



Clinical trial results:

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole as Adjunctive Therapy in the Maintenance Treatment of Adults With Major Depressive Disorder

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-000601-22 |
| Trial protocol | DE PL |
| Global end of trial date | 29 July 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 01 November 2023 |
| First version publication date | 01 November 2023 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | 331-201-00079 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03538691 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Otsuka Pharmaceutical Development & Commercialization, Inc. |
| Sponsor organisation address | 2440 Research Boulevard, Rockville, 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 | 29 July 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 July 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to compare the efficacy of brexpiprazole (2 to 3 milligrams per day [mg/day]) to placebo as adjunctive therapy to antidepressant therapy (ADT) for the maintenance treatment in subjects with major depressive disorder (MDD).

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 | 13 July 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 251 |
| Country: Number of subjects enrolled | Germany: 88 |
| Country: Number of subjects enrolled | United States: 810 |
| Worldwide total number of subjects | 1149 |
| EEA total number of subjects | 339 |

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) | 1141 |
| From 65 to 84 years | 8 |

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

Subject disposition

Recruitment

Recruitment details:

A total of 1149 subjects with MDD participated in the study from 13 July 2018 to 29 July 2022.

Pre-assignment

Screening details:

Of the 1149 subjects enrolled in Phase A (Acute Treatment) of the trial, 766 eligible subjects continued to Phase B (Stabilisation). Eligible subjects completing Phase B were randomised into Phase C (Double-blind Randomised Withdrawal) to receive brexpiprazole or placebo along with open-label antidepressant therapy (ADT) in 1:1 ratio for up to 26 weeks.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Phase A: Acute Treatment (up to 8 Weeks) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

Arms

| | |
|------------------|------------------------------|
| Arm title | Phase A: Brexpiprazole + ADT |
|------------------|------------------------------|

Arm description:

Subjects received brexpiprazole 2 or 3 milligrams per day (mg/day) along with protocol-specified antidepressant therapy (ADT), orally, for 6 to 8 weeks during Phase A. Subjects were initially titrated to a target dose of brexpiprazole 2 mg over a 2 to 4-week period. Thereafter, subjects who had not met response criteria as defined in the blinded addendum, did not have potentially dose-related adverse events (AEs), and had not achieved the maximum dose of medication had their dose increased up to 3 mg.

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

Dosage and administration details:

Brexpiprazole tablets 2 or 3 mg/day.

| | |
|--|------------------------|
| Investigational medicinal product name | Antidepressant therapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Protocol-specified oral ADTs included: citalopram hydrobromide (Celexa®) tablets, escitalopram (Lexapro®) tablets, fluoxetine (Prozac®) capsules, paroxetine (Paxil CR®) controlled-release tablets, sertraline (Zoloft®) tablets, duloxetine (Cymbalta®) delayed-release capsules, venlafaxine XR (Effexor XR®) extended-release (XR) capsules.

| Number of subjects in period 1 | Phase A: Brexpiprazole + ADT |
|---|---------------------------------|
| Started | 1149 |
| Phase A Safety Sample | 1136 |
| Completed | 766 |
| Not completed | 383 |
| Physician decision | 1 |
| Adverse Event | 82 |
| Subject Withdrew Consent | 54 |
| Death | 1 |
| Not Specified:Not due to COVID-19 Restriction | 15 |
| Non-Compliance With Study Drug | 9 |
| Lost to follow-up | 24 |
| Lack of efficacy | 185 |
| Protocol deviation | 12 |

Period 2

| | |
|------------------------------|-----------------------------------|
| Period 2 title | Phase B: Stabilisation (12 Weeks) |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

Arms

| | |
|------------------|------------------------------|
| Arm title | Phase B: Brexpiprazole + ADT |
|------------------|------------------------------|

Arm description:

Eligible subjects completing Phase A were enrolled in Phase B to receive brexpiprazole 2 or 3 mg/day along with protocol-specified ADT, orally, for 12 weeks.

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

Dosage and administration details:

Brexpiprazole tablets 2 or 3 mg/day.

| | |
|--|------------------------|
| Investigational medicinal product name | Antidepressant therapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Protocol-specified oral ADTs included: citalopram hydrobromide (Celexa®) tablets, escitalopram (Lexapro®) tablets, fluoxetine (Prozac®) capsules, paroxetine (Paxil CR®) controlled-release tablets,

sertraline (Zoloft®) tablets, duloxetine (Cymbalta®) delayed-release capsules, venlafaxine XR (Effexor XR®) extended-release (XR) capsules.

| Number of subjects in period 2 | Phase B: Brexpiprazole + ADT |
|---|---------------------------------|
| Started | 766 |
| Phase B Safety Sample | 765 |
| Completed | 489 |
| Not completed | 277 |
| Physician decision | 6 |
| Adverse Event | 52 |
| Subject Withdrew Consent | 47 |
| Due to COVID-19 Restriction | 1 |
| Not Specified:Not due to COVID-19 Restriction | 11 |
| Non-Compliance With Study Drug | 9 |
| Pregnancy | 1 |
| Lost to follow-up | 5 |
| Lack of efficacy | 136 |
| Protocol deviation | 9 |

Period 3

| | |
|------------------------------|--|
| Period 3 title | Phase C:Randomised Withdrawal (26 Weeks) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Phase C: Brexpiprazole + ADT |

Arm description:

Eligible subjects completing Phase B received brexpiprazole 2 or 3 mg/day (dose of brexpiprazole that they were receiving at Week 20 of the Stabilisation Phase) along with protocol-specified ADT, orally, for up to 26 weeks during Phase C.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------------------|
| Investigational medicinal product name | Brexpiprazole |
| Investigational medicinal product code | |
| Other name | OPC-34712, Rexulti |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Brexpiprazole tablets 2 or 3 mg/day.

| | |
|--|------------------------|
| Investigational medicinal product name | Antidepressant therapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Protocol-specified oral ADTs included: citalopram hydrobromide (Celexa®) tablets, escitalopram (Lexapro®) tablets, fluoxetine (Prozac®) capsules, paroxetine (Paxil CR®) controlled-release tablets, sertraline (Zoloft®) tablets, duloxetine (Cymbalta®) delayed-release capsules, venlafaxine XR (Effexor XR®) extended-release (XR) capsules.

| | |
|------------------|------------------------|
| Arm title | Phase C: Placebo + ADT |
|------------------|------------------------|

Arm description:

Eligible subjects completing Phase B received brexpiprazole-matching placebo along with protocol-specified ADT, orally, for up to 26 weeks during Phase C.

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

Dosage and administration details:

Brexpiprazole-matching placebo tablets.

| | |
|--|------------------------|
| Investigational medicinal product name | Antidepressant therapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Protocol-specified oral ADTs included: citalopram hydrobromide (Celexa®) tablets, escitalopram (Lexapro®) tablets, fluoxetine (Prozac®) capsules, paroxetine (Paxil CR®) controlled-release tablets, sertraline (Zoloft®) tablets, duloxetine (Cymbalta®) delayed-release capsules, venlafaxine XR (Effexor XR®) extended-release (XR) capsules.

| Number of subjects in period 3 | Phase C: Brexpiprazole + ADT | Phase C: Placebo + ADT |
|---------------------------------------|---------------------------------|---------------------------|
| Started | 240 | 249 |
| Phase C Safety Sample | 240 | 248 |
| Completed | 120 | 131 |
| Not completed | 120 | 118 |
| Physician decision | - | 1 |
| Adverse Event | 6 | 6 |
| Subject Withdrew Consent | 6 | 19 |

| | | |
|---|----|----|
| Lack of Efficacy (Phase C MDD Relapse) | 54 | 52 |
| Not Specified:Not due to COVID-19 Restriction | 4 | 6 |
| Non-Compliance With Study Drug | 1 | 2 |
| Non-compliant Subjects | 32 | 28 |
| Pregnancy | 1 | - |
| Lost to follow-up | 16 | 4 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Phase A: Brexpiprazole + ADT |
|-----------------------|------------------------------|

Reporting group description:

Subjects received brexpiprazole 2 or 3 milligrams per day (mg/day) along with protocol-specified antidepressant therapy (ADT), orally, for 6 to 8 weeks during Phase A. Subjects were initially titrated to a target dose of brexpiprazole 2 mg over a 2 to 4-week period. Thereafter, subjects who had not met response criteria as defined in the blinded addendum, did not have potentially dose-related adverse events (AEs), and had not achieved the maximum dose of medication had their dose increased up to 3 mg.

| Reporting group values | Phase A: Brexpiprazole + ADT | Total | |
|---|---------------------------------|-------|--|
| Number of subjects | 1149 | 1149 | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 42.3 ± 13.1 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 734 | 734 | |
| Male | 415 | 415 | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 110 | 110 | |
| Not Hispanic or Latino | 968 | 968 | |
| Unknown or Not Reported | 71 | 71 | |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 5 | 5 | |
| Asian | 22 | 22 | |
| Native Hawaiian or Other Pacific Islander | 5 | 5 | |
| Black or African American | 159 | 159 | |
| White | 868 | 868 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 90 | 90 | |

End points

End points reporting groups

| | |
|--|------------------------------|
| Reporting group title | Phase A: Brexpiprazole + ADT |
| Reporting group description: Subjects received brexpiprazole 2 or 3 milligrams per day (mg/day) along with protocol-specified antidepressant therapy (ADT), orally, for 6 to 8 weeks during Phase A. Subjects were initially titrated to a target dose of brexpiprazole 2 mg over a 2 to 4-week period. Thereafter, subjects who had not met response criteria as defined in the blinded addendum, did not have potentially dose-related adverse events (AEs), and had not achieved the maximum dose of medication had their dose increased up to 3 mg. | |
| Reporting group title | Phase B: Brexpiprazole + ADT |
| Reporting group description: Eligible subjects completing Phase A were enrolled in Phase B to receive brexpiprazole 2 or 3 mg/day along with protocol-specified ADT, orally, for 12 weeks. | |
| Reporting group title | Phase C: Brexpiprazole + ADT |
| Reporting group description: Eligible subjects completing Phase B received brexpiprazole 2 or 3 mg/day (dose of brexpiprazole that they were receiving at Week 20 of the Stabilisation Phase) along with protocol-specified ADT, orally, for up to 26 weeks during Phase C. | |
| Reporting group title | Phase C: Placebo + ADT |
| Reporting group description: Eligible subjects completing Phase B received brexpiprazole-matching placebo along with protocol-specified ADT, orally, for up to 26 weeks during Phase C. | |

Primary: Phase C: Time-to-Relapse by Any Criteria as Defined in Blinded Addendum

| | |
|--|---|
| End point title | Phase C: Time-to-Relapse by Any Criteria as Defined in Blinded Addendum |
| End point description: Relapse criteria: At same visit, increase in MADRS total score (10 items, 0 = no symptoms to 6 = severe symptoms) of 50% from randomisation and CGI-S (0 = not assessed to 7 = most extremely ill) score ≥ 4 , hospitalisation for depression, discontinuation for lack of efficacy/worsening of depression, active suicidality (score ≥ 4 on MADRS item 10 of suicidality) or 'yes' on question 4/5 of C-SSRS (Suicidal Ideation [SI] has 5 questions: wish to be dead, non-specific active suicidal thoughts, active SI with any methods [not plan] without intent to act, active SI with some intent to act without specific plan, active SI with specific plan, intent) or 'yes' to any question in suicidal behaviour (preparatory acts/behaviour, aborted attempt, interrupted attempt, actual attempt [non-fatal], completed suicide). Phase C Efficacy Sample = all subjects randomised to double-blind treatment who had taken at least 1 dose of investigational medicinal product (IMP). Number of subjects analysed for median time to | |
| End point type | Primary |
| End point timeframe: Up to 14 days post last dose in Phase C (up to 28 weeks) | |

| End point values | Phase C: Brexiprazole + ADT | Phase C: Placebo + ADT | | |
|-------------------------------|-----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 54 | 51 | | |
| Units: days | | | | |
| median (full range (min-max)) | 63.0 (8 to 185) | 63.0 (8 to 190) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Brexiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.51 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.138 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.776 |
| upper limit | 1.669 |

Notes:

[1] - The hazard ratio and 95% confidence interval (CI) were derived from the Cox proportional hazard model with treatment as fixed effect.

Secondary: Phase C: Change From Baseline for Randomisation Phase in Sheehan Disability Scale (SDS) Mean Total Score at Week 46

| | |
|-----------------|---|
| End point title | Phase C: Change From Baseline for Randomisation Phase in Sheehan Disability Scale (SDS) Mean Total Score at Week 46 |
|-----------------|---|

End point description:

The SDS is a self-rated instrument used to measure the effect of the participant's symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores range from 0 through 10. The number most representative of how much each area was disrupted by symptoms is marked along the line from 0=not at all, to 10=extremely. The SDS total score is the mean of the 3 item responses. The SDS total score ranges from 0 to 10, with higher scores indicating greater functional impairment. Baseline was defined as the last available assessment value between Week 14 and Week 20 in Phase B for this outcome measure. Analysis of covariance (ANCOVA) model was used for analysis. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed is the number of subjects with data available for analyses.

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

End point timeframe:

Baseline and Week 46

| End point values | Phase C: Brexiprazole + ADT | Phase C: Placebo + ADT | | |
|-------------------------------------|-----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 239 | 242 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 0.72 (± 0.18) | 0.48 (± 0.18) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Brexiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 481 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2393 ^[2] |
| Method | ANCOVA |
| Parameter estimate | Least Squares (LS) Mean Difference |
| Point estimate | 0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.16 |
| upper limit | 0.62 |

Notes:

[2] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

Secondary: Phase C: Time-to-functional Relapse Based on SDS Criteria

| | |
|------------------------|--|
| End point title | Phase C: Time-to-functional Relapse Based on SDS Criteria |
| End point description: | Time-to-functional relapse was based on a 30% increase in the SDS mean total score from Phase C Baseline, at least one SDS sub-score at 4 or greater, and an SDS total score ≥ 7 when all 3 sub-scores were available. The SDS is a self-rated instrument used to measure the effect of the subject's symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores range from 0 through 10. The number most representative of how much each area was disrupted by symptoms is marked along the line from 0=not at all, to 10=extremely. Higher scores of 5 and above are associated with significant functional impairment. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed for median time to functional relapse is the number of subjects with impending functional relapse. |
| End point type | Secondary |
| End point timeframe: | Up to 14 days post last dose in Phase C (up to 28 weeks) |

| End point values | Phase C: Brexiprazole + ADT | Phase C: Placebo + ADT | | |
|-------------------------------|-----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 73 | | |
| Units: days | | | | |
| median (full range (min-max)) | 36.0 (6 to 185) | 35.0 (8 to 176) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Brexpiprazole + ADT vs Placebo + ADT |
| Statistical analysis description: The hazard ratio and 95% CI were derived from the Cox proportional hazard model with treatment as fixed effect. | |
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3086 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.177 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.857 |
| upper limit | 1.615 |

Secondary: Phase C: Percentage of Subjects Meeting Any Relapse Criteria

| | |
|---|--|
| End point title | Phase C: Percentage of Subjects Meeting Any Relapse Criteria |
| End point description: Relapse criteria: 50% increase in MADRS total score (10 items, 7-point scale, 0=no symptoms to 6=severe symptoms, total score=0-60) from randomisation and CGI-S (8-point scale, 0=not assessed to 7=most extremely ill) score ≥ 4 , hospitalisation for depression, discontinuation for lack of efficacy/worsening of depression, active suicidality (score ≥ 4 on MADRS item 10 of suicidality) or answer 'yes' on question 4/5 of C-SSRS (SI=5 questions: wish to be dead, non-specific active suicidal thoughts, active SI with any methods [not plan] without intent to act, active SI with some intent to act without specific plan, active SI with specific plan, intent) or answer 'yes' to any question in suicidal behaviour section (5 questions: preparatory acts/behaviour, aborted attempt, interrupted attempt, actual attempt [non-fatal], completed suicide). Percentage of subjects were rounded off to single decimal point. Phase C Efficacy Sample=all subjects randomised to double-blind treatment who had taken at least one IMP dose | |
| End point type | Secondary |
| End point timeframe: Up to 26 weeks in Phase C | |

| End point values | Phase C: Brexiprazole + ADT | Phase C: Placebo + ADT | | |
|-------------------------------|-----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 248 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 22.5 | 20.6 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Brexiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 488 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.603 |
| Method | Chi-squared |

Secondary: Phase C: Percentage of Subjects Maintaining Remission

| | |
|---|---|
| End point title | Phase C: Percentage of Subjects Maintaining Remission |
| End point description: | |
| Subjects maintaining remission was defined as MADRS total score ≤ 10 . The MADRS is a clinician-rated scale to assess depressive symptomatology during the preceding week. Subjects were rated on 10 items (feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating, and a lack of interest) each on a 7-point scale from 0 (no symptoms) to 6 (symptoms of maximum severity). The total score ranges from 0 to 60 with a higher score indicating more depression. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed is the number of subjects with data available for analyses. 'n' is the number of subjects with data available for analysis at the specified timepoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 21, 23, 25, 29, 33, 37, 41, 45, and 46 | |

| End point values | Phase C: Brexiprazole + ADT | Phase C: Placebo + ADT | | |
|-------------------------------|-----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 238 | 242 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Week 21 (n=238, 242) | 90.34 | 91.3 | | |
| Week 23 (n=230, 237) | 85.22 | 82.7 | | |
| Week 25 (n=217, 224) | 84.79 | 82.6 | | |
| Week 29 (n=189, 200) | 79.89 | 85.5 | | |
| Week 33 (n=166, 181) | 88.55 | 88.4 | | |
| Week 37 (n=149, 164) | 87.92 | 89.0 | | |

| | | | | |
|----------------------|-------|------|--|--|
| Week 41 (n=138, 151) | 84.78 | 89.4 | | |
| Week 45 (n=118, 127) | 88.14 | 89.0 | | |
| Week 46 (n=121, 132) | 90.91 | 91.7 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Week 21: Brexpiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 480 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7081 |
| Method | Chi-squared |

| | |
|---|---|
| Statistical analysis title | Week 23: Brexpiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 480 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4589 |
| Method | Chi-squared |

| | |
|---|---|
| Statistical analysis title | Week 25: Brexpiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 480 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5314 |
| Method | Chi-squared |

| | |
|---|---|
| Statistical analysis title | Week 29: Brexpiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 480 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1433 |
| Method | Chi-squared |

| | |
|-----------------------------------|---|
| Statistical analysis title | Week 33: Brexpiprazole + ADT vs Placebo + ADT |
|-----------------------------------|---|

| | |
|---|---|
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 480 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9636 |
| Method | Chi-squared |

| | |
|---|---|
| Statistical analysis title | Week 37: Brexpiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 480 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7596 |
| Method | Chi-squared |

| | |
|---|---|
| Statistical analysis title | Week 41: Brexpiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 480 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2402 |
| Method | Chi-squared |

| | |
|---|---|
| Statistical analysis title | Week 45: Brexpiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 480 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8363 |
| Method | Chi-squared |

| | |
|---|---|
| Statistical analysis title | Week 46: Brexpiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 480 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8308 |
| Method | Chi-squared |

Secondary: Phase C: Change From Baseline for Randomisation Phase in MADRS Total Score at Week 46

| | |
|--|---|
| End point title | Phase C: Change From Baseline for Randomisation Phase in MADRS Total Score at Week 46 |
| End point description: The MADRS is a clinician-rated scale to assess depressive symptomatology during the preceding week. Subjects were rated on 10 items (feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating, and a lack of interest) each on a 7-point scale from 0 (no symptoms) to 6 (symptoms of maximum severity). The total score ranges from 0 to 60 with a higher score indicating more depression. A positive change from Baseline indicates worsening of symptoms. Baseline was defined as the last available assessment value in Phase B for this outcome measure. ANCOVA model was used for analysis. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed is the number of subjects with data available for analyses. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 46 | |

| End point values | Phase C: Brexiprazole + ADT | Phase C: Placebo + ADT | | |
|-------------------------------------|-----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 247 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 4.09 (± 0.75) | 4.21 (± 0.73) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Brexiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 487 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8806 ^[3] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.73 |
| upper limit | 1.49 |

Notes:

[3] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

Secondary: Phase C: Change From Baseline for Randomisation Phase in CGI-S Score at Week 46

| | |
|-----------------|---|
| End point title | Phase C: Change From Baseline for Randomisation Phase in CGI-S Score at Week 46 |
|-----------------|---|

End point description:

The CGI -S was used to rate the severity of illness for each subject on an 8-point scale ranging from 0 to 7 where 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. A positive change from Baseline indicates worsening of illness. Baseline was defined as the last available assessment value in Phase B for this outcome measure. ANCOVA model was used for analysis. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed is the number of subjects with data available for analyses.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 46 | |

| End point values | Phase C: Brexpiprazole + ADT | Phase C: Placebo + ADT | | |
|-------------------------------------|------------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 240 | 247 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 0.56 (± 0.10) | 0.53 (± 0.09) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Brexpiprazole + ADT vs Placebo + ADT |
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 487 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7956 ^[4] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.18 |
| upper limit | 0.24 |

Notes:

[4] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

Secondary: Phase C: Change From Baseline for Randomisation Phase in Each of the SDS Individual Item Scores at Week 46

| | |
|-----------------|--|
| End point title | Phase C: Change From Baseline for Randomisation Phase in Each of the SDS Individual Item Scores at Week 46 |
|-----------------|--|

End point description:

The SDS is a self-rated instrument used to measure the effect of the subject's symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores range from 0 through 10. The number most representative of how much each area was disrupted by symptoms is marked along the line from 0=not at all, to 10=extremely. Higher scores of 5 and above are associated with significant functional impairment. A positive change from Baseline indicates worsening of symptoms

impacting each area. Baseline was defined as the last available assessment value between Week 14 and Week 20 in Phase B for this outcome measure. ANCOVA model was used for analysis. Phase C Efficacy Sample included all subjects randomised to the double-blind treatment who had taken at least one dose of IMP in Phase C. Number of subjects analysed is the number of subjects with data available for analyses. 'n' is the number of subjects with data available for analysis for the specified category.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 46 | |

| End point values | Phase C: Brexiprazole + ADT | Phase C: Placebo + ADT | | |
|-------------------------------------|-----------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 239 | 244 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Work/School (n=195, 197) | 0.46 (± 0.22) | 0.31 (± 0.23) | | |
| Social Life (n=239, 244) | 0.91 (± 0.19) | 0.56 (± 0.19) | | |
| Family Life (n=239, 242) | 0.78 (± 0.19) | 0.52 (± 0.19) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | SDS Individual Item: Work/School |
| Comparison groups | Phase C: Brexiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 483 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5223 ^[5] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.31 |
| upper limit | 0.61 |

Notes:

[5] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

| | |
|---|--|
| Statistical analysis title | SDS Individual Item: Social Life |
| Comparison groups | Phase C: Brexiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 483 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0904 ^[6] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.36 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.06 |
| upper limit | 0.77 |

Notes:

[6] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

| | |
|---|---|
| Statistical analysis title | SDS Individual Item: Family Life |
| Comparison groups | Phase C: Brexpiprazole + ADT v Phase C: Placebo + ADT |
| Number of subjects included in analysis | 483 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2289 ^[7] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.16 |
| upper limit | 0.67 |

Notes:

[7] - P-value was derived from an ANCOVA model with treatment, pooled centre as factor and Baseline value as covariance.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to 21 days after the last dose (Up to 49 weeks)

Adverse event reporting additional description:

All-cause Mortality: Enrolled Sample=all subjects who signed ICF; entered Phase A.

Serious; Other AEs: Phase A and B Safety Sample=all subjects who received at least 1 dose of brexpiprazole in Phase A and B respectively. Phase C Safety Sample=all subjects who were randomised to double-blind treatment and received at least one 1 IMP dose in Phase C.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Phase A: Brexpiprazole + ADT |
|-----------------------|------------------------------|

Reporting group description:

Subjects received brexpiprazole 2 or 3 mg/day along with protocol-specified ADT, orally, for 6 to 8 weeks during Phase A. Subjects were initially titrated to a target dose of brexpiprazole 2 mg over a 2 to 4-week period. Thereafter, subjects who had not met response criteria as defined in the blinded addendum, did not have potentially dose-related AEs, and had not achieved the maximum dose of medication had their dose increased up to 3 mg.

| | |
|-----------------------|------------------------------|
| Reporting group title | Phase B: Brexpiprazole + ADT |
|-----------------------|------------------------------|

Reporting group description:

Eligible subjects completing Phase A were enrolled in Phase B to receive brexpiprazole 2 or 3 mg/day along with protocol-specified ADT, orally, for 12 weeks.

| | |
|-----------------------|------------------------------|
| Reporting group title | Phase C: Brexpiprazole + ADT |
|-----------------------|------------------------------|

Reporting group description:

Eligible subjects completing Phase B received brexpiprazole 2 or 3 mg/day (dose of brexpiprazole that they were receiving at Week 20 of the Stabilisation Phase) along with protocol-specified ADT, orally, for up to 26 weeks during Phase C.

| | |
|-----------------------|------------------------|
| Reporting group title | Phase C: Placebo + ADT |
|-----------------------|------------------------|

Reporting group description:

Eligible subjects completing Phase B received brexpiprazole-matching placebo along with protocol-specified ADT, orally, for up to 26 weeks during Phase C.

| Serious adverse events | Phase A: Brexpiprazole + ADT | Phase B: Brexpiprazole + ADT | Phase C: Brexpiprazole + ADT |
|---|---------------------------------|---------------------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 1136 (0.88%) | 12 / 765 (1.57%) | 1 / 240 (0.42%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | 1 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |

| | | | |
|---|------------------|-----------------|-----------------|
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 1136 (0.09%) | 0 / 765 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 1136 (0.09%) | 0 / 765 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 0 / 765 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Psychiatric disorders | | | |
| Major depression | | | |
| subjects affected / exposed | 1 / 1136 (0.09%) | 0 / 765 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Suicide attempt | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Investigations | | | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Injury, poisoning and procedural complications | | | |
| Dislocation of vertebra | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 0 / 765 (0.00%) | 0 / 240 (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 |
| Epicondylitis | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 0 / 765 (0.00%) | 0 / 240 (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 |
| Fall | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 0 / 765 (0.00%) | 0 / 240 (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 |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 1136 (0.09%) | 0 / 765 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 1136 (0.09%) | 0 / 765 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|-----------------|-----------------|
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Nervous system disorders | | | |
| Akathisia | | | |
| subjects affected / exposed | 1 / 1136 (0.09%) | 0 / 765 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 1 / 1136 (0.09%) | 0 / 765 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 0 / 765 (0.00%) | 0 / 240 (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 | | | |
| Abdominal pain upper | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 1136 (0.09%) | 0 / 765 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 1136 (0.09%) | 0 / 765 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bursitis | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 0 / 765 (0.00%) | 0 / 240 (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 |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 1136 (0.09%) | 0 / 765 (0.00%) | 0 / 240 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 |
| Metabolism and nutrition disorders | | | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 1136 (0.00%) | 1 / 765 (0.13%) | 0 / 240 (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 | Phase C: Placebo + ADT | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 248 (1.21%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaphylactic shock | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Major depression | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Dislocation of vertebra | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epicondylitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 248 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Akathisia | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Bursitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 248 (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 | Phase A: Brexpiprazole + ADT | Phase B: Brexpiprazole + ADT | Phase C: Brexpiprazole + ADT |
|---|---------------------------------|---------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 423 / 1136 (37.24%) | 232 / 765 (30.33%) | 40 / 240 (16.67%) |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 48 / 1136 (4.23%) | 122 / 765 (15.95%) | 25 / 240 (10.42%) |
| occurrences (all) | 51 | 161 | 45 |
| Nervous system disorders | | | |

| | | | |
|------------------------------------|--------------------|------------------|-----------------|
| Akathisia | | | |
| subjects affected / exposed | 109 / 1136 (9.60%) | 33 / 765 (4.31%) | 4 / 240 (1.67%) |
| occurrences (all) | 109 | 34 | 4 |
| Headache | | | |
| subjects affected / exposed | 113 / 1136 (9.95%) | 41 / 765 (5.36%) | 5 / 240 (2.08%) |
| occurrences (all) | 158 | 55 | 6 |
| Somnolence | | | |
| subjects affected / exposed | 90 / 1136 (7.92%) | 37 / 765 (4.84%) | 6 / 240 (2.50%) |
| occurrences (all) | 94 | 38 | 6 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 64 / 1136 (5.63%) | 18 / 765 (2.35%) | 1 / 240 (0.42%) |
| occurrences (all) | 78 | 20 | 1 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 72 / 1136 (6.34%) | 8 / 765 (1.05%) | 1 / 240 (0.42%) |
| occurrences (all) | 74 | 8 | 1 |
| Metabolism and nutrition disorders | | | |
| Increased appetite | | | |
| subjects affected / exposed | 60 / 1136 (5.28%) | 18 / 765 (2.35%) | 1 / 240 (0.42%) |
| occurrences (all) | 61 | 20 | 1 |

| | | | |
|---|------------------------|--|--|
| Non-serious adverse events | Phase C: Placebo + ADT | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 248 (14.92%) | | |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 13 / 248 (5.24%) | | |
| occurrences (all) | 14 | | |
| Nervous system disorders | | | |
| Akathisia | | | |
| subjects affected / exposed | 3 / 248 (1.21%) | | |
| occurrences (all) | 3 | | |
| Headache | | | |
| subjects affected / exposed | 14 / 248 (5.65%) | | |
| occurrences (all) | 18 | | |
| Somnolence | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 248 (1.21%) 3 | | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 0 / 248 (0.00%) 0 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 2 / 248 (0.81%) 2 | | |
| Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all) | 4 / 248 (1.61%) 4 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|--|
| 15 June 2018 | The following major changes were implemented based on Amendment 1: 1) Corrected EudraCT number.2) Updated trial design schematic noting Phase A Baseline Visit and corrected number of subjects planned to be enrolled in Phase A. 3) Aligned exclusion criteria for clinical laboratory values with other brexpiprazole protocols.4) Collection of pharmacogenomic sample was moved from baseline visit to Week 20/Randomisation visit. |
| 08 July 2020 | The following major changes were implemented based on Amendment 2: 1) Updated the names and contact information of Sponsor representatives. 2) Added trial conduct information after the title page to introduce the coronavirus disease (COVID-19) Addendum. 3) Incorporated the following items from the protocol clarification memo: a. Revised the following text: A QT Interval Corrected Using Fridericia's Formula (QTcF) ≥ 450 milliseconds (msec) for males and ≥ 470 msec for females at screening is exclusionary. b. Revised the following text: Based on the QTcF corrections reported by the central service, a subject will be excluded if the correction equals or exceeds 450 msec for males and 470 msec for females for 2 or more of the 3 time points of the electrocardiogram (ECGs) conducted. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported