Confidence interval | |
| --- | --- |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.91 |
| upper limit | -1.04 |

| **Statistical analysis title** | Statistical analysis 3 at Week 6 |
| --- | --- |

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 0.25mg |
| --- | --- |
| Number of subjects included in analysis | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3263 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.66 |
| upper limit | 0.89 |

## Secondary: Change from Baseline to Week 6 in PANSS Marder Factor score - Negative Symptoms Score

| End point title | Change from Baseline to Week 6 in PANSS Marder Factor score - Negative Symptoms Score |
| --- | --- |

End point description:

The PANSS Marder Factor score - Negative Symptoms Score consists of 7 PANSS items (blunted effect [N1], emotional withdrawal [N2], poor rapport [N3], passive/apathetic social withdrawal [N4], lack of spontaneity and conversation flow [N6], motor retardation [G7], active social avoidance [G16]). The PANSS Marder Factor score - Negative Symptoms Score for participants was calculated as the sum of the rating assigned to each of the 7 items, and ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

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

End point timeframe:

Baseline to Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 180 | 87 | 178 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -4.1 (± 0.37) | -4.48 (± 0.37) | -3.66 (± 0.54) | -2.8 (± 0.39) |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 6 |
|---|---|
| Statistical analysis description: | |

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 4 mg |
|---|---|
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0155 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.35 |
| upper limit | -0.25 |

| Statistical analysis title | Statistical analysis 2 at Week 6 |
|---|---|
| Statistical analysis description: | |

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 2mg |
|---|---|
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0019 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.68 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.73 |
| upper limit | -0.62 |

| **Statistical analysis title** | Statistical analysis 3 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 0.25mg |
|---|---|
| Number of subjects included in analysis | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1956 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.17 |
| upper limit | -0.44 |

### Secondary: Change from Baseline to Week 6 in PANSS Marder Disorganised Thought Score

| End point title | Change from Baseline to Week 6 in PANSS Marder Disorganised Thought Score |
|---|---|

End point description:

The PANSS Marder Factor score -Disorganized Thought Score consists of 7 PANSS items (conceptual disorganization [P2], difficulty in abstract thinking [N5], mannerisms and posturing [G5], disorientation [G10], poor attention [G11], disturbance of violation [G13], preoccupation [G15]). The PANSS Marder Factor score - Disorganized Thought Score for participants was calculated as the sum of the rating assigned to each of the 7 items, and ranged from 7 to 49 with a higher score indicating greater severity of symptoms. Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brexpiprazole 4mg, Brexpiprazole 2mg, Brexpiprazole 0.25 mg and placebo group, respectively had data.

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

End point timeframe:

Baseline to Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 180 | 87 | 180 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -3.72 (± 0.36) | -3.94 (± 0.36) | -2.69 (± 0.52) | -1.97 (± 0.37) |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Brexpiprazole 4 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0007 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.76 |
| upper limit | -0.75 |

| Statistical analysis title | Statistical analysis 2 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 2mg |
|---|---|
| Number of subjects included in analysis | 360 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.98 |

| Confidence interval | |
| --- | --- |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.98 |
| upper limit | -0.97 |

| **Statistical analysis title** | Statistical analysis 3 at Week 6 |
| --- | --- |

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 0.25mg |
| --- | --- |
| Number of subjects included in analysis | 267 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2572 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.96 |
| upper limit | 0.52 |

## Secondary: Change from Baseline to Week 6 in PANSS Marder Uncontrolled Hostility/Excitement Score

| End point title | Change from Baseline to Week 6 in PANSS Marder Uncontrolled Hostility/Excitement Score |
| --- | --- |

End point description:

The PANSS Marder Factor score - Uncontrolled Hostility/Excitement Score consists of 4 PANSS items (excitement [P4], hostility [P7], uncooperativeness [G8], poor impulse control [G14]). The PANSS Marder Factor score - Uncontrolled Hostility/Excitement Score for participants was calculated as the sum of the rating assigned to each of the 4 items, and ranged from 4 to 28 with a higher score indicating greater severity of symptoms. Efficacy: consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brex 4mg, Brex 2mg, Brex 0.25 mg and placebo group, respectively had data.

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

End point timeframe:

Baseline to Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 180 | 87 | 178 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -1.9 (± 0.28) | -1.91 (± 0.28) | -1.15 (± 0.41) | -0.82 (± 0.3) |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Brexpiprazole 4 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0085 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.87 |
| upper limit | -0.28 |

| Statistical analysis title | Statistical analysis 2 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Brexpiprazole 2mg v Placebo |
|---|---|
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0081 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.08 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.88 |
| upper limit | -0.28 |

| **Statistical analysis title** | Statistical analysis 3 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 0.25mg |
|---|---|
| Number of subjects included in analysis | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5172 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.31 |
| upper limit | 0.66 |

## Secondary: Change from Baseline to Week 6 in PANSS Marder Anxiety Depression Score

| End point title | Change from Baseline to Week 6 in PANSS Marder Anxiety Depression Score |
|---|---|

End point description:

The PANSS Marder Factor score - Anxiety/Depression Score consists of 4 PANSS items (anxiety [G2], guilt feelings [G3], tension [G4], depression [G6]). The PANSS Marder Factor score - Anxiety/Depression Score for participants was calculated as the sum of the rating assigned to each of the 4 items, and ranged from 4 to 28 with a higher score indicating greater severity of symptoms. Efficacy: consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. At Week 6, 121, 123, 56 and 108 participants in the Brex 4mg, Brex 2mg, Brex 0.25 mg and placebo group, respectively had data.

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

End point timeframe:

Baseline to Week 6

| End point values | Brexpiprazole 4 mg | Brexpiprazole 2mg | Brexpiprazole 0.25mg | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 178 | 180 | 87 | 178 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -3.4 (± 0.25) | -3.7 (± 0.25) | -3.27 (± 0.35) | -3.05 (± 0.26) |

## Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Brexpiprazole 4 mg v Placebo |
|---|---|
| Number of subjects included in analysis | 356 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3284 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.34 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -1.03 |
|     upper limit | 0.35 |

| Statistical analysis title | Statistical analysis 2 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| Comparison groups | Placebo v Brexpiprazole 2mg |
|---|---|
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0655 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.65 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.34 |
| upper limit | 0.04 |

| **Statistical analysis title** | Statistical analysis 3 at Week 6 |
|---|---|

Statistical analysis description:

Efficacy dataset consists of all participants who received at least one dose of study medication and have baseline and at least one post-baseline efficacy evaluation. The efficacy endpoint was analyzed using a mixed model repeated measures (MMRM) analysis. The model included treatment, visit, site, and treatment interacting with visit as fixed effects and the covariate baseline PANSS Total Score and its interaction with visit.

| | |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 0.25mg |
| Number of subjects included in analysis | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6251 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.07 |
| upper limit | 0.64 |

# Adverse events

## Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time the participant signs the informed consent form until 30 days after the last dose of study medication.

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

## Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 16.0 |

## Reporting groups

| Reporting group title | Brexpiprazole 4mg |
|---|---|

Reporting group description:

Brexpiprazole 4mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 1-week period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose the day after the Week 1 visit (ie, the beginning of Week 2).

| Reporting group title | Brexpiprazole 2 mg |
|---|---|

Reporting group description:

Brexpiprazole 2mg tablet once daily for 6 weeks. Participants were titrated to the target dose of brexpiprazole over a 5-day period beginning at the randomization (Day 1), and all participants were to have achieved the assigned dose by Day 5.

| Reporting group title | Brexpiprazole 0.25 mg |
|---|---|

Reporting group description:

Brexpiprazole 0.25mg tablet once daily for 6 weeks.

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

Reporting group description:

Placebo tablet once daily for 6 weeks.

| Serious adverse events | Brexpiprazole 4mg | Brexpiprazole 2 mg | Brexpiprazole 0.25 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 180 (1.11%) | 4 / 182 (2.20%) | 4 / 90 (4.44%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 0 / 182 (0.00%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Grand mal convulsion | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 0 / 182 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Gastrointestinal disorders | | | |
|---|---|---|---|
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 0 / 182 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 182 (0.55%) | 1 / 90 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Schizophrenia | | | |
| subjects affected / exposed | 2 / 180 (1.11%) | 2 / 182 (1.10%) | 2 / 90 (2.22%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Schizophrenia, paranoid type | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 0 / 182 (0.00%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 180 (0.00%) | 1 / 182 (0.55%) | 0 / 90 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Placebo | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 184 (3.80%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 184 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |

| Grand mal convulsion | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 184 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| **Gastrointestinal disorders** | | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 184 (0.54%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| **Psychiatric disorders** | | | |
| Psychotic disorder | | | |
| subjects affected / exposed | 2 / 184 (1.09%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Schizophrenia | | | |
| subjects affected / exposed | 2 / 184 (1.09%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Schizophrenia, paranoid type | | | |
| subjects affected / exposed | 1 / 184 (0.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| **Musculoskeletal and connective tissue disorders** | | | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 184 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Brexpiprazole 4mg | Brexpiprazole 2 mg | Brexpiprazole 0.25 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 64 / 180 (35.56%) | 53 / 182 (29.12%) | 25 / 90 (27.78%) |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Akathisia | | | |
| subjects affected / exposed | 13 / 180 (7.22%) | 8 / 182 (4.40%) | 0 / 90 (0.00%) |
| occurrences (all) | 14 | 8 | 0 |
| Headache | | | |
| subjects affected / exposed | 22 / 180 (12.22%) | 17 / 182 (9.34%) | 9 / 90 (10.00%) |
| occurrences (all) | 28 | 18 | 10 |
| **Gastrointestinal disorders** | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 180 (3.89%) | 3 / 182 (1.65%) | 5 / 90 (5.56%) |
| occurrences (all) | 8 | 3 | 5 |
| Nausea | | | |
| subjects affected / exposed | 6 / 180 (3.33%) | 10 / 182 (5.49%) | 1 / 90 (1.11%) |
| occurrences (all) | 6 | 10 | 1 |
| **Psychiatric disorders** | | | |
| Agitation | | | |
| subjects affected / exposed | 13 / 180 (7.22%) | 11 / 182 (6.04%) | 4 / 90 (4.44%) |
| occurrences (all) | 15 | 15 | 5 |
| Insomnia | | | |
| subjects affected / exposed | 15 / 180 (8.33%) | 16 / 182 (8.79%) | 8 / 90 (8.89%) |
| occurrences (all) | 17 | 20 | 10 |
| Schizophrenia | | | |
| subjects affected / exposed | 10 / 180 (5.56%) | 7 / 182 (3.85%) | 6 / 90 (6.67%) |
| occurrences (all) | 11 | 7 | 8 |

| **Non-serious adverse events** | Placebo | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 65 / 184 (35.33%) | | |
| Nervous system disorders | | | |
| Akathisia | | | |
| subjects affected / exposed | 4 / 184 (2.17%) | | |
| occurrences (all) | 4 | | |
| Headache | | | |
| subjects affected / exposed | 15 / 184 (8.15%) | | |
| occurrences (all) | 19 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 184 (1.63%) | | |
| occurrences (all) | 4 | | |
| Nausea | | | |
| subjects affected / exposed | 8 / 184 (4.35%) | | |
| occurrences (all) | 9 | | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 19 / 184 (10.33%) | | |
| occurrences (all) | 23 | | |
| Insomnia | | | |
| subjects affected / exposed | 18 / 184 (9.78%) | | |
| occurrences (all) | 20 | | |
| Schizophrenia | | | |
| subjects affected / exposed | 18 / 184 (9.78%) | | |
| occurrences (all) | 18 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  Yes

| Date | Amendment |
|---|---|
| 02 July 2012 | A formal amendment to the original protocol was done to change the primary efficacy analysis used from an Analysis of Covariance (ANCOVA) model based on the LOCF dataset. The MMRM model was included as a sensitivity analysis. Based on regulatory feedback, the MMRM approach was the primary analysis method, with the ANCOVA LOCF used as the sensitivity analysis. Clarified that every effort was made to complete efficacy scales prior to administering rescue medication at the last trial (or early termination) visit and that efficacy scales were not done if a new antipsychotic was given before the scales were completed. Clarified that participants may remain on stable doses of propranolol during the trial if the propranolol was being taken for an indication other than akathisia. Updated wording of select standard exclusion criteria for consistency with other protocols in the brexpiprazole clinical program. Clarified instructions for preparation of whole blood sample for metabolic profiling.  Clarified that participants who were sterile (ie, women who have had an oophorectomy and/or hysterectomy or have been postmenopausal for at least 12 consecutive months; or men who have had orchidectomy) were not required to use two different methods of birth control and add "other approved birth control device" to the list of acceptable birth control methods. Added change from Baseline in PANSS Excited Component and PANSS Marder Factor scores as secondary efficacy variables. Revised Appendix 9 to include the correct version of the PANSS (ie, 2006). The 2006 version of the PANSS was the version that was distributed to the sites at the start of the trial and has been used by raters throughout the trial. In addition, administrative changes were made and typographical errors identified during review of the protocol amendment were corrected. |
| 05 December 2013 | The second formal amendment to the original protocol was to change the statistical method for controlling multiplicity from the Hochberg procedure to the family-wise error rate. The actual protocol amendment was dated 20-Dec-2013 which was after the trial completed but before database lock. |

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial?  No

### Limitations and caveats

 None reported