



## Clinical trial results:

### A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of Fixed-dose Brexpiprazole (OPC-34712) as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder With and Without Anxious Distress

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-000062-22 |
| Trial protocol           | DE SK HU PL    |
| Global end of trial date | 20 May 2016    |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 13 July 2017 |
| First version publication date | 13 July 2017 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | 331-13-214 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |              |
|------------------------------------|--------------|
| ISRCTN number                      | -            |
| ClinicalTrials.gov id (NCT number) | NCT02196506  |
| WHO universal trial number (UTN)   | -            |
| Other trial identifiers            | IND: 103,958 |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Otsuka Pharmaceutical Development & Commercialization, Inc  |
| Sponsor organisation address | 2440 Research Boulevard, Rockville, United States, MD 20850   |
| Public contact               | Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp |
| Scientific contact           | Otsuka Transparency Department, Otsuka Pharmaceutical Development & Commercialization, Inc., DT-inquiry@otsuka.jp |

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                       | 20 May 2016   |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 01 April 2016 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 20 May 2016   |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To compare the efficacy of brexpiprazole (2.0 mg/day) to placebo as adjunctive therapy to an assigned open-label antidepressant therapy (ADT) in subjects who demonstrate an inadequate response to a prospective 8-week trial of the same assigned open-label ADT.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 09 July 2014     |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 1 Months         |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 506 |
| Country: Number of subjects enrolled | Poland: 95         |
| Country: Number of subjects enrolled | Slovakia: 77       |
| Country: Number of subjects enrolled | Germany: 95        |
| Country: Number of subjects enrolled | Hungary: 64        |
| Worldwide total number of subjects   | 837                |
| EEA total number of subjects         | 331                |

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)                     | 830 |
| From 65 to 84 years                      | 7   |
| 85 years and over                        | 0   |



## Subject disposition

### Recruitment

Recruitment details:

This trial was conducted in 837 subjects at 51 trial sites in the following 5 countries: Germany, Hungary, Poland, Slovakia, and United States (US). Total of 1144 subjects with major depressive disorder were screened for the trial, 837 enrolled into Phase A, 394 were randomized into Phase B and 322 continued treatment with placebo+ADT in Phase A+.

### Pre-assignment

Screening details:

Trial consisted of a screening phase and 3 phases. In phase A (8-week single-blind prospective treatment phase) and continued treatment in phase A+ (Single-blind phase A Responder), there was single treatment group. In phase B (6-week double-blind randomization phase), there were 2 treatment groups. All Outcome Measures were assessed in phase B.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Phase A                     |
| Is this the baseline period? | No                          |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Single blind                |
| Roles blinded                | Investigator <sup>[1]</sup> |

### Arms

|           |         |
|-----------|---------|
| Arm title | ALL ADT |
|-----------|---------|

Arm description:

Subjects meeting entrance criteria who were experiencing a major depressive episode with a HAM-D17 Total Score of greater than or equal 18 at baseline were enrolled into an 8-week Single-blind Prospective Treatment Phase (Phase A). All subjects received single-blind placebo plus an investigator determined, open-label, ADT (antidepressant therapy). Once assigned to an ADT by the investigator, subjects remained on the same ADT for the duration of the trial. At the Week 8 visit, the IWRS (Interactive web response system) determined based on scores entered by the investigator, whether a subject was a "Phase A Responder" or a "Phase A Inadequate Responder."

|  |                                |
|--|--------------------------------|
| Arm type                               | Experimental                   |
| Investigational medicinal product name | Escitalopram (Lexapro) tablets |
| Investigational medicinal product code |                                |
| Other name                             |                                |
| Pharmaceutical forms                   | Tablet                         |
| Routes of administration               | Oral use                       |

Dosage and administration details:

10 or 20 mg/day, Dosed once daily at the same time each day.

|  |                              |
|--|------------------------------|
| Investigational medicinal product name | Fluoxetine (Prozac) capsules |
| Investigational medicinal product code |                              |
| Other name                             |                              |
| Pharmaceutical forms                   | Capsule                      |
| Routes of administration               | Oral use                     |

Dosage and administration details:

20 or 40 mg/day, Fluoxetine 20 mg was dosed once daily. Fluoxetine 40 mg could be dosed once daily or in divided doses twice daily. All doses were taken at the same time each day.

|  |   |
|--|---|
| Investigational medicinal product name | Paroxetine (Paxil CR) controlled-release (CR) tablets |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Tablet  |
| Routes of administration               | Oral use  |

Dosage and administration details:

25, 37.5 or 50 mg/day, Dosed once daily at the same time each day.



|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | Sertraline (Zoloft) tablets |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Tablet                      |
| Routes of administration               | Oral use                    |

Dosage and administration details:

50, 100, 150, or 200 mg/day, Dosed once daily at the same time each day.

|  |  |
|--|--|
| Investigational medicinal product name | Duloxetine (Cymbalta) delayed-release capsules |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use                                       |

Dosage and administration details:

30, 40 or 60 mg/day, Duloxetine 60 mg was administered once daily or as duloxetine 30 mg twice daily; duloxetine 40 mg was administered once daily or as duloxetine 20 mg twice daily. All doses should be taken at the same time each day.

|  |  |
|--|--|
| Investigational medicinal product name | Venlafaxine XR (Effexor XR) extended-release (XR) capsules |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use   |

Dosage and administration details:

37.5, 75, 150 or 225 mg/day, Dosed once daily at the same time each day. Subjects assigned to venlafaxine XR received 37.5 mg/day from Days 1 through 4 and 75 mg/day from Days 5 through 7 during the first week of Phase A. Venlafaxine XR was to be taken with food.

|  |                           |
|--|---------------------------|
| Investigational medicinal product name | Placebo for brexpiprazole |
| Investigational medicinal product code |                           |
| Other name                             |                           |
| Pharmaceutical forms                   | Tablet                    |
| Routes of administration               | Oral use                  |

Dosage and administration details:

1 tablet along with ADT

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Phase A is a 8-week Single-blind Prospective Treatment Phase during which all subjects received single-blind placebo plus an investigator determined, open-label, ADT.

| Number of subjects in period 1            | ALL ADT |
|---|---------|
| Started                                   | 837     |
| Completed                                 | 716     |
| Not completed                             | 121     |
| Consent withdrawn by subject              | 34      |
| Subject Was Withdrawn By the investigator | 10      |
| Adverse Events                            | 22      |
| Lost to follow-up                         | 9       |
| Subject Met Withdrawal Criteria           | 34      |
| Protocol deviation                        | 12      |



## Period 2

|                              |  |
|------------------------------|--|
| Period 2 title               | Phase B                                |
| Is this the baseline period? | Yes <sup>[2]</sup>                     |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Carer, Assessor |

## Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | 2mg Brex+ADT |

### Arm description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Adjunctive 2 mg/day brexpiprazole-plus-ADT (2 mg/day brexpiprazole+ADT)

|  |                                |
|--|--------------------------------|
| Arm type                               | Experimental                   |
| Investigational medicinal product name | Escitalopram (Lexapro) tablets |
| Investigational medicinal product code |                                |
| Other name                             |                                |
| Pharmaceutical forms                   | Tablet                         |
| Routes of administration               | Oral use                       |

### Dosage and administration details:

10 or 20 mg/day, Dosed once daily at the same time each day.

|  |                              |
|--|------------------------------|
| Investigational medicinal product name | Fluoxetine (Prozac) capsules |
| Investigational medicinal product code |                              |
| Other name                             |                              |
| Pharmaceutical forms                   | Capsule                      |
| Routes of administration               | Oral use                     |

### Dosage and administration details:

20 or 40 mg/day, Fluoxetine 20 mg was dosed once daily. Fluoxetine 40 mg could be dosed once daily or in divided doses twice daily. All doses were taken at the same time each day.

|  |   |
|--|---|
| Investigational medicinal product name | Paroxetine (Paxil CR) controlled-release (CR) tablets |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Tablet  |
| Routes of administration               | Oral use  |

### Dosage and administration details:

25, 37.5 or 50 mg/day, Dosed once daily at the same time each day.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | Sertraline (Zoloft) tablets |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Tablet                      |
| Routes of administration               | Oral use                    |

### Dosage and administration details:

50, 100, 150, or 200 mg/day, Dosed once daily at the same time each day.

|  |  |
|--|--|
| Investigational medicinal product name | Duloxetine (Cymbalta) delayed-release capsules |
| Investigational medicinal product code |  |
| Other name                             |  |



|  |  |
|--|--|
| Pharmaceutical forms   | Capsule  |
| Routes of administration   | Oral use   |
| Dosage and administration details:   |  |
| 30, 40 or 60 mg/day, Duloxetine 60 mg was administered once daily or as duloxetine 30 mg twice daily; duloxetine 40 mg was administered once daily or as duloxetine 20 mg twice daily. All doses should be taken at the same time each day.  |  |
| Investigational medicinal product name   | Venlafaxine XR (Effexor XR) extended-release (XR) capsules |
| Investigational medicinal product code   |  |
| Other name   |  |
| Pharmaceutical forms   | Capsule  |
| Routes of administration   | Oral use   |
| Dosage and administration details:   |  |
| 37.5, 75, 150 or 225 mg/day, Dosed once daily at the same time each day. Subjects assigned to venlafaxine XR received 37.5 mg/day from Days 1 through 4 and 75 mg/day from Days 5 through 7 during the first week of Phase A. Venlafaxine XR was to be taken with food.  |  |
| Investigational medicinal product name   | Brexipiprazole 2.0 mg/day                                  |
| Investigational medicinal product code   |  |
| Other name   |  |
| Pharmaceutical forms   | Tablet   |
| Routes of administration   | Oral use   |
| Dosage and administration details:   |  |
| 0.5 mg/day in week 8, 1 mg/day in week 9, 2.0 mg/day from week 10 to week 13.  |  |
| <b>Arm title</b>   | Placebo+ADT  |
| Arm description:   |  |
| Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen: |  |
| Continued placebo-plus-ADT (placebo+ADT)   |  |
| Arm type   | Placebo  |
| Investigational medicinal product name   | Escitalopram (Lexapro) tablets                             |
| Investigational medicinal product code   |  |
| Other name   |  |
| Pharmaceutical forms   | Tablet   |
| Routes of administration   | Oral use   |
| Dosage and administration details:   |  |
| 10 or 20 mg/day, Dosed once daily at the same time each day.   |  |
| Investigational medicinal product name   | Fluoxetine (Prozac) capsules                               |
| Investigational medicinal product code   |  |
| Other name   |  |
| Pharmaceutical forms   | Capsule  |
| Routes of administration   | Oral use   |
| Dosage and administration details:   |  |
| 20 or 40 mg/day, Fluoxetine 20 mg was dosed once daily. Fluoxetine 40 mg could be dosed once daily or in divided doses twice daily. All doses were taken at the same time each day.  |  |
| Investigational medicinal product name   | Paroxetine (Paxil CR) controlled-release (CR) tablets      |
| Investigational medicinal product code   |  |
| Other name   |  |
| Pharmaceutical forms   | Tablet   |
| Routes of administration   | Oral use   |
| Dosage and administration details:   |  |
| 25, 37.5 or 50 mg/day, Dosed once daily at the same time each day.   |  |



|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | Sertraline (Zoloft) tablets |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Tablet                      |
| Routes of administration               | Oral use                    |

Dosage and administration details:

50, 100, 150, or 200 mg/day, Dosed once daily at the same time each day.

|  |  |
|--|--|
| Investigational medicinal product name | Duloxetine (Cymbalta) delayed-release capsules |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use                                       |

Dosage and administration details:

30, 40 or 60 mg/day, Duloxetine 60 mg was administered once daily or as duloxetine 30 mg twice daily; duloxetine 40 mg was administered once daily or as duloxetine 20 mg twice daily. All doses should be taken at the same time each day.

|  |  |
|--|--|
| Investigational medicinal product name | Venlafaxine XR (Effexor XR) extended-release (XR) capsules |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use   |

Dosage and administration details:

37.5, 75, 150 or 225 mg/day, Dosed once daily at the same time each day. Subjects assigned to venlafaxine XR received 37.5 mg/day from Days 1 through 4 and 75 mg/day from Days 5 through 7 during the first week of Phase A. Venlafaxine XR was to be taken with food.

|  |                           |
|--|---------------------------|
| Investigational medicinal product name | Placebo for brexpiprazole |
| Investigational medicinal product code |                           |
| Other name                             |                           |
| Pharmaceutical forms                   | Tablet                    |
| Routes of administration               | Oral use                  |

Dosage and administration details:

1 tablet along with ADT

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 2 (Phase B) is the baseline period for this study.

| <b>Number of subjects in period 2<sup>[3]</sup>[4]</b> | 2mg Brex+ADT | Placebo+ADT |
|--|--------------|-------------|
| Started  | 192          | 202         |
| Completed  | 177          | 196         |
| Not completed  | 15           | 6           |
| Consent withdrawn by subject                           | 8            | 1           |
| Adverse Events   | 4            | 1           |
| Lost to follow-up                                      | 2            | 1           |
| Subject Met Withdrawal Criteria                        | -            | 1           |
| Lack of efficacy                                       | 1            | 2           |

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Period 2 (Phase B) is the baseline period for this study. A total of 1144 subjects were



screened for this trial and 837 subjects enrolled into Phase A. Of these subjects, 121 subjects (14.5%) discontinued the trial during Phase A, 394 subjects (47.1%) were subsequently randomized to double-blind IMP in Phase B (192 subjects randomized to 2 mg/day brexpiprazole+ADT and 202 randomized to placebo+ADT), and 322 subjects (38.5%) continued placebo+ADT in Phase A+.

[4] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 1144 subjects were screened for this trial and 837 subjects enrolled into Phase A. A total of 837 subjects received at least 1 dose of ADT during Phase A. Of these subjects, 121 subjects (14.5%) discontinued the trial during Phase A, 394 subjects (47.1%) were subsequently randomized to double-blind IMP in Phase B (192 subjects randomized to 2 mg/day brexpiprazole+ADT and 202 randomized to placebo+ADT), and 322 subjects (38.5%) continued placebo+ADT in Phase A+.

### Period 3

|                              |                             |
|------------------------------|-----------------------------|
| Period 3 title               | Phase A +                   |
| Is this the baseline period? | No                          |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Single blind                |
| Roles blinded                | Investigator <sup>[5]</sup> |

### Arms

|                  |         |
|------------------|---------|
| <b>Arm title</b> | ALL ADT |
|------------------|---------|

Arm description:

Phase A+ included subjects who met criteria for a response at the end of the prospective treatment phase (Week 8 visit of Phase A) and subjects who were not suitable for randomization in Phase B per the judgment of the investigator or medical monitor. Treatment response in Phase A was determined at the Week 8 visit based on improvement or lack of improvement of the subject's depressive symptoms, which was confirmed by clinical criteria that prospectively defined response. Subject response was determined from clinical data that were entered into the IWRS at each visit. Subjects in Phase A+ received single-blind placebo+ADT for an additional 6 weeks, for a total of 14 weeks, and attended visits at Weeks 11 and 14.

|  |                                |
|--|--------------------------------|
| Arm type                               | Experimental                   |
| Investigational medicinal product name | Escitalopram (Lexapro) tablets |
| Investigational medicinal product code |                                |
| Other name                             |                                |
| Pharmaceutical forms                   | Tablet                         |
| Routes of administration               | Oral use                       |

Dosage and administration details:

10 or 20 mg/day, Dosed once daily at the same time each day.

|  |                              |
|--|------------------------------|
| Investigational medicinal product name | Fluoxetine (Prozac) capsules |
| Investigational medicinal product code |                              |
| Other name                             |                              |
| Pharmaceutical forms                   | Capsule                      |
| Routes of administration               | Oral use                     |

Dosage and administration details:

20 or 40 mg/day, Fluoxetine 20 mg was dosed once daily. Fluoxetine 40 mg could be dosed once daily or in divided doses twice daily. All doses were taken at the same time each day.

|  |   |
|--|---|
| Investigational medicinal product name | Paroxetine (Paxil CR) controlled-release (CR) tablets |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Tablet  |
| Routes of administration               | Oral use  |

Dosage and administration details:

25, 37.5 or 50 mg/day, Dosed once daily at the same time each day.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | Sertraline (Zoloft) tablets |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Tablet                      |



|  |  |
|--|--|
| Routes of administration   | Oral use                                       |
| Dosage and administration details:<br>50, 100, 150, or 200 mg/day, Dosed once daily at the same time each day. |  |
| Investigational medicinal product name   | Duloxetine (Cymbalta) delayed-release capsules |
| Investigational medicinal product code   |  |
| Other name   |  |
| Pharmaceutical forms   | Capsule  |
| Routes of administration   | Oral use                                       |

Dosage and administration details:

30, 40 or 60 mg/day, Duloxetine 60 mg was administered once daily or as duloxetine 30 mg twice daily; duloxetine 40 mg was administered once daily or as duloxetine 20 mg twice daily. All doses should be taken at the same time each day.

|  |  |
|--|--|
| Investigational medicinal product name | Venlafaxine XR (Effexor XR) extended-release (XR) capsules |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use   |

Dosage and administration details:

37.5, 75, 150 or 225 mg/day, Dosed once daily at the same time each day. Subjects assigned to venlafaxine XR received 37.5 mg/day from Days 1 through 4 and 75 mg/day from Days 5 through 7 during the first week of Phase A. Venlafaxine XR was to be taken with food.

|  |                           |
|--|---------------------------|
| Investigational medicinal product name | Placebo for brexpiprazole |
| Investigational medicinal product code |                           |
| Other name                             |                           |
| Pharmaceutical forms                   | Tablet                    |
| Routes of administration               | Oral use                  |

Dosage and administration details:

1 tablet along with ADT

Notes:

[5] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Phase A+ included subjects who met criteria for a response at the end of the prospective treatment phase (Week 8 visit of Phase A) and subjects who were not suitable for randomization in Phase B per the judgment of the investigator or medical monitor. Subjects in Phase A+ received single-blind placebo+ADT for an additional 6 weeks, for a total of 14 weeks.

| <b>Number of subjects in period 3<sup>[6]</sup></b> | ALL ADT |
|---|---------|
| Started   | 322     |
| Completed   | 308     |
| Not completed                                       | 14      |
| Consent withdrawn by subject                        | 5       |
| Subject Was Withdrawn By the investigator           | 1       |
| Adverse Events                                      | 1       |
| Lost to follow-up                                   | 6       |
| Subject Met Withdrawal Criteria                     | 1       |

Notes:

[6] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 1144 subjects were screened for this trial and 837 subjects enrolled into Phase A. A total of 837 subjects received at least 1 dose of ADT during Phase A. Of these subjects, 121 subjects (14.5%) discontinued the trial during Phase A, 394 subjects (47.1%) were subsequently randomized to



double-blind IMP in Phase B (192 subjects randomized to 2 mg/day brexpiprazole+ADT and 202 randomized to placebo+ADT), and 322 subjects (38.5%) continued placebo+ADT in Phase A+.



## Baseline characteristics

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | 2mg Brex+ADT |
|-----------------------|--------------|

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Adjunctive 2 mg/day brexpiprazole-plus-ADT (2 mg/day brexpiprazole+ADT)

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

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Continued placebo-plus-ADT (placebo+ADT)

| Reporting group values   | 2mg Brex+ADT | Placebo+ADT | Total |
|--|--------------|-------------|-------|
| Number of subjects   | 192          | 202         | 394   |
| Age categorical  |              |             |       |
| Baseline measures are based on the subjects from the Double-blind Placebo-controlled Phase |              |             |       |
| 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)   | 192          | 200         | 392   |
| From 65-84 years   | 0            | 2           | 2     |
| 85 years and over  | 0            | 0           | 0     |
| Age continuous   |              |             |       |
| Units: years   |              |             |       |
| arithmetic mean  | 43           | 42.7        |       |
| standard deviation   | ± 12.7       | ± 12.5      | -     |
| Gender categorical   |              |             |       |
| Units: Subjects  |              |             |       |
| Female   | 147          | 144         | 291   |
| Male   | 45           | 58          | 103   |
| Type of Episode [n (%)]  |              |             |       |
| Units: Subjects  |              |             |       |
| Single Episode   | 32           | 35          | 67    |
| Recurrent Episode  | 160          | 167         | 327   |
| Duration of Current Episode (Months)   |              |             |       |
| Units: Months  |              |             |       |
| arithmetic mean  | 13.3         | 19.4        |       |
| standard deviation   | ± 14.2       | ± 46.8      | -     |



|                             |           |           |   |
|-----------------------------|-----------|-----------|---|
| Number of Lifetime Episodes |           |           |   |
| Units: Number               |           |           |   |
| arithmetic mean             | 3.1       | 3.2       |   |
| standard deviation          | $\pm 1.8$ | $\pm 2.4$ | - |



## End points

### End points reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | ALL ADT |
|-----------------------|---------|

Reporting group description:

Subjects meeting entrance criteria who were experiencing a major depressive episode with a HAM-D17 Total Score of greater than or equal 18 at baseline were enrolled into an 8-week Single-blind Prospective Treatment Phase (Phase A). All subjects received single-blind placebo plus an investigator determined, open-label, ADT (antidepressant therapy). Once assigned to an ADT by the investigator, subjects remained on the same ADT for the duration of the trial. At the Week 8 visit, the IWRS (Interactive web response system) determined based on scores entered by the investigator, whether a subject was a "Phase A Responder" or a "Phase A Inadequate Responder."

|                       |              |
|-----------------------|--------------|
| Reporting group title | 2mg Brex+ADT |
|-----------------------|--------------|

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Adjunctive 2 mg/day brexpiprazole-plus-ADT (2 mg/day brexpiprazole+ADT)

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

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Continued placebo-plus-ADT (placebo+ADT)

|                       |         |
|-----------------------|---------|
| Reporting group title | ALL ADT |
|-----------------------|---------|

Reporting group description:

Phase A+ included subjects who met criteria for a response at the end of the prospective treatment phase (Week 8 visit of Phase A) and subjects who were not suitable for randomization in Phase B per the judgment of the investigator or medical monitor. Treatment response in Phase A was determined at the Week 8 visit based on improvement or lack of improvement of the subject's depressive symptoms, which was confirmed by clinical criteria that prospectively defined response. Subject response was determined from clinical data that were entered into the IWRS at each visit. Subjects in Phase A+ received single-blind placebo+ADT for an additional 6 weeks, for a total of 14 weeks, and attended visits at Weeks 11 and 14.

### Primary: Change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in the Montgomery Asberg Depression Rating Scale (MADRS) Total Score

|                 |  |
|-----------------|--|
| End point title | Change from the end of Phase A (Week 8 visit) to the end of Phase B (Week 14 visit) in the Montgomery Asberg Depression Rating Scale (MADRS) Total Score |
|-----------------|--|

End point description:

The MADRS was utilized as the primary efficacy assessment of the subject's level of depression and was administered utilizing the Structured Interview Guide for the MADRS (SIGMA). Detailed instructions for administration of this structured interview was provided in the SIGMA. The MADRS consisted of 10 items each with 7 defined grades of severity. The rating was based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allowed a precise rating of severity. The rater decided whether the rating lied on predefined scale steps (0, 2, 4, 6) or between them (1, 3, 5). The 10 items were Apparent sadness, Reported sadness, Inner tension, Reduced sleep, Reduced appetite, Concentration difficulties, Lassitude, Inability to feel, Pessimistic thoughts, Suicidal thoughts.

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

End point timeframe:

From baseline (end of Phase A [Week 8]) to Week 14



|                                     |                 |                 |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>             | 2mg Brex+ADT    | Placebo+ADT     |  |  |
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 191             | 202             |  |  |
| Units: Participants                 |                 |                 |  |  |
| least squares mean (standard error) | -10.4 (± 0.63)  | -8.07 (± 0.61)  |  |  |

## Statistical analyses

|   |                                 |
|---|---------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis At Week 14 |
| Comparison groups                       | 2mg Brex+ADT v Placebo+ADT      |
| Number of subjects included in analysis | 393                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | superiority                     |
| P-value                                 | = 0.0074 <sup>[1]</sup>         |
| Method                                  | Mixed models analysis           |
| Parameter estimate                      | Mean difference (final values)  |
| Point estimate                          | -2.3                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -3.97                           |
| upper limit                             | -0.62                           |

Notes:

[1] - Comparison between treatment groups was carried out using MMRM (Mixed-model repeated measures), with trial site, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate.

## Secondary: Change from Baseline (end of Phase A [Week 8 visit] to end of Phase B (Week 14 visit) in Sheehan Disability Scale (SDS) Mean Score for the Efficacy Sample

|                 |  |
|-----------------|--|
| End point title | Change from Baseline (end of Phase A [Week 8 visit] to end of Phase B (Week 14 visit) in Sheehan Disability Scale (SDS) Mean Score for the Efficacy Sample |
|-----------------|--|

End point description:

The SDS was a self-rated instrument used to measure the effect of the subject's symptoms on work/school, social life, and family/home responsibilities. The SDS was a visual analogue scale that used spatio-visual, numeric, and verbal descriptive anchors simultaneously to assess disability across the 3 domains. 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. Scores of 5 and above were associated with significant functional impairment. In addition to the visual scale, the SDS included 2 questions related to productivity losses due to the psychiatric symptoms and impairment.

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

End point timeframe:

From baseline (end of Phase A [Week 8]) to Week 14



|                                     |                 |                 |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>             | 2mg Brex+ADT    | Placebo+ADT     |  |  |
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 187             | 200             |  |  |
| Units: Participants                 |                 |                 |  |  |
| least squares mean (standard error) | -1.63 (± 0.18)  | -1.41 (± 0.17)  |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical Analysis for Change At Week 14 |
| Comparison groups                       | 2mg Brex+ADT v Placebo+ADT                 |
| Number of subjects included in analysis | 387  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | = 0.3331 [2]                               |
| Method                                  | Mixed models analysis                      |
| Parameter estimate                      | Mean difference (final values)             |
| Point estimate                          | -0.22                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -0.66                                      |
| upper limit                             | 0.23                                       |

Notes:

[2] - Comparison between treatment groups was carried out using MMRM, with trial site, treatment group, visit, and treatment.group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

## Secondary: Change from Baseline (End of Phase A [Week 8 visit] to end of Phase B (Week 14 visit) in MADRS Total Score for the subpopulation with < 25% improvement from baseline of Phase A (Week 0) to end of Phase A (Week 8) in MADRS Total Score

|                 |   |
|-----------------|---|
| End point title | Change from Baseline (End of Phase A [Week 8 visit] to end of Phase B (Week 14 visit) in MADRS Total Score for the subpopulation with < 25% improvement from baseline of Phase A (Week 0) to end of Phase A (Week 8) in MADRS Total Score |
|-----------------|---|

End point description:

The MADRS was utilized as the efficacy assessment of the subject's level of depression and was administered utilizing the Structured Interview Guide for the MADRS (SIGMA). Detailed instructions for administration of this structured interview was provided in the SIGMA. The MADRS consisted of 10 items each with 7 defined grades of severity.

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

End point timeframe:

From baseline (end of Phase A [Week 8]) to Week 14



| End point values                    | 2mg Brex+ADT        | Placebo+ADT         |  |  |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type                  | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed         | 161                 | 158                 |  |  |
| Units: Participants                 |                     |                     |  |  |
| least squares mean (standard error) | -11.1 ( $\pm$ 0.71) | -8.87 ( $\pm$ 0.71) |  |  |

## Statistical analyses

| Statistical analysis title              | Statistical Analysis At Week 14 |
|---|---------------------------------|
| Comparison groups                       | 2mg Brex+ADT v Placebo+ADT      |
| Number of subjects included in analysis | 319                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | superiority                     |
| P-value                                 | = 0.0263 <sup>[3]</sup>         |
| Method                                  | Mixed models analysis           |
| Parameter estimate                      | Mean difference (final values)  |
| Point estimate                          | -2.25                           |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -4.23                           |
| upper limit                             | -0.27                           |

Notes:

[3] - Comparison between treatment groups was carried out using MMRM, with treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

## Secondary: Change from Baseline (End of Phase A [Week 8]) to end of Phase B (Week 14 visit) in MADRS Total Score for the subpopulation with anxious distress as specified in DSM-V.

|                 |  |
|-----------------|--|
| End point title | Change from Baseline (End of Phase A [Week 8]) to end of Phase B (Week 14 visit) in MADRS Total Score for the subpopulation with anxious distress as specified in DSM-V. |
|-----------------|--|

End point description:

To assess the change From End of Phase A to End of Phase B in MADRS Total Score for the Subpopulations With Anxious Distress as Specified in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V).

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

End point timeframe:

From baseline (end of Phase A [Week 8]) to Week 14

| End point values                    | 2mg Brex+ADT        | Placebo+ADT         |  |  |
|-------------------------------------|---------------------|---------------------|--|--|
| Subject group type                  | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed         | 124                 | 124                 |  |  |
| Units: Participants                 |                     |                     |  |  |
| least squares mean (standard error) | -11.8 ( $\pm$ 0.81) | -8.87 ( $\pm$ 0.81) |  |  |



## Statistical analyses

|   |                                 |
|---|---------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis At Week 14 |
| Comparison groups                       | 2mg Brex+ADT v Placebo+ADT      |
| Number of subjects included in analysis | 248                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | superiority                     |
| P-value                                 | = 0.0099 <sup>[4]</sup>         |
| Method                                  | Mixed models analysis           |
| Parameter estimate                      | Mean difference (final values)  |
| Point estimate                          | -2.98                           |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -5.24                           |
| upper limit                             | -0.72                           |

Notes:

[4] - Comparison between treatment groups was carried out using MMRM, with treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded throughout the trial.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | 2mg Brex+ADT |
|-----------------------|--------------|

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Adjunctive 2 mg/day brexpiprazole-plus-ADT (2 mg/day brexpiprazole+ADT)

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

Reporting group description:

Subjects with an inadequate response in Phase A who were negative for cocaine, marijuana, and other illicit drugs at the Week 6 visit and who, in the investigator's judgment, were suitable for randomization, were randomized at the end of prospective treatment (Week 8 visit of Phase A) to the following double-blind treatment regimen:

Continued placebo-plus-ADT (placebo+ADT)

| Serious adverse events                            | 2mg Brex+ADT    | Placebo+ADT     |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 1 / 192 (0.52%) | 0 / 202 (0.00%) |  |
| number of deaths (all causes)                     | 0               | 0               |  |
| number of deaths resulting from adverse events    | 0               | 0               |  |
| Ear and labyrinth disorders                       |                 |                 |  |
| Vertigo   |                 |                 |  |
| subjects affected / exposed                       | 1 / 192 (0.52%) | 0 / 202 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |

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

| Non-serious adverse events                            | 2mg Brex+ADT      | Placebo+ADT       |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 49 / 192 (25.52%) | 35 / 202 (17.33%) |  |



|   |  |  |  |
|---|--|--|--|
| Investigations<br>Weight increased<br>subjects affected / exposed<br>occurrences (all)  | 10 / 192 (5.21%)<br>10                             | 1 / 202 (0.50%)<br>1                                 |  |
| Nervous system disorders<br>Akathisia<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all) | 16 / 192 (8.33%)<br>17<br><br>7 / 192 (3.65%)<br>7 | 10 / 202 (4.95%)<br>12<br><br>15 / 202 (7.43%)<br>24 |  |
| Psychiatric disorders<br>Restlessness<br>subjects affected / exposed<br>occurrences (all)   | 16 / 192 (8.33%)<br>16                             | 4 / 202 (1.98%)<br>4                                 |  |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)  | 10 / 192 (5.21%)<br>11                             | 10 / 202 (4.95%)<br>11                               |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment  |
|----------------|--|
| 17 June 2014   | Amendment 1: Updated the title of the study to include one of the prespecified populations and changing the Director of Clinical Management.<br>Added additional analyses for prespecified populations; specifically:<br>Subjects who showed minimal improvement in Phase A of the trial (< 25% improvement from baseline of Phase A [Week 0] to end of Phase A [Week 8 visit] on MADRS Total Score).<br>Subjects with anxious distress as specified in DSM-V. |
| 15 August 2014 | Amendment 2: Changes were made to text because rollover to the open-label extension trial following participation in this trial was no longer available to subjects. The open-label extension trial was no longer allowing subjects to rollover because it had already exceeded the requirement for long-term exposure as defined by the International Conference on Harmonisation guidance (ICH E1A).   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported