# Clinical trial results:
# A Phase 3, 12-Week, Multicenter, Randomized, Double-blind, Placebo controlled, 2 Arm, Fixed-dose Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) in the Treatment of Subjects With Agitation Associated With Dementia of the Alzheimer's Type

## Summary

| | |
|---|---|
| EudraCT number | 2017-003940-19 |
| Trial protocol | BG ES HU SK |
| Global end of trial date | 01 June 2022 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 30 September 2023 |
| First version publication date | 30 September 2023 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 331-14-213 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03548584 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Otsuka Pharmaceutical Development & Commercialization, Inc. |
| Sponsor organisation address | 2440 Research Blvd, Rockville, Maryland, United States, 20850 |
| Public contact | Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 609 524-6788, clinicaltransparency@otsuka-us.com |
| Scientific contact | Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 609 524-6788, clinicaltransparency@otsuka-us.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 01 June 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 01 June 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

This study compares the efficacy of 2 doses of brexpiprazole with placebo in subjects with agitation associated with dementia of the Alzheimer's type.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 16 May 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Slovakia: 13 |
| Country: Number of subjects enrolled | Spain: 11 |
| Country: Number of subjects enrolled | Bulgaria: 37 |
| Country: Number of subjects enrolled | Hungary: 6 |
| Country: Number of subjects enrolled | Serbia: 19 |
| Country: Number of subjects enrolled | Ukraine: 107 |
| Country: Number of subjects enrolled | United States: 152 |
| Worldwide total number of subjects | 345 |
| EEA total number of subjects | 67 |

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) | 37 |
| From 65 to 84 years | 283 |
| 85 years and over | 25 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 345 subjects were randomised, and participated in the study from 16 May 2018 to 1 June 2022.

### Pre-assignment

Screening details:

The enrolled subjects were randomised to, brexpiprazole or placebo group in a ratio of 2:1. Within the brexpiprazole arm group, subjects were further randomised in a 1:2 ratio to 2 milligrams per day (mg/day) or 3 mg/day.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Brexpiprazole 2 mg |

Arm description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 2 mg/day from Day 15. Subjects continued to receive brexpiprazole 2 milligrams (mg), once daily until Week 12.

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

Dosage and administration details:

Brexpiprazole was administered orally in gradually increasing doses starting from 0.5 mg/day to 2 mg/day from Day 15. Brexpiprazole 2 mg was then given once daily until Week 12.

| | |
|---|---|
| **Arm title** | Brexpiprazole 3 mg |

Arm description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 3 mg/day from Day 29. Subjects continued to receive brexpiprazole 3 mg, once daily until Week 12.

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

Dosage and administration details:

Brexpiprazole was administered orally in gradually increasing doses starting from 0.5 mg/day in the starting to 3 mg/day from Day 29. Brexpiprazole 3 mg was then given, once daily until Week 12.

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

Arm description:

Subjects received matching placebo, once daily for 12 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:

Matching placebo, once daily for 12 weeks.

| **Number of subjects in period 1** | Brexpiprazole 2 mg | Brexpiprazole 3 mg | Placebo |
|---|---|---|---|
| Started | 75 | 153 | 117 |
| Intent-to-treat Population | 73 | 153 | 116 |
| Completed | 68 | 130 | 104 |
| Not completed | 7 | 23 | 13 |
| Reason not specified (unrelated to COVID-19) | - | 2 | 2 |
| Site terminated by sponsor | 1 | 3 | 2 |
| Adverse event | 1 | 11 | 5 |
| Non-compliance with study drug | - | 1 | - |
| Lost to follow-up | - | - | 1 |
| Subject withdrew consent to participate | 5 | 5 | 3 |
| Lack of efficacy | - | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Brexpiprazole 2 mg |
| Reporting group description: | |
| Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 2 mg/day from Day 15. Subjects continued to receive brexpiprazole 2 milligrams (mg), once daily until Week 12. | |
| Reporting group title | Brexpiprazole 3 mg |
| Reporting group description: | |
| Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 3 mg/day from Day 29. Subjects continued to receive brexpiprazole 3 mg, once daily until Week 12. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received matching placebo, once daily for 12 weeks. | |

| Reporting group values | Brexpiprazole 2 mg | Brexpiprazole 3 mg | Placebo |
|---|---|---|---|
| Number of subjects | 75 | 153 | 117 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 74.3 | 74.6 | 73.0 |
| standard deviation | ± 7.3 | ± 8.0 | ± 7.0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 43 | 92 | 60 |
| Male | 32 | 61 | 57 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 25 | 46 | 37 |
| Not Hispanic or Latino | 50 | 107 | 80 |
| Race<br>Units: Subjects | | | |
| Asian | 0 | 3 | 1 |
| Black or African American | 5 | 6 | 1 |
| White | 70 | 144 | 115 |
| Cohen-Mansfield Agitation Inventory (CMAI) Total Score | | | |
| The CMAI assesses frequency of agitated behaviours in elderly persons. The scale consists of 29 agitated behaviours that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation. Each of the agitated behaviours are scored 1 (never) to 7 (several times an hours), with the total scale score ranging from 29 to 203. Higher score indicates greater frequency of agitated behaviour. | | | |
| Units: score on a scale | | | |
| arithmetic mean | 78.6 | 81.2 | 79.4 |
| standard deviation | ± 15.5 | ± 17.2 | ± 17.6 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 345 | | |

| | | | |
|---|---|---|---|
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 195 | | |
| Male | 150 | | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 108 | | |
| Not Hispanic or Latino | 237 | | |
| Race<br>Units: Subjects | | | |
| Asian | 4 | | |
| Black or African American | 12 | | |
| White | 329 | | |
| Cohen-Mansfield Agitation Inventory (CMAI) Total Score | | | |
| The CMAI assesses frequency of agitated behaviours in elderly persons. The scale consists of 29 agitated behaviours that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation. Each of the agitated behaviours are scored 1 (never) to 7 (several times an hours), with the total scale score ranging from 29 to 203. Higher score indicates greater frequency of agitated behaviour. | | | |
| Units: score on a scale<br>arithmetic mean<br>standard deviation | <br><br>- | | |

## End points

### End points reporting groups

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

Reporting group description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 2 mg/day from Day 15. Subjects continued to receive brexpiprazole 2 milligrams (mg), once daily until Week 12.

| | |
|---|---|
| Reporting group title | Brexpiprazole 3 mg |

Reporting group description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 3 mg/day from Day 29. Subjects continued to receive brexpiprazole 3 mg, once daily until Week 12.

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

Reporting group description:

Subjects received matching placebo, once daily for 12 weeks.

| | |
|---|---|
| Subject analysis set title | Brexpiprazole 2 and 3 mg |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 2 mg/day from Day 15 or from 0.5 mg/day in the starting to 3 mg/day from Day 29.
Subjects continued to receive brexpiprazole 2 or 3 mg, once daily until Week 12.

### Primary: Change From Baseline to Week 12 in the CMAI Total Score

| | |
|---|---|
| End point title | Change From Baseline to Week 12 in the CMAI Total Score[1] |

End point description:

The CMAI score is used to assess the frequency of manifestations of agitated behaviours in subjects. The CMAI consists of 29 agitated behaviours, rated on a 7-point scale of frequency across four subscales of aggressive behaviour, physically nonaggressive behaviour, verbally agitated behaviour and hiding and hoarding ranging from 1=never to 7=several times an hour. The CMAI total score ranges from 29 to 203. Higher scores indicate worsening of the condition. A negative change from baseline indicates improvement. Mixed model repeated measures (MMRM) was used for the analysis. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of investigational medical product (IMP) and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses.

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

End point timeframe:

Baseline and Week 12

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

| End point values | Placebo | Brexpiprazole 2 and 3 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 116 | 225 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -17.3 (± 1.44) | -22.6 (± 1.08) | | |

## Statistical analyses

| Statistical analysis title | Change From Baseline in the CMAI Total Score |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | = 0.0026 [3] |
| Method | MMRM |
| Parameter estimate | Least Squares (LS) Mean Difference |
| Point estimate | -5.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.77 |
| upper limit | -1.87 |

Notes:

[2] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[3] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

## Secondary: Change From Baseline to Week 12 in the Clinical Global Impression Severity of Illness (CGI-S) Score, as Related to Agitation

| End point title | Change From Baseline to Week 12 in the Clinical Global Impression Severity of Illness (CGI-S) Score, as Related to Agitation[4] |
|---|---|

End point description:

CGI-S was used to rate the severity of agitation. The score ranges from 0 to 7 with response choices as, 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 subjects. The higher the value, the more severe the agitation. A negative change from baseline indicates improvement. MMRM was used for the analysis. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses.

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

End point timeframe:

Baseline and Week 12

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

| End point values | Placebo | Brexpiprazole 2 and 3 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 116 | 225 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -0.93 (± 0.08) | -1.20 (± 0.06) | | |

## Statistical analyses

| Statistical analysis title | Change From Baseline to Week 12 in the CGI-S Score |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |

| | |
|---|---|
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[5] |
| P-value | = 0.0078 [6] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.47 |
| upper limit | -0.07 |

Notes:

[5] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[6] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

## Secondary: Change From Baseline to Week 12 in CMAI Subscale Scores

| | |
|---|---|
| End point title | Change From Baseline to Week 12 in CMAI Subscale Scores[7] |

End point description:

The CMAI score is used to assess the frequency of manifestations of agitated behaviours in subjects. The CMAI consists of 29 agitated behaviours that are rated on a 7-point scale of frequency across four subscales of aggressive behaviour, physically nonaggressive behaviour, verbally agitated behaviour and hiding and hoarding as: 1=never; 2=less than once a week; 3=once or twice a week; 4=several times a week; 5=once or twice a day; 6=several times a day; 7=several times an hour. Higher scores indicate worsening of the condition. A negative change from baseline indicates improvement. MMRM was used for the analysis. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses.

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

End point timeframe:

Baseline and Week 12

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

| End point values | Placebo | Brexpiprazole 2 and 3 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 116 | 225 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Aggressive Behaviour | -7.13 (± 0.56) | -9.09 (± 0.42) | | |
| Physically Nonaggressive Behaviour | -5.04 (± 0.53) | -6.45 (± 0.40) | | |
| Verbally Agitated Behaviour | -3.14 (± 0.40) | -4.39 (± 0.31) | | |
| Hiding and Hoarding | -1.14 (± 0.23) | -1.50 (± 0.17) | | |

## Statistical analyses

| **Statistical analysis title** | Change From Baseline in CMAI Subscale Scores |
|---|---|
| Statistical analysis description: | |
| Aggressive Behaviour | |
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[8] |
| P-value | = 0.004 [9] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.28 |
| upper limit | -0.63 |

Notes:

[8] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[9] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CMAI Subscale Scores |
|---|---|
| Statistical analysis description: | |
| Physically Nonaggressive Behaviour | |
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[10] |
| P-value | = 0.0296 [11] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.68 |
| upper limit | -0.14 |

Notes:

[10] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[11] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CMAI Subscale Scores |
|---|---|
| Statistical analysis description: | |
| Verbally Agitated Behaviour | |
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |

| | |
|---|---|
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[12] |
| P-value | = 0.0113 [13] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.21 |
| upper limit | -0.28 |

Notes:

[12] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[13] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CMAI Subscale Scores |
|---|---|

Statistical analysis description:

Hiding and Hoarding

| | |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[14] |
| P-value | = 0.1941 [15] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.18 |

Notes:

[14] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[15] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

## Secondary: Change From Baseline in CMAI Total Score for Each Trial Visit During the Double-blind Treatment Period

| End point title | Change From Baseline in CMAI Total Score for Each Trial Visit During the Double-blind Treatment Period[16] |
|---|---|

End point description:

The CMAI score is used to assess the frequency of manifestations of agitated behaviours in subjects. The CMAI consists of 29 agitated behaviours, rated on a 7-point scale of frequency across four subscales of aggressive behaviour, physically nonaggressive behaviour, verbally agitated behaviour and hiding and hoarding ranging from 1=never to 7=several times an hour. The CMAI total score ranges from 29 to 203. Higher scores indicate worsening of the condition. A negative change from baseline indicates improvement. MMRM was used for the analysis. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses.

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

End point timeframe:

Baseline, Weeks 2, 4, 6, 8, 10, and 12

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the Statistical Analysis Plan (SAP), data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

| **End point values** | Placebo | Brexpiprazole 2 and 3 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 116 | 225 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Change From Baseline at Week 2 | -6.61 (± 0.90) | -5.76 (± 0.71) | | |
| Change From Baseline at Week 4 | -11.0 (± 1.06) | -12.1 (± 0.82) | | |
| Change From Baseline at Week 6 | -13.9 (± 1.19) | -16.2 (± 0.91) | | |
| Change From Baseline at Week 8 | -14.4 (± 1.28) | -19.4 (± 0.96) | | |
| Change From Baseline at Week 10 | -15.7 (± 1.29) | -22.2 (± 0.97) | | |
| Change From Baseline at Week 12 | -17.3 (± 1.44) | -22.6 (± 1.08) | | |

## Statistical analyses

| **Statistical analysis title** | Change From Baseline in CMAI Total Score - Week 2 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[17] |
| P-value | = 0.4242 [18] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.24 |
| upper limit | 2.93 |

Notes:

[17] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[18] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CMAI Total Score - Week 4 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |

| | |
|---|---|
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[19] |
| P-value | = 0.3665 [20] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.63 |
| upper limit | 1.34 |

Notes:

[19] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[20] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CMAI Total Score - Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[21] |
| P-value | = 0.1065 [22] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.15 |
| upper limit | 0.5 |

Notes:

[21] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[22] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CMAI Total Score - Week 8 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[23] |
| P-value | = 0.0011 [24] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -5.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.12 |
| upper limit | -2.05 |

Notes:

[23] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[24] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CMAI Total Score - Week 10 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[25] |
| P-value | < 0.0001 [26] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -6.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.54 |
| upper limit | -3.4 |

Notes:

[25] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[26] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CMAI Total Score - Week 12 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[27] |
| P-value | = 0.0026 [28] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -5.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.77 |
| upper limit | -1.87 |

Notes:

[27] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[28] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

## Secondary: Change From Baseline in CGI-S for Each Trial Visit During the Double-Blind Treatment Period

| End point title | Change From Baseline in CGI-S for Each Trial Visit During the Double-Blind Treatment Period[29] |
|---|---|

End point description:

CGI-S was used to rate the severity of agitation. The score ranges from 0 to 7 with response choices as, 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 subjects. The higher the value, the more severe the agitation. A negative change from baseline indicates improvement. MMRM was used for the analysis. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score.

Number of subjects analysed is the number of subjects with data available for analyses.

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

End point timeframe:

Baseline, Weeks 2, 4, 6, 8, 10, and 12

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

| **End point values** | Placebo | Brexpiprazole 2 and 3 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 116 | 225 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Change From Baseline at Week 2 | -0.27 (± 0.04) | -0.21 (± 0.03) | | |
| Change From Baseline at Week 4 | -0.50 (± 0.06) | -0.53 (± 0.05) | | |
| Change From Baseline at Week 6 | -0.68 (± 0.07) | -0.74 (± 0.05) | | |
| Change From Baseline at Week 8 | -0.70 (± 0.08) | -0.97 (± 0.06) | | |
| Change From Baseline at Week 10 | -0.86 (± 0.08) | -1.14 (± 0.06) | | |
| Change From Baseline at Week 12 | -0.93 (± 0.08) | -1.20 (± 0.06) | | |

## Statistical analyses

| **Statistical analysis title** | Change From Baseline in CGI-S Score at Week 2 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[30] |
| P-value | = 0.3048 [31] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.16 |

Notes:

[30] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[31] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CGI-S Score at Week 4 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |

| | |
|---|---|
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[32] |
| P-value | = 0.7058 [33] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.17 |
| upper limit | 0.12 |

Notes:

[32] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[33] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CGI-S Score at Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[34] |
| P-value | = 0.4516 [35] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.23 |
| upper limit | 0.1 |

Notes:

[34] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[35] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CGI-S Score at Week 8 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[36] |
| P-value | = 0.0052 [37] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | -0.08 |

Notes:

[36] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[37] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CGI-S Score at Week 10 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[38] |
| P-value | = 0.006 [39] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.47 |
| upper limit | -0.08 |

Notes:

[38] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[39] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

| **Statistical analysis title** | Change From Baseline in CGI-S Score at Week 12 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[40] |
| P-value | = 0.0078 [41] |
| Method | MMRM |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.47 |
| upper limit | -0.07 |

Notes:

[40] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.
[41] - MMRM method with model terms of treatment, trial site, visit, treatment-by-visit and baseline-by-visit interaction were used for analysis.

## Secondary: Clinical Global Impressions-Improvement (CGI-I) Score at Each Trial Visit During the Double-Blind Treatment Period

| End point title | Clinical Global Impressions-Improvement (CGI-I) Score at Each Trial Visit During the Double-Blind Treatment Period[42] |
|---|---|

End point description:

CGI-I is a 7-point scale that requires the clinician to assess whether a subject's condition has improved or worsened relative to a baseline state at the beginning of the intervention. This was rated as: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; or 7=very much worse. Higher scores indicate worse condition. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the

number of subjects with data available for analyses. 'n' indicates number analysed is the number of subjects with data available for analysis at the specified time point.

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

End point timeframe:

Baseline, Weeks 2, 4, 6, 8, 10, and 12

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

| **End point values** | Placebo | Brexpiprazole 2 and 3 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 116 | 225 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 2 (n=114, 221) | 3.57 (± 0.69) | 3.70 (± 0.75) | | |
| Week 4 (n=116, 225) | 3.39 (± 0.87) | 3.19 (± 0.85) | | |
| Week 6 (n=116, 225) | 3.19 (± 0.95) | 2.92 (± 0.94) | | |
| Week 8 (n=116, 225) | 3.16 (± 1.01) | 2.80 (± 1.00) | | |
| Week 10 (n=116, 225) | 2.97 (± 1.00) | 2.62 (± 0.99) | | |
| Week 12 (n=116, 225) | 2.97 (± 1.12) | 2.66 (± 1.09) | | |

## Statistical analyses

| **Statistical analysis title** | CGI-I Score at Week 2 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[43] |
| P-value | = 0.1975 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.26 |

Notes:

[43] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CGI-I Score at Week 4 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |

| | |
|---|---|
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[44] |
| P-value | = 0.0084 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.44 |
| upper limit | -0.06 |

Notes:

[44] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CGI-I Score at Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[45] |
| P-value | = 0.0101 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | -0.06 |

Notes:

[45] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CGI-I Score at Week 8 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[46] |
| P-value | = 0.0008 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.59 |
| upper limit | -0.15 |

Notes:

[46] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CGI-I Score at Week 10 |
|---|---|

| | |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[47] |
| P-value | = 0.0023 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.55 |
| upper limit | -0.12 |

Notes:

[47] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CGI-I Score at Week 12 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[48] |
| P-value | = 0.007 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.57 |
| upper limit | -0.09 |

Notes:

[48] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

## Secondary: CMAI Response Rate Assessed as Percentage of Subjects With CMAI Response at Every Scheduled Trial Visit in the Double-Blind Treatment Period

| | |
|---|---|
| End point title | CMAI Response Rate Assessed as Percentage of Subjects With CMAI Response at Every Scheduled Trial Visit in the Double-Blind Treatment Period[49] |

End point description:

The CMAI assesses frequency of agitated behaviours in elderly persons. The scale consists of 29 agitated behaviours that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation. Each of the agitated behaviours are scored 1 (never) to 7 (several times an hours), with the total scale score ranging from 29 to 203. Higher score indicates greater frequency of agitated behaviour. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses. 'n' indicates number analysed is the number of subjects with data available for analysis at the specified time point.

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

End point timeframe:

Weeks 2, 4, 6, 8, 10, and 12

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

| **End point values** | Placebo | Brexpiprazole 2 and 3 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 116 | 225 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| >/= 20%: Week 2 (n=114, 221) | 13.2 | 11.3 | | |
| >/= 20%: Week 4 (n=116, 225) | 27.6 | 29.3 | | |
| >/= 20%: Week 6 (n=116, 225) | 37.9 | 43.1 | | |
| >/= 20%: Week 8 (n=116, 225) | 38.8 | 59.6 | | |
| >/= 20%: Week 10 (n=116, 225) | 45.7 | 65.8 | | |
| >/= 20%: Week 12 (n=116, 225) | 47.4 | 68.4 | | |
| >/= 30%: Week 2 (n=114, 221) | 3.51 | 3.62 | | |
| >/= 30%: Week 4 (n=116, 225) | 10.3 | 10.7 | | |
| >/= 30%: Week 6 (n=116, 225) | 20.7 | 22.7 | | |
| >/= 30%: Week 8 (n=116, 225) | 19.0 | 32.9 | | |
| >/= 30%: Week 10 (n=116, 225) | 24.1 | 38.2 | | |
| >/= 30%: Week 12 (n=116, 225) | 25.9 | 42.7 | | |
| >/= 40%: Week 2 (n=114, 221) | 1.75 | 1.81 | | |
| >/= 40%: Week 4 (n=116, 225) | 5.17 | 4.89 | | |
| >/= 40%: Week 6 (n=116, 225) | 8.62 | 10.7 | | |
| >/= 40%: Week 8 (n=116, 225) | 8.62 | 16.9 | | |
| >/= 40%: Week 10 (n=116, 225) | 11.2 | 20.9 | | |
| >/= 40%: Week 12 (n=116, 225) | 14.7 | 23.1 | | |

## Statistical analyses

| **Statistical analysis title** | CMAI Response Rate- >/= 20%: Week 2 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[50] |
| P-value | = 0.729 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 1.91 |

Notes:

[50] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 20%: Week 4 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[51] |
| P-value | = 0.6196 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 1.52 |

Notes:

[51] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 20%: Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[52] |
| P-value | = 0.2718 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.53 |

Notes:

[52] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 20%: Week 8 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[53] |
| P-value | = 0.0004 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.52 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.19 |
| upper limit | 1.93 |

Notes:

[53] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 20%: Week 10 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[54] |
| P-value | = 0.0006 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.15 |
| upper limit | 1.76 |

Notes:

[54] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 20%: Week 12 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[55] |
| P-value | = 0.0004 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.15 |
| upper limit | 1.72 |

Notes:

[55] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 30%: Week 2 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |

| | |
|---|---|
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[56] |
| P-value | = 0.7211 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 3.85 |

Notes:

[56] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 30%: Week 4 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[57] |
| P-value | = 0.7606 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 2.14 |

Notes:

[57] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 30%: Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[58] |
| P-value | = 0.5902 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.68 |

Notes:

[58] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 30%: Week 8 |
|---|---|

| | |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[59] |
| P-value | = 0.0054 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.14 |
| upper limit | 2.54 |

Notes:

[59] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 30%: Week 10 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[60] |
| P-value | = 0.0066 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.11 |
| upper limit | 2.26 |

Notes:

[60] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 30%: Week 12 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[61] |
| P-value | = 0.0017 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.18 |
| upper limit | 2.23 |

Notes:

[61] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 40%: Week 2 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[62] |
| P-value | = 0.9074 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 5.97 |

Notes:

[62] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 40%: Week 4 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[63] |
| P-value | = 0.9625 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.36 |
| upper limit | 2.64 |

Notes:

[63] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 40%: Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[64] |
| P-value | = 0.512 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 2.53 |

Notes:

[64] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 40%: Week 8 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[65] |
| P-value | = 0.0244 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.03 |
| upper limit | 3.79 |

Notes:

[65] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 40%: Week 10 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[66] |
| P-value | = 0.0161 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.08 |
| upper limit | 3.18 |

Notes:

[66] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate- >/= 40%: Week 12 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[67] |
| P-value | = 0.0347 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.62 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 2.61 |

Notes:

[67] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

## Secondary: CMAI Response Rate Assessed as Percentage of Subjects With CMAI Response Based on Improvement From Baseline in Agitation Status at Every Scheduled Trial Visit in the Double-Blind Treatment Period

| End point title | CMAI Response Rate Assessed as Percentage of Subjects With CMAI Response Based on Improvement From Baseline in Agitation Status at Every Scheduled Trial Visit in the Double-Blind Treatment Period[68] |
|---|---|

End point description:

The CMAI assesses frequency of agitated behaviours in elderly persons. The scale consists of 29 agitated behaviours that are further categorized into distinct agitation syndromes, also known as CMAI factors of agitation. Each of the agitated behaviours are scored 1 (never) to 7 (several times an hours), with the total scale score ranging from 29 to 203. Higher score indicates greater frequency of agitated behaviour. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses. 'n' indicates number analysed is the number of subjects with data available for analysis at the specified time point.

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

End point timeframe:

Baseline, Weeks 2, 4, 6, 8, 10, and 12

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

| **End point values** | Placebo | Brexpiprazole 2 and 3 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 116 | 225 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Week 2 (n=114, 221) | 14.0 | 8.14 | | |
| Week 4 (n=116, 225) | 19.0 | 20.4 | | |
| Week 6 (n=116, 225) | 26.7 | 33.8 | | |
| Week 8 (n=116, 225) | 31.0 | 44.0 | | |
| Week 10 (n=116, 225) | 34.5 | 50.2 | | |
| Week 12 (n=116, 225) | 37.1 | 52.4 | | |

### Statistical analyses

| **Statistical analysis title** | CMAI Response Rate at Week 2 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |

| | |
|---|---|
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[69] |
| P-value | = 0.1503 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 0.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.35 |
| upper limit | 1.16 |

Notes:

[69] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate at Week 4 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[70] |
| P-value | = 0.7559 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.67 |

Notes:

[70] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate at Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[71] |
| P-value | = 0.2246 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.72 |

Notes:

[71] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate at Week 8 |
|---|---|

| | |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[72] |
| P-value | = 0.0276 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.02 |
| upper limit | 1.87 |

Notes:

[72] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate at Week 10 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[73] |
| P-value | = 0.0031 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.12 |
| upper limit | 1.89 |

Notes:

[73] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CMAI Response Rate at Week 12 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[74] |
| P-value | = 0.0017 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.14 |
| upper limit | 1.89 |

Notes:

[74] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

## Secondary: CGI-I Response Rate Assessed as Percentage of Subjects With CGI-I Response at Every Scheduled Trial Visit in the Double-Blind Treatment Period

| End point title | CGI-I Response Rate Assessed as Percentage of Subjects With CGI-I Response at Every Scheduled Trial Visit in the Double-Blind Treatment Period[75] |
|---|---|

End point description:

CGI-I is a 7-point scale that requires the clinician to assess whether a subject's condition has improved or worsened relative to a baseline state at the beginning of the intervention. This was rated as: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; or 7=very much worse. Higher scores indicate worse condition. The ITT Population consisted of all subjects in the randomised sample, who took at least 1 dose of IMP and had a baseline and at least one post-baseline evaluation for the CMAI total score. Number of subjects analysed is the number of subjects with data available for analyses. 'n' indicates number analysed is the number of subjects with data available for analysis at the specified time point.

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

End point timeframe:

Baseline, Weeks 2, 4, 6, 8, 10, and 12

Notes:

[75] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the SAP, data for this endpoint was analysed and reported in a combined way for brexpiprazole 2 and 3 mg.

| **End point values** | Placebo | Brexpiprazole 2 and 3 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 116 | 225 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Week 2 (n=114, 221) | 5.26 | 4.98 | | |
| Week 4 (n=116, 225) | 12.1 | 21.8 | | |
| Week 6 (n=116, 225) | 23.3 | 35.1 | | |
| Week 8 (n=116, 225) | 24.1 | 44.4 | | |
| Week 10 (n=116, 225) | 33.6 | 52.4 | | |
| Week 12 (n=116, 225) | 40.5 | 52.4 | | |

### Statistical analyses

| **Statistical analysis title** | CGI-I Response Rate at Week 2 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[76] |
| P-value | = 0.8549 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 3.03 |

Notes:

[76] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CGI-I Response Rate at Week 4 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[77] |
| P-value | = 0.0093 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.14 |
| upper limit | 3.32 |

Notes:

[77] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CGI-I Response Rate at Week 6 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[78] |
| P-value | = 0.0083 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.1 |
| upper limit | 2.22 |

Notes:

[78] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CGI-I Response Rate at Week 8 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[79] |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.85 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.32 |
| upper limit | 2.58 |

Notes:

[79] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CGI-I Response Rate at Week 10 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[80] |
| P-value | = 0.0005 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.18 |
| upper limit | 2.09 |

Notes:

[80] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

| **Statistical analysis title** | CGI-I Response Rate at Week 12 |
|---|---|
| Comparison groups | Placebo v Brexpiprazole 2 and 3 mg |
| Number of subjects included in analysis | 341 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[81] |
| P-value | = 0.016 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of Response Rate |
| Point estimate | 1.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.03 |
| upper limit | 1.69 |

Notes:

[81] - Comparison groups are Brexpiprazole 2 and 3 mg v Placebo. Point estimate and confidence interval are based on Brexpiprazole 2 and 3 mg v Placebo.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent up to end of study (Week 16)

Adverse event reporting additional description:

Randomised Sample was used to assess all-cause deaths. It consisted of all subjects who were randomised into this trial. Safety Sample was used to assess serious adverse events (SAEs) and non-serious adverse events (NSAEs) and consisted of all subjects who were administered at least one dose of IMP.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25.1 |

### Reporting groups

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

Reporting group description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 2 mg/day from Day 15. Subjects continued to receive brexpiprazole 2 mg, once daily until Week 12.

| | |
|---|---|
| Reporting group title | Brexpiprazole 3 mg |

Reporting group description:

Subjects followed a titration schedule, to gradually increase their dose from 0.5 mg/day in the starting to 3 mg/day from Day 29. Subjects continued to receive brexpiprazole 3 mg, once daily until Week 12.

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

Reporting group description:

Subjects received matching placebo, once daily for 12 weeks.

| Serious adverse events | Brexpiprazole 2 mg | Brexpiprazole 3 mg | Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 6 / 153 (3.92%) | 3 / 116 (2.59%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 1 | 0 |
| Investigations | | | |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 153 (0.00%) | 1 / 116 (0.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 153 (0.65%) | 0 / 116 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Hip fracture | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 153 (0.65%) | 1 / 116 (0.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 153 (0.65%) | 0 / 116 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 153 (0.65%) | 0 / 116 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 153 (0.65%) | 0 / 116 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 0 / 153 (0.00%) | 1 / 116 (0.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 153 (0.65%) | 0 / 116 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 153 (0.65%) | 0 / 116 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 153 (0.65%) | 0 / 116 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 2 / 153 (1.31%) | 0 / 116 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 153 (0.65%) | 0 / 116 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 153 (0.65%) | 0 / 116 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 73 (0.00%) | 1 / 153 (0.65%) | 0 / 116 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 8 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Brexpiprazole 2 mg | Brexpiprazole 3 mg | Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 73 (6.85%) | 10 / 153 (6.54%) | 8 / 116 (6.90%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 73 (6.85%) | 10 / 153 (6.54%) | 8 / 116 (6.90%) |
| occurrences (all) | 5 | 12 | 8 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 03 December 2019 | The following changes were implemented as per Amendment 1: 1. Sample size was increased from 225 subjects to 255 subjects. 2. The number of trial sites was increased from 60 to 80 sites. |
| 06 August 2020 | The following change was implemented as per Amendment 2: A Coronavirus disease 2019 (COVID-19) addendum was introduced for any protocol specified activities that were not able to be performed or could not be performed due to COVID-19 considerations. |
| 14 September 2020 | The following changes were implemented as per Amendment 3: 1. Sample size was increased from approximately 255 subjects to approximately 330 subjects. 2. References to German sites were removed. 3. Trial duration was increased. 4. Details were added regarding the interim analysis and possible rollover of subjects. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported