



## Clinical trial results:

### A Multicenter, Randomized, Double-blind, Placebo-Controlled, Relapse Prevention Study With Vilazodone in Patients With Major Depressive Disorder

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2012-001950-25  |
| Trial protocol           | DE FI BG        |
| Global end of trial date | 11 October 2014 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 18 November 2017 |
| First version publication date | 18 November 2017 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | VLZ-MD-02 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01573598 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Forest Laboratories Inc, an Affiliate of Allergan plc; Allergan Limited                               |
| Sponsor organisation address | Allergan Limited Marlow International The Parkway, Marlow, United Kingdom, SL7 1YL                    |
| Public contact               | Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.com |
| Scientific contact           | Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.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:

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**Results analysis stage**

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|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 17 September 2015 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 11 October 2014   |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 11 October 2014   |
| Was the trial ended prematurely?                     | No                |

Notes:

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**General information about the trial**

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Main objective of the trial:

Evaluate the efficacy, safety, and tolerability of vilazodone relative to placebo in the prevention of depression relapse in patients with major depressive disorder

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 09 April 2012 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Bulgaria: 5        |
| Country: Number of subjects enrolled | Finland: 41        |
| Country: Number of subjects enrolled | Germany: 62        |
| Country: Number of subjects enrolled | Romania: 17        |
| Country: Number of subjects enrolled | Serbia: 39         |
| Country: Number of subjects enrolled | Ukraine: 15        |
| Country: Number of subjects enrolled | United States: 384 |
| Worldwide total number of subjects   | 563                |
| EEA total number of subjects         | 125                |

Notes:

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**Subjects enrolled per age group**

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|   |   |
|---|---|
| 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) | 539 |
| From 65 to 84 years  | 24  |
| 85 years and over    | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The 1-2 week Screening/Wash-Out Phase was followed by the 8 week Run-In Phase of open-label treatment with vilazodone 40 mg/day. The Run-In phase included 1213 patients. The Run-In Phase was followed by the 12-week open-label Stabilization Phase; 879 patients entered the Stabilization Phase. Subsequently, 563 patients were randomized.

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for the first 4 days of Week 21, vilazodone 10 mg for the last 3 days of Week 21, and matched placebo capsules from Week 22 through Week 50.

|  |          |
|--|----------|
| 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:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for the first 4 days of Week 21, vilazodone 10 mg for the last 3 days of Week 21, and matched placebo capsules from Week 22 through Week 50.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Vilazodone 20 mg |
|------------------|------------------|

Arm description:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for Weeks 21 through 49, vilazodone 10 mg for Week 49, and matching placebo for Week 50.

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

Dosage and administration details:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for Weeks 21 through 49, vilazodone 10 mg for Week 49, and matching placebo for Week 50.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Vilazodone 40 mg |
|------------------|------------------|

Arm description:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 to 48, vilazodone 20 mg for the first 4 days of Week 49, vilazodone 10 mg for the last 3 days of Week 49, and

matching placebo for Week 50.

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

Dosage and administration details:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 to 48, vilazodone 20 mg for the first 4 days of Week 49, vilazodone 10 mg for the last 3 days of Week 49, and matching placebo for Week 50.

| <b>Number of subjects in period 1</b> | Placebo | Vilazodone 20 mg | Vilazodone 40 mg |
|---------------------------------------|---------|------------------|------------------|
| Started                               | 192     | 185              | 186              |
| Completed                             | 136     | 119              | 121              |
| Not completed                         | 56      | 66               | 65               |
| Consent withdrawn by subject          | 17      | 16               | 9                |
| Adverse event, non-fatal              | 2       | 4                | 1                |
| Other Reasons                         | 4       | 4                | 5                |
| Lost to follow-up                     | 3       | 10               | 11               |
| Relapse Event                         | 23      | 20               | 25               |
| Protocol deviation                    | 7       | 12               | 14               |

## Baseline characteristics

### Reporting groups

|  |                  |
|--|------------------|
| Reporting group title  | Placebo          |
| Reporting group description:<br>Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for the first 4 days of Week 21, vilazodone 10 mg for the last 3 days of Week 21, and matched placebo capsules from Week 22 through Week 50. |                  |
| Reporting group title  | Vilazodone 20 mg |
| Reporting group description:<br>Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for Weeks 21 through 49, vilazodone 10 mg for Week 49, and matching placebo for Week 50.   |                  |
| Reporting group title  | Vilazodone 40 mg |
| Reporting group description:<br>Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 to 48, vilazodone 20 mg for the first 4 days of Week 49, vilazodone 10 mg for the last 3 days of Week 49, and matching placebo for Week 50.                               |                  |

| Reporting group values                | Placebo | Vilazodone 20 mg | Vilazodone 40 mg |
|---------------------------------------|---------|------------------|------------------|
| Number of subjects                    | 192     | 185              | 186              |
| Age categorical<br>Units: Subjects    |         |                  |                  |
| Adults (18-64 years)                  | 184     | 174              | 181              |
| From 65-84 years                      | 8       | 11               | 5                |
| Age Continuous  <br>Units: years      |         |                  |                  |
| arithmetic mean                       | 46.7    | 45.2             | 43.8             |
| standard deviation                    | ± 11.9  | ± 12.6           | ± 12.0           |
| Gender categorical<br>Units: Subjects |         |                  |                  |
| Female                                | 116     | 113              | 126              |
| Male                                  | 76      | 72               | 60               |

| Reporting group values                | Total |  |  |
|---------------------------------------|-------|--|--|
| Number of subjects                    | 563   |  |  |
| Age categorical<br>Units: Subjects    |       |  |  |
| Adults (18-64 years)                  | 539   |  |  |
| From 65-84 years                      | 24    |  |  |
| Age Continuous  <br>Units: years      |       |  |  |
| arithmetic mean                       | -     |  |  |
| standard deviation                    | -     |  |  |
| Gender categorical<br>Units: Subjects |       |  |  |
| Female                                | 355   |  |  |
| Male                                  | 208   |  |  |

## End points

### End points reporting groups

|  |                  |
|--|------------------|
| Reporting group title  | Placebo          |
| Reporting group description:<br>Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for the first 4 days of Week 21, vilazodone 10 mg for the last 3 days of Week 21, and matched placebo capsules from Week 22 through Week 50. |                  |
| Reporting group title  | Vilazodone 20 mg |
| Reporting group description:<br>Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for Weeks 21 through 49, vilazodone 10 mg for Week 49, and matching placebo for Week 50.   |                  |
| Reporting group title  | Vilazodone 40 mg |
| Reporting group description:<br>Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 to 48, vilazodone 20 mg for the first 4 days of Week 49, vilazodone 10 mg for the last 3 days of Week 49, and matching placebo for Week 50.                               |                  |

### Primary: Time to First Relapse During the Double-Blind Treatment Phase (DBP)

|   |  |
|---|--|
| End point title   | Time to First Relapse During the Double-Blind Treatment Phase (DBP) <sup>[1]</sup> |
| End point description:<br>Relapse is defined as meeting any 1 or more of the following: 1) Montgomery-Åsberg Depression Rating Scale (MADRS) score of $\geq 18$ and meeting criteria for a major depressive episode (MDE) per the MDE Checklist; 2) MADRS total score (from 0 [absence of symptoms] to 60 [maximum severity]) $\geq 18$ at 2 consecutive visits (where the second visit is in the 7-14 day period after the first visit); 3) Discontinuation for insufficient therapeutic response during the DBP. Insufficient therapeutic response is defined by: a) The inability to continue in the study due to worsening of depression, as determined by a need for change in pharmacological treatment and an increase in Clinical Global Impressions-Severity (CGI-S) score (from 0 [normal state] to 7 [among the most extremely ill]) of $\geq 2$ compared with that obtained at Week 20; b) Need for hospitalization due to worsening of depression. |  |
| End point type  | Primary  |
| End point timeframe:<br>Randomization date (Week 20) to the relapse date, up to 28 weeks (Week 48)  |  |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: No statistical analyses for this end point.   |  |

| End point values                 | Placebo            | Vilazodone 20 mg   | Vilazodone 40 mg   |  |
|----------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type               | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed      | 190 <sup>[2]</sup> | 185 <sup>[3]</sup> | 186 <sup>[4]</sup> |  |
| Units: Days                      |                    |                    |                    |  |
| median (confidence interval 95%) | 999 (999 to 999)   | 999 (999 to 999)   | 999 (999 to 999)   |  |

Notes:

[2] - No differences between treatment groups; 999 represents N/A

[3] - No differences between treatment groups; 999 represents N/A

[4] - No differences between treatment groups; 999 represents N/A

### Statistical analyses





## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored from informed consent signature to the end of study for each subject.

Adverse event reporting additional description:

The Run-In Phase (RIP) Safety Population consists of all screened pts who have a screening number, signed informed consent, and who took at least 1 dose of open-label vilazodone during the RIP of the study. The Double-blind (DB) Safety Population consists of all randomized pts who took at least 1 dose of DB investigational product.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Placebo - Double Blind Phase |
|-----------------------|------------------------------|

Reporting group description:

Vilazodone 20 mg taken orally once per day the first 4 days of Week 21, vilazodone 10 mg for the last 3 days of Week 21, and matched placebo capsules taken orally once per day from Weeks 22 through Week 50.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Vilazodone 40 mg - Double Blind Phase |
|-----------------------|---------------------------------------|

Reporting group description:

Vilazodone 40 mg taken orally once per day for Weeks 3 through 48, vilazodone 20 mg for the first 4 days of Week 49, vilazodone 10 mg for the last 3 days of Week 49, and matching placebo for Week 50.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Vilazodone 20 mg - Double Blind Phase |
|-----------------------|---------------------------------------|

Reporting group description:

Vilazodone 20 mg taken orally once per day for Weeks 21 through 48, vilazodone 10 mg for Week 49, and matching placebo for Week 50.

| Serious adverse events  | Placebo - Double Blind Phase | Vilazodone 40 mg - Double Blind Phase | Vilazodone 20 mg - Double Blind Phase |
|---|------------------------------|---------------------------------------|---------------------------------------|
| Total subjects affected by serious adverse events                   |                              |                                       |                                       |
| subjects affected / exposed   | 4 / 192 (2.08%)              | 1 / 186 (0.54%)                       | 5 / 185 (2.70%)                       |
| number of deaths (all causes)                                       | 0                            | 0                                     | 0                                     |
| number of deaths resulting from adverse events                      | 0                            | 0                                     | 0                                     |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                              |                                       |                                       |
| Pancreatic neoplasm   |                              |                                       |                                       |
| subjects affected / exposed   | 0 / 192 (0.00%)              | 0 / 186 (0.00%)                       | 1 / 185 (0.54%)                       |
| occurrences causally related to treatment / all                     | 0 / 0                        | 0 / 0                                 | 0 / 1                                 |
| deaths causally related to treatment / all                          | 0 / 0                        | 0 / 0                                 | 0 / 0                                 |
| Prostate cancer   |                              |                                       |                                       |
| subjects affected / exposed   | 0 / 192 (0.00%)              | 0 / 186 (0.00%)                       | 1 / 185 (0.54%)                       |
| occurrences causally related to treatment / all                     | 0 / 0                        | 0 / 0                                 | 0 / 1                                 |
| deaths causally related to treatment / all                          | 0 / 0                        | 0 / 0                                 | 0 / 0                                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Investigations                                       |                 |                 |                 |
| Urine output decreased                               |                 |                 |                 |
| subjects affected / exposed                          | 1 / 192 (0.52%) | 0 / 186 (0.00%) | 0 / 185 (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           |
| Injury, poisoning and procedural complications       |                 |                 |                 |
| Overdose   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 192 (0.00%) | 0 / 186 (0.00%) | 1 / 185 (0.54%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                             |                 |                 |                 |
| Hypoaesthesia  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 192 (0.00%) | 0 / 186 (0.00%) | 1 / 185 (0.54%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Cervical radiculopathy                               |                 |                 |                 |
| subjects affected / exposed                          | 1 / 192 (0.52%) | 0 / 186 (0.00%) | 0 / 185 (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           |
| General disorders and administration site conditions |                 |                 |                 |
| Chest pain   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 192 (0.52%) | 0 / 186 (0.00%) | 0 / 185 (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           |
| Gastrointestinal disorders                           |                 |                 |                 |
| Melaena  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 192 (0.52%) | 0 / 186 (0.00%) | 0 / 185 (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           |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |                 |
| Pneumothorax   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 192 (0.00%) | 0 / 186 (0.00%) | 1 / 185 (0.54%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Renal and urinary disorders                     |                 |                 |                 |
| Calculus ureteric                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 192 (0.00%) | 1 / 186 (0.54%) | 0 / 185 (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           |
| Obstructive uropathy                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 192 (0.00%) | 1 / 186 (0.54%) | 0 / 185 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Suicidal ideation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 192 (0.00%) | 0 / 186 (0.00%) | 1 / 185 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 192 (0.52%) | 0 / 186 (0.00%) | 0 / 185 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Fibromyalgia                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 192 (0.52%) | 0 / 186 (0.00%) | 0 / 185 (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           |
| Intervertebral disc displacement                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 192 (0.52%) | 0 / 186 (0.00%) | 0 / 185 (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                            | Placebo - Double Blind Phase | Vilazodone 40 mg - Double Blind Phase | Vilazodone 20 mg - Double Blind Phase |
|---|------------------------------|---------------------------------------|---------------------------------------|
| Total subjects affected by non-serious adverse events |                              |                                       |                                       |
| subjects affected / exposed                           | 103 / 192 (53.65%)           | 115 / 186 (61.83%)                    | 101 / 185 (54.59%)                    |
| Investigations  |                              |                                       |                                       |

|  |                        |                        |                        |
|--|------------------------|------------------------|------------------------|
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                               | 4 / 192 (2.08%)<br>4   | 10 / 186 (5.38%)<br>10 | 7 / 185 (3.78%)<br>8   |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)           | 9 / 192 (4.69%)<br>11  | 18 / 186 (9.68%)<br>26 | 15 / 185 (8.11%)<br>20 |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)        | 9 / 192 (4.69%)<br>11  | 15 / 186 (8.06%)<br>16 | 13 / 185 (7.03%)<br>13 |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 14 / 192 (7.29%)<br>16 | 15 / 186 (8.06%)<br>20 | 16 / 185 (8.65%)<br>19 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)              | 12 / 192 (6.25%)<br>16 | 10 / 186 (5.38%)<br>11 | 12 / 185 (6.49%)<br>13 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 17 July 2012      | (1) add recurrent depression as an inclusion criteria; (2) change the inclusion MADRS score to 26; (3) add AE assessment at Visit 1; (4) allow for changes in MADRS scores during the Screening Period; (5) change the relapse criteria and add Major Depressive Episode Checklist; (6) add justification of the use of the placebo arm in relapse prevention; (7) revise 3 exclusion criteria; (8) delete a laboratory test from the Chemistry panel; (9) add washout language; (10) add the MADRS at every visit; (11) revise the efficacy analyses section to clarify relapse criteria; (12) add the description of the MMRM approach for analysis of additional efficacy parameters; (13) adjust the assumption on relapse event rates and recalculating the power of the study; (14) update Gastrointestinal and Sedatives/Hypnotics medications |
| 21 May 2013       | change the developmental phase of the trial for Non-US countries from Phase 4 to Phase 3  |
| 27 January 2014   | (1) clarify the approximate number of planned enrolled patients; (2) revise the language in the introduction related to the IB version date and adverse reactions in previous trials; (3) correct a discrepancy regarding down-titration duration at the beginning of the DBP; (4) perform an administrative update to exclusion criteria to accommodate for Non-US sites; (5) clarify open-label down-taper language; (6) update the list of anti-insomnia agents; (7) clarify the definition of CGI-S and correct the training requirements; (8) update the relapse assumptions; (9) update hypnotics and antineoplastic medications  |
| 29 September 2014 | (1) add the description of sensitivity analyses on the primary efficacy parameter in response to FDA statistical comments; (2) delete the protocol deviation section; (3) add a stratification factor of US/non-US category in the primary efficacy analysis based on a FDA statistical comment; (4) add summaries on exposure, concomitant medication, and safety parameters during RIP and SP combined based on RIP Safety Population; (5) modify protocol deviation language   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported