



Clinical trial results:

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of Two Fixed Doses of OPC-34712 as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder, the Polaris Trial.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2011-001349-33 |
| Trial protocol | DE HU |
| Global end of trial date | 12 September 2013 |

Results information

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

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | 331-10-227 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01360632 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND No. : 103,958 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Otsuka Pharmaceutical Development & Commercialization, Inc. |
| Sponsor organisation address | 2440 Research Boulevard, Rockville, United States, Maryland 20850 |
| Public contact | Mary Hobart, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 240-683-3194, Mary.Hobart@otsuka-us.com |
| Scientific contact | Mary Hobart, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 240-683-3194, Mary.Hobart@otsuka-us.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 04 June 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 September 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 September 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of OPC-34712 (1.0 and 3.0 milligrams (mg)/day) to placebo as adjunctive therapy to an assigned open-label antidepressant therapy (ADT) in participants who demonstrated an incomplete response after 8 weeks of prospective treatment with the same assigned open-label ADT.

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent had been obtained from them. The informed consent form (ICF), protocol, and amendments for this trial were submitted to and approved by the institutional review board (IRB) or independent ethics committee (IEC) for each respective trial site or country.

Background therapy:

At enrollment the physician carefully considered the participants' antidepressant treatment (ADT) history and made an ADT assignment for each enrolled participant from the following list of sponsor-provided ADTs: escitalopram, fluoxetine, paroxetine controlled release (CR), sertraline, duloxetine, and venlafaxine extended release (XR). Once assigned to one of these ADTs by the physician in Phase A, participants remained on that ADT for the duration of the trial (ie, baseline through Week 14/end of treatment) or were withdrawn if a change in ADT was needed.

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 25 June 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Romania: 12 |
| Country: Number of subjects enrolled | Germany: 77 |
| Country: Number of subjects enrolled | Hungary: 28 |
| Country: Number of subjects enrolled | Canada: 15 |
| Country: Number of subjects enrolled | Russian Federation: 48 |
| Country: Number of subjects enrolled | Ukraine: 55 |
| Country: Number of subjects enrolled | United States: 442 |
| Worldwide total number of subjects | 677 |
| EEA total number of subjects | 117 |

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) | 676 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 1539 participants at 92 trial sites in 7 countries. A total of 677 participants were into Phase B (period 2) and 675 received treatment.

Pre-assignment

Screening details:

The study consisted of a 7 to 28-day Screening period, an 8-Week single-blind placebo + ADT prospective Phase-A, a 6-Week double-blind randomization Phase-B or single-blind Phase A+ for those participants who did not meet criteria for randomization and a Follow-up of 30 (+2) days after the last dose of study medication.

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 |

Blinding implementation details:

Treatment assignment code list was available to an independent biostatistician and access to randomized treatment codes restricted to personnel charged with generating/ maintaining randomization files, packaging double-blind treatment, operating interactive voice recognition system and reporting serious adverse events (SAEs) to regulatory agencies. All other trial personnel remained blinded to the identity of the treatment until every participant had completed treatment and the database locked.

Arms

| | |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Brexpiprazole (1mg) + ADT |

Arm description:

Participants were administered brexpiprazole (1mg/day) as an adjunctive therapy to an assigned open label ADT (anti-depressant therapy).

| | |
|--|---------------|
| 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 1mg/day as an adjunctive therapy to an assigned open label ADT.

| | |
|------------------|---------------------------|
| Arm title | Brexpiprazole (3mg) + ADT |
|------------------|---------------------------|

Arm description:

Participants were administered brexpiprazole 3mg/day as an adjunctive therapy to an assigned open-label ADT.

| | |
|--|---------------|
| 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 3mg/day as an adjunctive therapy to an assigned open-label ADT.

| | |
|---|--------------|
| Arm title | Placebo +ADT |
| Arm description: Participants were administered placebo daily as an adjunctive therapy to an open label ADT. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo daily as adjunctive therapy to an open label ADT.

| Number of subjects in period 1 | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT |
|---------------------------------------|------------------------------|------------------------------|--------------|
| Started | 226 | 230 | 221 |
| Completed | 216 | 210 | 208 |
| Not completed | 10 | 20 | 13 |
| Consent withdrawn by subject | 4 | 4 | 7 |
| Physician decision | - | - | 1 |
| Met withdrawal criteria | - | 2 | 1 |
| Adverse event | 3 | 9 | 3 |
| Lost to follow-up | 1 | 1 | - |
| Protocol deviation | 1 | 4 | 1 |
| Lack of efficacy | 1 | - | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Brexpiprazole (1mg) + ADT |
|-----------------------|---------------------------|

Reporting group description:

Participants were administered brexpiprazole (1mg/day) as an adjunctive therapy to an assigned open label ADT (anti-depressant therapy).

| | |
|-----------------------|---------------------------|
| Reporting group title | Brexpiprazole (3mg) + ADT |
|-----------------------|---------------------------|

Reporting group description:

Participants were administered brexpiprazole 3mg/day as an adjunctive therapy to an assigned open-label ADT.

| | |
|-----------------------|--------------|
| Reporting group title | Placebo +ADT |
|-----------------------|--------------|

Reporting group description:

Participants were administered placebo daily as an adjunctive therapy to an open label ADT.

| Reporting group values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT |
|--|---------------------------|---------------------------|--------------|
| Number of subjects | 226 | 230 | 221 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 225 | 230 | 221 |
| From 65-84 years | 1 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 45.7 | 44.5 | 46.6 |
| standard deviation | ± 11.6 | ± 11.2 | ± 11 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 158 | 156 | 146 |
| Male | 68 | 74 | 75 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 677 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 676 | | |
| From 65-84 years | 1 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 460 | | |
| Male | 217 | | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Brexpiprazole (1mg) + ADT |
| Reporting group description: Participants were administered brexpiprazole (1mg/day) as an adjunctive therapy to an assigned open label ADT (anti-depressant therapy). | |
| Reporting group title | Brexpiprazole (3mg) + ADT |
| Reporting group description: Participants were administered brexpiprazole 3mg/day as an adjunctive therapy to an assigned open-label ADT. | |
| Reporting group title | Placebo +ADT |
| Reporting group description: Participants were administered placebo daily as an adjunctive therapy to an open label ADT. | |
| Subject analysis set title | Efficacy Sample |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for Montgomery-Asberg Depression Rating Scale (MADRS) Total Score in Phase B. | |
| Subject analysis set title | Efficacy Sample Per Protocol Amendment 3 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. | |

Primary: Mean change from the end of Phase A (Week 8 visit) to Phase B (Week 14 visit) in the Montgomery-Asberg Depression Rating Scale for the Efficacy Sample Set

| | |
|--|--|
| End point title | Mean change from the end of Phase A (Week 8 visit) to Phase B (Week 14 visit) in the Montgomery-Asberg Depression Rating Scale for the Efficacy Sample Set |
| End point description: The MADRS was utilized as the primary efficacy assessment of a participant's level of depression. The MADRS consisted of 10 items, all rated on a 0 to 6 scale with 0 being the "best" rating and 6 being the "worst" rating. The MADRS total score were to be unevaluable if less than 8 of the 10 items were recorded. If 8 or 9 of the 10 items were recorded, the MADRS total score was the mean of the recorded items multiplied by 10 and then rounded of to the first decimal place. The MADRS Total Score is the sum of ratings for all 10 items. The possible total scores are from 0 to 60, with higher values indicating worse outcome. | |
| End point type | Primary |
| End point timeframe: Baseline and Week 14 | |

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 225 | 226 | 218 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -7.65 (± 0.5) | -7.98 (± 0.51) | -6.45 (± 0.51) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
| Statistical analysis description: | |
| The primary analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0925 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.58 |
| upper limit | 0.2 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
| Statistical analysis description: | |
| The primary analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0327 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.92 |
| upper limit | -0.13 |

Primary: Mean Change in MADRS Total Score from Baseline End of Week 8 to Week 14 for the Efficacy Sample per final protocol

| | |
|-----------------|--|
| End point title | Mean Change in MADRS Total Score from Baseline End of Week 8 to Week 14 for the Efficacy Sample per final protocol |
|-----------------|--|

End point description:

The MADRS was utilized as the primary efficacy assessment of a participants level of depression. The MADRS consisted of 10 items, all rated on a 0 to 6 scale with 0 being the "best" rating and 6 being the "worst" rating. The possible total scores were from 0 to 6. The MADRS total score were to be unevaluable if less than 8 of the 10 items were recorded. If 8 or 9 of the 10 items were recorded, the MADRS total score was the mean of the recorded items multiplied by 10 and then rounded of to the first decimal place. Analysis was based on all participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

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

End point timeframe:

Baseline and Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 211 | 213 | 203 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -7.64 (± 0.52) | -8.29 (± 0.53) | -6.33 (± 0.53) | |

Statistical analyses

| | |
|----------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|----------------------------|-----------------------------------|

Statistical analysis description:

The primary analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0737 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.73 |
| upper limit | 0.13 |

| | |
|---|---|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
| Statistical analysis description: | |
| The primary analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpirazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0079 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.39 |
| upper limit | -0.51 |

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in Sheehan Disability Scale (SDS) Mean Scores for the Efficacy Sample Set

| | |
|-----------------|--|
| End point title | Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in Sheehan Disability Scale (SDS) Mean Scores for the Efficacy Sample Set |
|-----------------|--|

End point description:

This is the key secondary outcome measure. The SDS was a self-rated instrument used to measure the effect of the participants symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores ranged from 0 through 10. The number most representative of how much each area was disrupted by symptoms was marked along the line from 0= not at all to 10= extremely. For the work/school item, no response was to be entered if the participant did not work or go to school for reasons unrelated to the disorder and a response therefore not being applicable. The Mean SDS score were calculated over the three item scores. All three item scores were needed to be available with the exception of the work/school item score when this item was not applicable. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation.

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

End point timeframe:

Week 11 and Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 225 | 226 | 218 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 11 | -1.13 (± 0.13) | -0.67 (± 0.13) | -0.58 (± 0.11) | |
| Week 14 | -1.33 (± 0.14) | -1.21 (± 0.13) | -0.84 (± 0.13) | |

Statistical analyses

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0091 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.87 |
| upper limit | -0.12 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0474 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.37 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.73 |
| upper limit | 0 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 3 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|---|
| Comparison groups | Brexipiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0008 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.87 |
| upper limit | -0.23 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 4 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|---|
| Comparison groups | Brexipiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5792 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.41 |
| upper limit | 0.23 |

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in SDS Mean Scores for the Efficacy Sample per final protocol

| | |
|-----------------|--|
| End point title | Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in SDS Mean Scores for the Efficacy Sample per final protocol |
|-----------------|--|

End point description:

The SDS was a self-rated instrument used to measure the effect of the participants symptoms on work/school, social life, and family/home responsibilities. For each of the three items, scores ranged from 0 through 10. The number most representative of how much each area was disrupted by symptoms was marked along the line from 0= not at all, to 10= extremely. For the work/school item, no response was to be entered if the participant did not work or go to school for reasons unrelated to the disorder and a response therefore not being applicable. The Mean SDS score were calculated over the three item scores. All three item scores were needed to be available with the exception of the work/school item score when this item was not applicable. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

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

End point timeframe:

Week 11 and Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 211 | 213 | 203 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 11 | -1.11 (± 0.13) | -0.74 (± 0.13) | -0.53 (± 0.14) | |
| Week 14 | -1.27 (± 0.15) | -1.26 (± 0.15) | -0.78 (± 0.15) | |

Statistical analyses

| | |
|----------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|----------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0158 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.89 |
| upper limit | -0.09 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0191 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.88 |
| upper limit | -0.08 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 3 at Week 11 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0015 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.94 |
| upper limit | -0.22 |

| | |
|---|-----------------------------------|
| Statistical analysis title | Statistical analysis 4 at Week 11 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial | |

site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2627 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.56 |
| upper limit | 0.15 |

Secondary: Mean change from end of Phase A (Week 8 visit) in MADRS Total Score for every Study Week visit in Phase B other than Week 14 visit for the Efficacy Sample Set

| | |
|-----------------|--|
| End point title | Mean change from end of Phase A (Week 8 visit) in MADRS Total Score for every Study Week visit in Phase B other than Week 14 visit for the Efficacy Sample Set |
|-----------------|--|

End point description:

The MADRS consisted of 10 items, all rated on a 0 to 6 scale with 0 being the "best" rating and 6 being the "worst" rating. The possible total scores were from 0 to 6. The MADRS total score were to be unevaluable if less than 8 of the 10 items were recorded. If 8 or 9 of the 10 items were recorded, the MADRS total score was the mean of the recorded items multiplied by 10 and then rounded of to the first decimal place. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 8 to Week 13 | |

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 225 | 226 | 218 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 9 (N= 222, 221, 214) | -3.25 (± 0.3) | -2.53 (± 0.3) | -2.19 (± 0.31) | |
| Week 10 (N= 222, 221, 213) | -5.34 (± 0.38) | -4.8 (± 0.38) | -3.91 (± 0.39) | |
| Week 11 (N= 221, 218, 213) | -6.25 (± 0.41) | -5.56 (± 0.41) | -4.85 (± 0.41) | |
| Week 12 (N= 216, 213, 210) | -7.08 (± 0.43) | -6.8 (± 0.44) | -5.52 (± 0.44) | |
| Week 13 (N= 213, 212, 204) | -7.55 (± 0.46) | -7.73 (± 0.46) | -6.02 (± 0.47) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0096 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.86 |
| upper limit | -0.26 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4137 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.14 |
| upper limit | 0.47 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0065 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.47 |
| upper limit | -0.4 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0914 ^[1] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.93 |
| upper limit | 0.14 |

Notes:

[1] - MMRM method with an unstructured variance covariance matrix was used, with model terms trial site, treatment group, visit, treatment group-by-visit and Baseline-by-visit interaction.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0139 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.39 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | -0.28 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|---|
| Comparison groups | Brexiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2097 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.82 |
| upper limit | 0.4 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|---|
| Comparison groups | Brexiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0099 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.75 |
| upper limit | -0.38 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.034 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.48 |
| upper limit | -0.1 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0177 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | -0.27 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0085 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.98 |
| upper limit | -0.44 |

Secondary: Mean Change from end of Phase A (Week 8 visit) in MADRS Total Score for every Study Week visit in Phase B other than Week 14 visit for the Efficacy Sample per final protocol

| | |
|-----------------|---|
| End point title | Mean Change from end of Phase A (Week 8 visit) in MADRS Total Score for every Study Week visit in Phase B other than Week 14 visit for the Efficacy Sample per final protocol |
|-----------------|---|

End point description:

The MADRS consisted of 10 items, all rated on a 0 to 6 scale with 0 being the "best" rating and 6 being the "worst" rating. The possible total scores were from 0 to 6. The MADRS total score were to be unevaluable if less than 8 of the 10 items were recorded. If 8 or 9 of the 10 items were recorded, the MADRS total score was the mean of the recorded items multiplied by 10 and then rounded of to the first decimal place. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3

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

End point timeframe:

Week 8 to Week 13

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 211 | 213 | 203 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 9 (N=208, 210, 199) | -3.09 (± 0.31) | -2.6 (± 0.31) | -2.18 (± 0.32) | |
| Week 10 (N=208, 208, 199) | -5.12 (± 0.39) | -4.92 (± 0.39) | -3.95 (± 0.4) | |
| Week 11 (N=207, 205, 199) | -6.22 (± 0.42) | -5.76 (± 0.43) | -4.86 (± 0.43) | |
| Week 12 (N=203, 202, 195) | -7.09 (± 0.45) | -7.11 (± 0.45) | -5.48 (± 0.46) | |
| Week 13 (N=200, 199, 191) | -7.56 (± 0.47) | -8.05 (± 0.48) | -5.93 (± 0.49) | |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured

variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0286 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.74 |
| upper limit | -0.1 |

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3173 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.24 |
| upper limit | 0.4 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|-------------------|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
|-------------------|--|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0313 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.23 |
| upper limit | -0.11 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0732 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.04 |
| upper limit | 0.09 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0206 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.36 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.51 |
| upper limit | -0.21 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1233 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.06 |
| upper limit | 0.25 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0097 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.84 |
| upper limit | -0.39 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0092 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.86 |
| upper limit | -0.41 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0139 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.94 |
| upper limit | -0.33 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0015 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.42 |
| upper limit | -0.81 |

Secondary: Mean change from end of Phase A (Week 8 visit) to every study week visit in Phase B in Clinical Global Impression Severity of Illness (CGI-S) for the Efficacy Sample Set

| | |
|-----------------|---|
| End point title | Mean change from end of Phase A (Week 8 visit) to every study week visit in Phase B in Clinical Global Impression Severity of Illness (CGI-S) for the Efficacy Sample Set |
|-----------------|---|

End point description:

The severity of illness for each participant was rated using the CGI-S. To perform this assessment, the study physician had to answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the participant at this time?" Response choices included: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

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

End point timeframe:

Week 8 to Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 225 | 226 | 218 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 9 (N= 222, 221, 214) | -0.25 (± 0.03) | -0.22 (± 0.03) | -0.16 (± 0.03) | |
| Week 10 (N= 222, 221, 213) | -0.52 (± 0.05) | -0.46 (± 0.05) | -0.31 (± 0.05) | |
| Week 11 (N= 221, 218, 213) | -0.64 (± 0.05) | -0.51 (± 0.05) | -0.44 (± 0.05) | |
| Week 12 (N= 216, 213, 210) | -0.73 (± 0.05) | -0.72 (± 0.05) | -0.59 (± 0.05) | |
| Week 13 (N= 213, 212, 204) | -0.78 (± 0.06) | -0.77 (± 0.06) | -0.66 (± 0.06) | |
| Week 14 (N= 216, 208, 207) | -0.86 (± 0.06) | -0.9 (± 0.06) | -0.75 (± 0.06) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0436 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.18 |
| upper limit | 0 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1741 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.15 |
| upper limit | 0.03 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0012 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.34 |
| upper limit | -0.08 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0266 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | -0.02 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0034 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.33 |
| upper limit | -0.07 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3053 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 0.06 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0541 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.29 |
| upper limit | 0 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0912 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | 0.02 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1553 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | 0.04 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1855 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | 0.05 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2015 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | 0.06 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0852 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.15 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | 0.02 |

Secondary: Mean change from end of Phase A (Week 8 visit) to every study week visit in Phase B Week in Clinical CGI-S for the Efficacy Sample per final protocol

| | |
|-----------------|---|
| End point title | Mean change from end of Phase A (Week 8 visit) to every study week visit in Phase B Week in Clinical CGI-S for the Efficacy Sample per final protocol |
|-----------------|---|

End point description:

The severity of illness for each participant was rated using the CGI-S. To perform this assessment, the study physician had to answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the participant at this time?" Response choices included: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

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

End point timeframe:

Week 8 to Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 211 | 213 | 203 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 9 (N=208, 210, 199) | -0.24 (± 0.03) | -0.23 (± 0.03) | -0.16 (± 0.03) | |
| Week 10 (N=208, 208, 199) | -0.5 (± 0.05) | -0.47 (± 0.05) | -0.33 (± 0.05) | |
| Week 11 (N=207, 205, 199) | -0.64 (± 0.05) | -0.53 (± 0.05) | -0.45 (± 0.05) | |
| Week 12 (N=203, 202, 195) | -0.73 (± 0.06) | -0.74 (± 0.06) | -0.58 (± 0.06) | |
| Week 13 (N=200, 199, 191) | -0.77 (± 0.06) | -0.8 (± 0.06) | -0.64 (± 0.06) | |
| Week 14 (N=204, 196, 193) | -0.87 (± 0.06) | -0.92 (± 0.06) | -0.72 (± 0.06) | |

Statistical analyses

| | |
|----------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
|----------------------------|----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|-------------------|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
|-------------------|--|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0817 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.17 |
| upper limit | 0.01 |

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1406 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.16 |
| upper limit | 0.02 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.011 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.17 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.29 |
| upper limit | -0.04 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0287 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | -0.02 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0071 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | -0.05 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2503 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.22 |
| upper limit | 0.06 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0539 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0398 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.31 |
| upper limit | -0.01 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1168 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0.03 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0621 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.16 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | 0.01 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.089 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (final values) |
| Point estimate | -0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.32 |
| upper limit | 0.02 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0213 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.38 |
| upper limit | -0.03 |

Secondary: Mean change from end of Phase A (Week 8 visit) for every study week visit in Phase B in Inventory of Depressive Symptomatology (Self-Report) IDS-SR Total Score for the Efficacy Sample Set

| | |
|-----------------|---|
| End point title | Mean change from end of Phase A (Week 8 visit) for every study week visit in Phase B in Inventory of Depressive Symptomatology (Self-Report) IDS-SR Total Score for the Efficacy Sample Set |
|-----------------|---|

End point description:

IDS-SR was a 30-item self-report measured to assess core diagnostic depressive symptoms and atypical and melancholic symptom features of major depressive disorders. The IDS-SR consists of 30 items, all rated on a 0 to 3 scale with 0 being the "best" rating and 3 being the "worst" rating. Besides item 9, two sub-items 9A and 9B exist, with possible scores of 1, 2 or 3 for item 9A, and 0 or 1 for item 9B. The scores for these two sub-items were not included in the calculation of the total score. The IDS-SR Total Score was the sum of ratings of 28 item scores. The possible IDSSR Total Score ranged from 0 to 84. The IDS-SR Total Score was un-evaluable if less than 23 of the 28 items were recorded. If the number of items recorded was at least 23 and at most 27, the IDS-SR Total Score was the mean of the recorded items multiplied by 28, and was then rounded off to the first decimal place.

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

End point timeframe:

Week 8 to Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 225 | 226 | 218 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 9 (N= 222, 221, 214) | -3.58 (± 0.41) | -2.68 (± 0.42) | -2.31 (± 0.42) | |
| Week 10 (N= 222, 221, 213) | -4.97 (± 0.49) | -4 (± 0.5) | -3.11 (± 0.5) | |
| Week 11 (N= 220, 218, 213) | -5.83 (± 0.56) | -4.15 (± 0.56) | -3.74 (± 0.57) | |
| Week 12 (N= 216, 213, 210) | -6.33 (± 0.59) | -5.77 (± 0.59) | -4.43 (± 0.6) | |
| Week 13 (N= 213, 212, 204) | -6.96 (± 0.63) | -6.62 (± 0.63) | -5.66 (± 0.64) | |
| Week 14 (N= 216, 208, 207) | -7.02 (± 0.66) | -6.94 (± 0.66) | -5.42 (± 0.67) | |

Statistical analyses

| | |
|----------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
|----------------------------|----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0228 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.28 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.37 |
| upper limit | -0.18 |

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5081 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.47 |
| upper limit | 0.73 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0064 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | -0.53 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1898 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.23 |
| upper limit | 0.44 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0074 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.62 |
| upper limit | -0.56 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5935 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.95 |
| upper limit | 1.11 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0211 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.52 |
| upper limit | -0.29 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1031 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.34 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.96 |
| upper limit | 0.27 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1366 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.02 |
| upper limit | 0.41 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2709 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.68 |
| upper limit | 0.75 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0812 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 0.2 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.33 |
| upper limit | 0.29 |

Secondary: Mean change from end of Phase A (Week 8 visit) for every study week visit in Phase B in IDS-SR Total Score for the Efficacy Sample per final protocol

| | |
|-----------------|---|
| End point title | Mean change from end of Phase A (Week 8 visit) for every study week visit in Phase B in IDS-SR Total Score for the Efficacy Sample per final protocol |
|-----------------|---|

End point description:

The IDS-SR was a 30-item self-report measured to assess core diagnostic depressive symptoms as well as atypical and melancholic symptom features of major depressive disorders. The IDS-SR consists of 30 items, all rated on a 0 to 3 scale with 0 being the "best" rating and 3 being the "worst" rating. Besides

item 9, two sub-items 9A and 9B exist, with possible scores of 1, 2 or 3 for item 9A, and 0 or 1 for item 9B. The scores for these two sub-items were not included in the calculation of the total score. The IDS-SR Total Score was the sum of ratings of 28 item scores. The possible IDSSR Total Score ranged from 0 to 84. The IDS-SR Total Score was un-evaluable if less than 23 of the 28 items were recorded. If the number of items recorded was at least 23 and at most 27, the IDS-SR Total Score was the mean of the recorded items multiplied by 28, and was then rounded off to the first decimal place.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 8 to Week 14 | |

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 211 | 213 | 203 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 9 (N=208, 210, 199) | -3.27 (± 0.42) | -2.65 (± 0.42) | -2.15 (± 0.43) | |
| Week 10 (N=208, 209, 199) | -4.7 (± 0.51) | -4.13 (± 0.51) | -2.94 (± 0.52) | |
| Week 11 (N=206, 205, 199) | -5.77 (± 0.57) | -4.29 (± 0.58) | -3.46 (± 0.59) | |
| Week 12 (N=203, 202, 195) | -6.33 (± 0.61) | -6.05 (± 0.61) | -4.18 (± 0.63) | |
| Week 13 (N=200, 199, 191) | -6.88 (± 0.64) | -6.97 (± 0.64) | -5.25 (± 0.66) | |
| Week 14 (N=204, 196, 193) | -6.97 (± 0.67) | -7.2 (± 0.68) | -5.07 (± 0.69) | |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0496 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.24 |
| upper limit | 0 |

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.387 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.61 |
| upper limit | 0.63 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0125 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.13 |
| upper limit | -0.38 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|-------------------|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
|-------------------|--|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0898 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.57 |
| upper limit | 0.19 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|---|
| Comparison groups | Brexiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.88 |
| upper limit | -0.74 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|---|
| Comparison groups | Brexiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.301 [2] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.83 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.4 |
| upper limit | 0.74 |

Notes:

[2] - MMRM method with an unstructured variance covariance matrix was used, with model terms trial site, treatment group, visit, treatment group-by-visit and Baseline-by-visit interaction.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|---|
| Comparison groups | Brexipiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0118 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.82 |
| upper limit | -0.48 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|---|
| Comparison groups | Brexipiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0287 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.54 |
| upper limit | -0.19 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0686 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.39 |
| upper limit | 0.12 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.056 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.47 |
| upper limit | 0.04 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
| Statistical analysis description: | |
| The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0448 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.75 |
| upper limit | -0.04 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0251 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.98 |
| upper limit | -0.27 |

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) Hamilton Depression Scale 17 Item Version (HAM)-D17 Total Score for the Efficacy Sample Set

| | |
|-----------------|--|
| End point title | Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) Hamilton Depression Scale 17 Item Version (HAM)-D17 Total Score for the Efficacy Sample Set |
|-----------------|--|

End point description:

The HAM-D17 was utilized as a secondary assessment of a participants level of depression. The HAM-D (17-Item) consisted of 17 items. Eight items were rated on a 0 to 2 scale (items 4, 5, 6, 12, 13, 14, 16 and 17), while nine items (items 1, 2, 3, 7, 8, 9, 10, 11, and 15) were rated on a 0 to 4 scale (twice the weight of the other items). For all of these items, 0 was the "best" rating and the highest score (2 or 4) was the "worst" rating. The possible total scores were from 0 to 52. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

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

End point timeframe:

Baseline and Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 222 | 220 | 213 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -5.47 (± 0.36) | -6.14 (± 0.36) | -4.8 (± 0.37) | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 14 |
|-----------------------------------|-----------------------------------|
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The last observation carried forward (LOCF) method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1732 [3] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.63 |
| upper limit | 0.29 |

Notes:

[3] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 433 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0066 [4] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.34 |

| Confidence interval | |
|---------------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.31 |
| upper limit | -0.37 |

Notes:

[4] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in HAM-D17 Total Score for the Efficacy Sample Set per final protocol

| | |
|-----------------|--|
| End point title | Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in HAM-D17 Total Score for the Efficacy Sample Set per final protocol |
|-----------------|--|

End point description:

The HAM-D17 was utilized as a secondary assessment of a participants level of depression. The HAM-D (17-Item) consisted of 17 items. Eight items were rated on a 0 to 2 scale (items 4, 5, 6, 12, 13, 14, 16 and 17), while nine items (items 1, 2, 3, 7, 8, 9, 10, 11, and 15) were rated on a 0 to 4 scale (twice the weight of the other items). For all of these items, 0 was the "best" rating and the highest score (2 or 4) was the "worst" rating. The possible total scores were from 0 to 52. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

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

End point timeframe:

Baseline and Week 14

| End point values | Brexiprazole (1mg) + ADT | Brexiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 208 | 207 | 198 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -5.36 (± 0.37) | -6.26 (± 0.38) | -4.57 (± 0.39) | |

Statistical analyses

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 406 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1226 ^[5] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.78 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.78 |
| upper limit | 0.21 |

Notes:

[5] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 405 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 ^[6] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.69 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.69 |
| upper limit | -0.68 |

Notes:

[6] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in Hamilton Anxiety Rating Scale (HAM-A) Total Score for the Efficacy Sample Set

| | |
|-----------------|---|
| End point title | Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in Hamilton Anxiety Rating Scale (HAM-A) Total Score for the Efficacy Sample Set |
|-----------------|---|

End point description:

The HAM-A is utilized for the evaluation of anxiety symptoms. The HAM-A consists of 14 items. Each item is rated on a 0 to 4 scale. For all of these items, 0 is the "best" rating and 4 is the "worst" rating. If no item scores are missing, then the HAM-A total score is the sum of all 14 item scores. The possible total scores are from 0 to 56. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

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

End point timeframe:

Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 220 | 216 | 210 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -3.43 (± 0.31) | -3.89 (± 0.31) | -3.33 (± 0.32) | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 14 |
|--|--|
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 430 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8164 ^[7] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.93 |
| upper limit | 0.73 |

Notes:

[7] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

| Statistical analysis title | Statistical analysis 2 at Week 14 |
|--|--|
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 426 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1939 ^[8] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.39 |
| upper limit | 0.28 |

Notes:

[8] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariate

Secondary: Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in HAM-A Total for the Efficacy Sample per final protocol

| | |
|-----------------|--|
| End point title | Mean change from end of Phase A (Week 8 visit) to end of Phase B (Week 14 visit) in HAM-A Total for the Efficacy Sample per final protocol |
|-----------------|--|

End point description:

The HAM-A is utilized for the evaluation of anxiety symptoms. The HAM-A consists of 14 items. Each item is rated on a 0 to 4 scale. For all of these items, 0 is the "best" rating and 4 is the "worst" rating. If no item scores are missing, then the HAM-A total score is the sum of all 14 item scores. The possible total scores are from 0 to 56. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

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

End point timeframe:

Baseline and Week 14

| End point values | Brexiprazole (1mg) + ADT | Brexiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 206 | 204 | 195 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -3.35 (± 0.32) | -3.96 (± 0.33) | -3.07 (± 0.33) | |

Statistical analyses

| | |
|----------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|----------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 401 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5192 [9] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.14 |
| upper limit | 0.57 |

Notes:

[9] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

| | |
|----------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|----------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 399 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0443 ^[10] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.75 |
| upper limit | -0.02 |

Notes:

[10] - ANCOVA model, with treatment as main effects, study centre and Week 8 value as covariates

Secondary: Mean CGI-I Score at each trial week visit in Phase B for the Efficacy Sample Set

| | |
|-----------------|--|
| End point title | Mean CGI-I Score at each trial week visit in Phase B for the Efficacy Sample Set |
|-----------------|--|

End point description:

The efficacy of study medication was rated for each participant using the CGI-I. The study physician would rate the participant's total improvement whether or not it is due entirely to drug treatment. Response choices included: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

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

End point timeframe:

Week 8 to Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|--------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 225 | 226 | 218 | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 9 (N= 222, 221, 214) | 3.36 (± 0.68) | 3.4 (± 0.75) | 3.51 (± 0.67) | |
| Week 10 (N= 225, 226, 218) | 3.08 (± 0.85) | 3.09 (± 0.85) | 3.34 (± 0.85) | |
| Week 11 (N= 225, 226, 218) | 2.91 (± 0.82) | 2.99 (± 0.89) | 3.17 (± 0.88) | |
| Week 12 (N= 225, 226, 218) | 2.78 (± 0.87) | 2.81 (± 0.95) | 3.02 (± 0.95) | |
| Week 13 (N= 225, 226, 218) | 2.72 (± 0.87) | 2.73 (± 1.01) | 2.97 (± 1) | |
| Week 14 (N= 225, 226, 218) | 2.69 (± 0.89) | 2.66 (± 1.1) | 2.85 (± 1.01) | |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0248 ^[11] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.26 |
| upper limit | -0.02 |

Notes:

[11] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1334 ^[12] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.22 |
| upper limit | 0.03 |

Notes:

[12] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|-------------------|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
|-------------------|--|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0009 ^[13] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.42 |
| upper limit | -0.11 |

Notes:

[13] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexipiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0019 ^[14] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.38 |
| upper limit | -0.09 |

Notes:

[14] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexipiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0009 ^[15] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.26 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.42 |
| upper limit | -0.11 |

Notes:

[15] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0254 ^[16] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.34 |
| upper limit | -0.02 |

Notes:

[16] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0035 ^[17] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.41 |
| upper limit | -0.08 |

Notes:

[17] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0152 ^[18] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.39 |
| upper limit | -0.04 |

Notes:

[18] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 ^[19] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.42 |
| upper limit | -0.08 |

Notes:

[19] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

| | |
|-------------------|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
|-------------------|--|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.013 ^[20] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.42 |
| upper limit | -0.05 |

Notes:

[20] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexipiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0755 ^[21] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.33 |
| upper limit | 0.02 |

Notes:

[21] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexipiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0527 ^[22] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.39 |
| upper limit | 0 |

Notes:

[22] - P-value and treatment difference (CI) are derived from CMH row mean scores statistics controlling for study center

Secondary: Mean CGI-I Score at each trial week visit in Phase B for the Efficacy Sample per final protocol

| | |
|-----------------|---|
| End point title | Mean CGI-I Score at each trial week visit in Phase B for the Efficacy Sample per final protocol |
|-----------------|---|

End point description:

The efficacy of study medication was rated for each participant using the CGI-I. The study physician would rate the participant's total improvement whether or not it is due entirely to drug treatment. Response choices included: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

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

End point timeframe:

Week 8 to Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|--------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 211 | 213 | 203 | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 9 (N=208, 210, 199) | 3.39 (± 0.65) | 3.42 (± 0.74) | 3.54 (± 0.65) | |
| Week 10 (N=211, 213, 203) | 3.1 (± 0.82) | 3.08 (± 0.84) | 3.35 (± 0.84) | |
| Week 11 (N=211, 213, 203) | 2.93 (± 0.8) | 2.99 (± 0.89) | 3.19 (± 0.86) | |
| Week 12 (N=211, 213, 203) | 2.8 (± 0.86) | 2.81 (± 0.94) | 3.06 (± 0.94) | |
| Week 13 (N=211, 213, 203) | 2.75 (± 0.86) | 2.72 (± 1) | 3.01 (± 0.96) | |
| Week 14 (N=211, 213, 203) | 2.71 (± 0.88) | 2.65 (± 1.09) | 2.9 (± 0.99) | |

Statistical analyses

| | |
|----------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
|----------------------------|----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|-------------------|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
|-------------------|--|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0275 [23] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.26 |
| upper limit | -0.01 |

Notes:

[23] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1583 [24] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.22 |
| upper limit | 0.04 |

Notes:

[24] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0021 [25] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.25 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.41 |
| upper limit | -0.09 |

Notes:

[25] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0018 ^[26] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | -0.09 |

Notes:

[26] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0011 ^[27] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.43 |
| upper limit | -0.11 |

Notes:

[27] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0021 [28] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.44 |
| upper limit | -0.1 |

Notes:

[28] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0111 [29] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.42 |
| upper limit | -0.05 |

Notes:

[29] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.26 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.44 |
| upper limit | -0.09 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0046 ^[30] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.47 |
| upper limit | -0.09 |

Notes:

[30] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0237 ^[31] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.39 |
| upper limit | -0.03 |

Notes:

[31] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0171 ^[32] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.45 |
| upper limit | -0.04 |

Notes:

[32] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0235 ^[33] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.36 |
| upper limit | -0.03 |

Notes:

[33] - P-value and treatment difference (CI) are derived from Cochran-Mantel-Haenszel (CMH) row mean scores statistics controlling for study center.

Secondary: Percentage of participants with a MADRS response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample Set.

| | |
|-----------------|--|
| End point title | Percentage of participants with a MADRS response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample Set. |
|-----------------|--|

End point description:

MADRS response was defined as ≥ 50 percent reduction in MADRS Total Score from end of Phase A (Week 8). The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

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

End point timeframe:

Week 8 to Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-----------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 222 | 221 | 214 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 9 (N= 222, 221, 214) | 4.5 | 0.45 | 2.8 | |
| Week 10 (N= 225, 226, 218) | 10.2 | 6.19 | 5.05 | |
| Week 11 (N= 225, 226, 218) | 13.3 | 10.6 | 8.72 | |
| Week 12 (N= 225, 226, 218) | 16.9 | 15.5 | 10.1 | |
| Week 13 (N= 225, 226, 218) | 18.2 | 18.6 | 15.6 | |
| Week 14 (N= 225, 226, 218) | 23.1 | 22.1 | 15.1 | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 9 |
|---|--|
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5279 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 3.68 |

| Statistical analysis title | Statistical analysis 2 at Week 9 |
|--|--|
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0141 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.02 |
| upper limit | 0.94 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0484 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.99 |
| upper limit | 3.72 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5813 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.23 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 2.5 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1236 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 2.54 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.
The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4998 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 2.1 |

| | |
|--|--|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0365 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.03 |
| upper limit | 2.61 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0822 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 2.43 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4049 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.78 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2951 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 1.8 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0248 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.53 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 2.2 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexipiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0326 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.03 |
| upper limit | 2.21 |

Secondary: Percentage of participants with a MADRS response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample per final protocol

| | |
|-----------------|--|
| End point title | Percentage of participants with a MADRS response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample per final protocol |
|-----------------|--|

End point description:

MADRS response was defined as ≥ 50 percent reduction in MADRS Total Score from end of Phase A (Week 8). All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

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

End point timeframe:

Week 8 to Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-----------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 211 | 213 | 203 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 9 (N=208, 210, 199) | 3.37 | 0.48 | 3.02 | |
| Week 10 (N=211, 213, 203) | 7.58 | 6.1 | 4.93 | |
| Week 11 (N=211, 213, 203) | 13.3 | 11.3 | 8.37 | |
| Week 12 (N=211, 213, 203) | 16.6 | 16.4 | 10.3 | |
| Week 13 (N=211, 213, 203) | 18 | 19.2 | 14.3 | |
| Week 14 (N=211, 213, 203) | 23.2 | 23 | 14.3 | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 at Week 9 |
|---|--|
| Statistical analysis description: | |
| All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7993 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 2.55 |

| Statistical analysis title | Statistical analysis 2 at Week 9 |
|---|--|
| Statistical analysis description: | |
| All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0118 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 0.11 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.01 |
| upper limit | 0.93 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2825 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 3.16 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6375 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 2.5 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0923 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 2.82 |

Statistical analysis title Statistical analysis 2 at Week 11**Statistical analysis description:**

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3812 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 2.3 |

Statistical analysis title Statistical analysis 1 at Week 12**Statistical analysis description:**

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0464 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.63 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 2.65 |

| | |
|---|---|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
| Comparison groups | Brexiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.049 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 2.64 |

| | |
|---|---|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
| Statistical analysis description: | |
| All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2124 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 2.06 |

| | |
|--|---|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
| Statistical analysis description: | |
| All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data | |
| Comparison groups | Brexiprazole (3mg) + ADT v Placebo +ADT |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1078 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 2.14 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0094 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.14 |
| upper limit | 2.5 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0162 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.65 |

| Confidence interval | |
|---------------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.09 |
| upper limit | 2.5 |

Secondary: Percentage of participants with a MADRS Remission during Phase B relative to the end of Phase A (Week 8) for the Efficacy Sample Set.

| | |
|------------------------|--|
| End point title | Percentage of participants with a MADRS Remission during Phase B relative to the end of Phase A (Week 8) for the Efficacy Sample Set. |
| End point description: | MADRS remission was defined as a < or equal to 10 and > or equal to 50% reduction in MADRS Total Score from end of Phase A (Week 8). The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. |
| End point type | Secondary |
| End point timeframe: | Week to Week 14 |

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-----------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 222 | 221 | 214 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 9 (N= 222, 221, 214) | 3.15 | 0.45 | 2.8 | |
| Week 10 (N= 225, 226, 218) | 4 | 2.65 | 4.13 | |
| Week 11 (N= 225, 226, 218) | 8.44 | 6.19 | 5.5 | |
| Week 12 (N= 225, 226, 218) | 11.1 | 8.85 | 5.96 | |
| Week 13 (N= 225, 226, 218) | 10.7 | 12.8 | 9.17 | |
| Week 14 (N= 225, 226, 218) | 15.1 | 13.7 | 11.9 | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
| Statistical analysis description: | The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data. |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9498 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 2.9 |

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0141 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.02 |
| upper limit | 0.94 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8609 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 0.93 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 2.17 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2846 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.22 |
| upper limit | 1.54 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.248 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 2.99 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7513 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 2.37 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0554 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.99 |
| upper limit | 3.35 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|-------------------|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
|-------------------|--|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2409 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 2.87 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5538 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 2.02 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1743 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.44 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 2.41 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2843 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 2.07 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 435 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.464 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.92 |

Secondary: Percentage of participants with a MADRS Remission during Phase B

relative to the end of Phase A (Week 8) for the Efficacy Sample per final protocol

| | |
|-----------------|---|
| End point title | Percentage of participants with a MADRS Remission during Phase B relative to the end of Phase A (Week 8) for the Efficacy Sample per final protocol |
|-----------------|---|

End point description:

MADRS remission was defined as a < or equal to 10 and > or equal to 50% reduction in MADRS Total Score from end of Phase A (Week 8). All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

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

End point timeframe:

Week 8 to Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-----------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 211 | 213 | 203 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 9 (N=208, 210, 199) | 1.92 | 0.48 | 3.02 | |
| Week 10 (N=211, 213, 203) | 2.37 | 2.82 | 3.94 | |
| Week 11 (N=211, 213, 203) | 8.06 | 6.57 | 5.42 | |
| Week 12 (N=211, 213, 203) | 10.4 | 9.39 | 6.4 | |
| Week 13 (N=211, 213, 203) | 9.95 | 13.1 | 8.37 | |
| Week 14 (N=211, 213, 203) | 14.7 | 14.1 | 10.8 | |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3867 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.18 |
| upper limit | 1.97 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
| Statistical analysis description: | |
| All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0118 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.01 |
| upper limit | 0.93 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
| Statistical analysis description: | |
| All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.21 |
| upper limit | 1.66 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
| Statistical analysis description: | |
| All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3266 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.23 |
| upper limit | 1.62 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3027 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 3.1 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.696 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.17 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 2.52 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1368 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 3.07 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2387 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 2.89 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4498 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 2.28 |

Statistical analysis title

Statistical analysis 2 at Week 13

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1009 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 2.82 |

Statistical analysis title

Statistical analysis 1 at Week 14

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1499 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.45 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 2.41 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3012 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of remission rate |
| Point estimate | 1.31 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 2.18 |

Secondary: Percentage of participants with a CGI-I response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample Set

| | |
|-----------------|---|
| End point title | Percentage of participants with a CGI-I response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample Set |
|-----------------|---|

End point description:

A CGI-I response was defined as a CGI-I score of 1 (very much improved) or 2 (much improved). The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

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

End point timeframe:

Week 8 to Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-----------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 225 | 226 | 218 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 9 (N= 222, 221, 214) | 9.46 | 10.4 | 6.54 | |
| Week 10 (N= 225, 226, 218) | 23.6 | 23 | 13.3 | |

| | | | | |
|----------------------------|------|------|------|--|
| Week 11 (N= 225, 226, 218) | 28.4 | 30.1 | 21.6 | |
| Week 12 (N= 225, 226, 218) | 35.1 | 38.1 | 29.4 | |
| Week 13 (N= 225, 226, 218) | 40 | 43.4 | 28.9 | |
| Week 14 (N= 225, 226, 218) | 41.8 | 47.8 | 36.7 | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2873 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 2.65 |

| | |
|--|--|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2677 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 2.36 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0031 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.21 |
| upper limit | 2.68 |

| | |
|--|--|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0066 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.15 |
| upper limit | 2.5 |

| | |
|--|--|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
| Statistical analysis description: | |
| The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0665 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.98 |
| upper limit | 1.83 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.025 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.05 |
| upper limit | 1.91 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|---|
| Comparison groups | Brexiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2224 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.18 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.54 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 12 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0369 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.01 |
| upper limit | 1.68 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0179 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.05 |
| upper limit | 1.75 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0011 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.17 |
| upper limit | 1.89 |

Statistical analysis title

Statistical analysis 1 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3249 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.89 |
| upper limit | 1.41 |

Statistical analysis title

Statistical analysis 2 at Week 14

Statistical analysis description:

The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B. The LOCF method was used to impute missing data.

| | |
|-------------------|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
|-------------------|--|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0122 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 1.66 |

Secondary: Percentage of participants with a CGI-I response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample per final protocol

| | |
|-----------------|--|
| End point title | Percentage of participants with a CGI-I response during Phase B relative to the end of Phase A (Week 8 visit) for the Efficacy Sample per final protocol |
|-----------------|--|

End point description:

A CGI-I response was defined as a CGI-I score of 1 (very much improved) or 2 (much improved). All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3.

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

End point timeframe:

Week 8 to Week 14

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|---|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 211 | 213 | 203 | |
| Units: Percentage of participants number (not applicable) | | | | |
| Week 9 (N=208, 210, 199) | 7.69 | 9.52 | 5.53 | |
| Week 10 (N=211, 213, 203) | 21.8 | 23 | 12.3 | |
| Week 11 (N=211, 213, 203) | 27.5 | 30 | 19.7 | |
| Week 12 (N=211, 213, 203) | 34.1 | 38 | 27.6 | |
| Week 13 (N=211, 213, 203) | 38.9 | 44.1 | 27.1 | |
| Week 14 (N=211, 213, 203) | 41.2 | 48.4 | 34 | |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|-------------------|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
|-------------------|--|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5836 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 2.49 |

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 9 |
|-----------------------------------|----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3792 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 2.37 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0101 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.77 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.14 |
| upper limit | 2.74 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 10 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0065 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.17 |
| upper limit | 2.63 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0526 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 1.99 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 11 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0156 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.08 |
| upper limit | 2.11 |

Statistical analysis title Statistical analysis 1 at Week 12**Statistical analysis description:**

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1689 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.63 |

Statistical analysis title Statistical analysis 2 at Week 12**Statistical analysis description:**

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0231 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.37 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.04 |
| upper limit | 1.8 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0175 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 1.84 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 13 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0004 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.22 |
| upper limit | 2.07 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1396 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.55 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 at Week 14 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

All participants in the Efficacy Sample who met the revised randomization criteria for incomplete response as defined in Protocol Amendment 3. The LOCF method was used to impute missing data.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0016 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Ratio of response rate |
| Point estimate | 1.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.15 |
| upper limit | 1.86 |

Secondary: Change From Baseline (End of Phase A [Week 8]) in SDS Item Scores for the Efficacy Sample Set

| | |
|-----------------|---|
| End point title | Change From Baseline (End of Phase A [Week 8]) in SDS Item Scores for the Efficacy Sample Set |
|-----------------|---|

End point description:

The SDS is a self-rated instrument used to measure the effect of the patient'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. For the work/school item, no response was to be entered if the patient did not work or go to school for reasons unrelated to the disorder and a response therefore not being applicable. The Mean SDS Score will be calculated over the three item scores. All three item scores need to be available with the exception of the work/school item score when this item is not applicable. The Efficacy Sample Set included all participants who had received at least one dose of study treatment and had both an end of Phase A (Week 8) value and at least 1 post randomization efficacy evaluation for MADRS Total Score in Phase B.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 11 and Week 14 | |

| End point values | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|---------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 225 | 226 | 218 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Work/school: Week 11 | -1 (± 0.16) | -0.18 (± 0.18) | -0.55 (± 0.15) | |
| Work/school: Week 14 | -1.16 (± 0.17) | -0.91 (± 0.18) | -0.73 (± 0.17) | |
| Social life: Week 11 | -1.13 (± 0.14) | -0.76 (± 0.14) | -0.72 (± 0.14) | |
| Social life: Week 14 | -1.39 (± 0.15) | -1.31 (± 0.15) | -0.91 (± 0.15) | |
| Family life: Week 11 | -1.14 (± 0.14) | -0.74 (± 0.14) | -0.51 (± 0.12) | |
| Family life: Week 14 | -1.35 (± 0.15) | -1.28 (± 0.16) | -0.8 (± 0.15) | |

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

For Item: Work/School: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0377 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.88 |
| upper limit | -0.03 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

For Item: Work/School: Week 14 . The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and

interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0741 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.91 |
| upper limit | 0.04 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

For Item: Work/School: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0966 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.07 |
| upper limit | 0.81 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

For Item: Work/School: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|-------------------|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
|-------------------|--|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4774 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.66 |
| upper limit | 0.31 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Social life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0263 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.76 |
| upper limit | -0.05 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Social life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0214 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.48 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.89 |
| upper limit | -0.07 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Social life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8281 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.32 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Social life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.054 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.01 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 9 |
| Statistical analysis description: | |
| Family life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0008 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.99 |
| upper limit | -0.26 |

| | |
|---|--|
| Statistical analysis title | Statistical analysis 10 |
| Statistical analysis description: | |
| Family life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0093 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.97 |
| upper limit | -0.14 |

| | |
|--|-------------------------|
| Statistical analysis title | Statistical analysis 11 |
| Statistical analysis description: | |
| Family life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis | |

with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2182 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.59 |
| upper limit | -0.14 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Family life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0256 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | -0.06 |

Secondary: Change From Baseline (End of Phase A [Week 8]) in SDS Item Scores for the Efficacy Sample Set Per Final Protocol

| | |
|-----------------|--|
| End point title | Change From Baseline (End of Phase A [Week 8]) in SDS Item Scores for the Efficacy Sample Set Per Final Protocol |
|-----------------|--|

End point description:

The SDS is a self-rated instrument used to measure the effect of the patient'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. For the work/school item, no response was to be entered if the patient did not work or go to school for reasons unrelated to the disorder and a response therefore not being applicable. The Mean SDS Score will be calculated over the three item

scores. All three item scores need to be available with the exception of the work/school item score when this item is not applicable. All participants in the efficacy sample who met the revised randomization criteria for incomplete response as defined in protocol amendment 3.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 11 and Week 14 | |

| End point values | Brexiprazole (1mg) + ADT | Brexiprazole (3mg) + ADT | Placebo +ADT | |
|-------------------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 211 | 213 | 203 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Work/school: Week 11 | -1.01 (± 0.18) | -0.2 (± 0.2) | -0.48 (± 0.19) | |
| Work/school: Week 14 | -1.11 (± 0.2) | -0.93 (± 0.21) | -0.65 (± 0.2) | |
| Social life: Week 11 | -1.11 (± 0.15) | -0.82 (± 0.15) | -0.68 (± 0.15) | |
| Social life: Week 14 | -1.34 (± 0.16) | -1.37 (± 0.16) | -0.88 (± 0.17) | |
| Family life: Week 11 | -1.17 (± 0.14) | -0.89 (± 0.15) | -0.54 (± 0.15) | |
| Family life: Week 14 | -1.32 (± 0.16) | -1.39 (± 0.16) | -0.81 (± 0.16) | |

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

Work/school: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|---|
| Comparison groups | Brexiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0341 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.01 |
| upper limit | -0.04 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

School/work: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis

with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0816 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.99 |
| upper limit | 0.06 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Work/school: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2561 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.21 |
| upper limit | 0.78 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Work/school: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|-------------------|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
|-------------------|--|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2561 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.99 |
| upper limit | 0.06 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Social life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0331 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.82 |
| upper limit | -0.03 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

Social life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0352 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.47 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | -0.03 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Social life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.486 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.54 |
| upper limit | 0.25 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Social life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0282 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.93 |
| upper limit | -0.05 |

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 9 |
| Statistical analysis description: | |
| Family life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0016 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.01 |
| upper limit | -0.24 |

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 10 |
| Statistical analysis description: | |
| Family life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit. | |
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0186 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.94 |
| upper limit | -0.09 |

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 11 |
| Statistical analysis description: | |
| Family life: Week 11. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis | |

with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (3mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 416 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0824 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.73 |
| upper limit | 0.04 |

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical Analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

Family life: Week 14. The analysis was performed on the Efficacy Sample by fitting a MMRM analysis with an unstructured variance covariance structure, in which the change from the end of Phase A (Week 8) in MADRS Total Score (at Weeks 9 to 14) was the dependent variable. The model included terms for treatment, trial site, visit week, interaction term of treatment by visit week, and interaction term of baseline-by-visit.

| | |
|---|--|
| Comparison groups | Brexpiprazole (1mg) + ADT v Placebo +ADT |
| Number of subjects included in analysis | 414 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0077 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.02 |
| upper limit | -0.16 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were captured from randomization to double-blind treatment at Week 8, throughout the 6 week double blind phase to Follow-up 30 (+ 2) days after last dose of study medication.

Adverse event reporting additional description:

Safety sample comprised of randomized participants in Phase B who received at least one dose of double-blind trial medication. Participants were excluded only if there was evidence that the participant did not take trial medication. If a participant was dispensed trial medication and is lost to follow-up that participant was considered exposed.

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

Dictionary used

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

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Brexpiprazole (1mg) + ADT |
|-----------------------|---------------------------|

Reporting group description:

Participants were administered brexpiprazole (1mg/day) as an adjunctive therapy to an assigned open label ADT.

| | |
|-----------------------|---------------------------|
| Reporting group title | Brexpiprazole (3mg) + ADT |
|-----------------------|---------------------------|

Reporting group description:

Participants were administered brexpiprazole 3mg/day as an adjunctive therapy to an assigned open-label ADT.

| | |
|-----------------------|--------------|
| Reporting group title | Placebo +ADT |
|-----------------------|--------------|

Reporting group description:

Participants were administered placebo daily as an adjunctive therapy to an open label ADT.

| Serious adverse events | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT |
|--|------------------------------|------------------------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 1 / 229 (0.44%) | 0 / 220 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 229 (0.44%) | 0 / 220 (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 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 229 (0.00%) | 0 / 220 (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 |

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

| Non-serious adverse events | Brexpiprazole (1mg) + ADT | Brexpiprazole (3mg) + ADT | Placebo +ADT |
|--|------------------------------|------------------------------|-------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 63 / 226 (27.88%) | 72 / 229 (31.44%) | 29 / 220 (13.18%) |
| Investigations | | | |
| Weight increased subjects affected / exposed | 15 / 226 (6.64%) | 13 / 229 (5.68%) | 2 / 220 (0.91%) |
| occurrences (all) | 15 | 13 | 2 |
| Nervous system disorders | | | |
| Akathisia subjects affected / exposed | 10 / 226 (4.42%) | 31 / 229 (13.54%) | 5 / 220 (2.27%) |
| occurrences (all) | 10 | 35 | 5 |
| Headache subjects affected / exposed | 21 / 226 (9.29%) | 14 / 229 (6.11%) | 17 / 220 (7.73%) |
| occurrences (all) | 24 | 18 | 21 |
| Somnolence subjects affected / exposed | 9 / 226 (3.98%) | 13 / 229 (5.68%) | 1 / 220 (0.45%) |
| occurrences (all) | 9 | 15 | 1 |
| Tremor subjects affected / exposed | 9 / 226 (3.98%) | 12 / 229 (5.24%) | 7 / 220 (3.18%) |
| occurrences (all) | 15 | 16 | 11 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed | 15 / 226 (6.64%) | 7 / 229 (3.06%) | 4 / 220 (1.82%) |
| occurrences (all) | 15 | 9 | 4 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 27 May 2011 | Changed history of inadequate response from "3 or fewer adequate antidepressant treatments" to "at least 1 and no more than 3 adequate antidepressant treatments."; clarified instructions for preparation of whole blood sample for metabolic profiling; made administrative changes and corrected typographical errors. |
| 08 November 2011 | Clarified dosing of duloxetine to allow participants to titrate from 30 to 40 mg/day rather than forcing titration from 30 to 60 mg/day; specified that participants taking desvenlafaxine at screening should not be assigned to venlafaxine XR in Phase A; clarified requirements for collection of pharmacogenomic sample to indicate that a sample was not required from participants who withdrew during Phase A. In the protocol, clarified rules for ADT dose adjustment at Week 8 (ie, no change for participants entering Phase B, adjustments permitted for participants entering Phase A+); clarified that the serum pregnancy test was the definitive test for determining pregnancy, irrespective of urine pregnancy test result; added language to the prohibited therapies section to indicate that participants who received electroconvulsive for the current major depressive episode were excluded from the trial; Clarified that participants who were sterile (ie, women who had an oophorectomy and/or hysterectomy or had been postmenopausal for at least 12 consecutive months; or men who had orchidectomy) were not required to use two different methods of birth control; per posting from Food and Drug Administration, added linezolid and methylene blue to list of drugs that could result in serotonin syndrome if co-administered with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitor; made administrative changes. |
| 23 March 2012 | Revised statistical method in response to regulatory feedback; based on the review of completed phase 2 data, revised randomization criteria into Phase B, and trial procedures to increase the precision in the estimation of treatment effects: In the original protocol, the primary efficacy analysis used an analysis of covariance (ANCOVA) model based on the last observation carried forward (LOCF) dataset. The mixed models repeated measures (MMRM) model was included as a sensitivity analysis. Based on feedback from the FDA, the primary analysis method was changed to the MMRM model, with the ANCOVA LOCF used as the sensitivity analysis; Score-based criteria for determination of incomplete response for entry into Phase B were amended to better define incomplete responders as those participants who did not show a response at any visit during the single-blind prospective Phase A. Whereas before Protocol Amendment 3 response was assessed only at Week 8, after Protocol Amendment 3 participants who met response criteria at any time during Phase A were excluded from randomization. This change resulted from review of the data from the completed phase 2 trials (331-08-211 and 331-09-222). In addition, the criteria for response and incomplete response were removed from the main protocol to an addendum so that investigators and raters would be blinded to the randomization criteria in order to minimize potential rater inflation of efficacy scale scores. Eligibility for randomization was confirmed by the medical surveillance team from INC Research and/or through preprogrammed calculations made by the Interactive Voice/Web Recognition System using the prospectively defined score-based criteria. No new visits or assessments were added to the conduct of the trial as a result of this amendment. Therefore, the blinded changes to the randomization criteria did not pose any additional risk to trial participants. |

| | |
|---------------|--|
| 23 March 2012 | The investigator retained the option not to randomize any participant who met criteria for score-based eligibility, but who, in the investigator's judgment, should not have been randomized due to safety concerns or other reasons; in order to ensure a more even distribution of ADTs across the participant population, individual sites were not permitted to assign more than 2 out of every 6 participants at a site to any one ADT without permission of the medical monitor; item 32 of the exclusion criteria was clarified to exclude any participant who, in the opinion of the investigator or medical monitor, should not participate in the trial; due to the changes implemented in Amendment 3, the number of participants screened and enrolled into Phase A and randomized into Phase B was increased and the enrollment period and overall trial duration were extended 3 months to allow for enrollment of the additional participants in Phase A. The number of sites was reduced from 90 to 63 to minimize variability introduced by inclusion of multiple sites; made administrative changes. |
|---------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported