



Clinical trial results:

A 6-Month, Open-Label, Flexible-Dosage (150 to 200 mg/day) Extension Study of the Safety and Efficacy of Armodafinil Treatment as Adjunctive Therapy in Adults With Major Depression Associated With Bipolar I Disorder

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2009-016648-38 |
| Trial protocol | FR BG ES DE FI SK HU IT |
| Global end of trial date | 09 October 2013 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 17 July 2016 |
| First version publication date | 26 June 2015 |
| Version creation reason | • Correction of full data set QC'd, no differences found |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | C10953/3074 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01121536 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Teva Branded Pharmaceutical Products R&D, Inc. |
| Sponsor organisation address | 41 Moores Road, Frazer, PA, United States, 19355-1113 |
| Public contact | Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 1 215-591-3000, ustevatrials@tevapharm.com |
| Scientific contact | Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 1 215-591-3000, ustevatrials@tevapharm.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 | 30 June 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-----------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 09 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety and tolerability of long term (6 months) armodafinil treatment as adjunctive therapy to mood-stabilizing medications in adults with bipolar I disorder whose most recent episode was a depressive episode.

Protection of trial subjects:

This study was conducted in full accordance with the Good Clinical Practice (GCP): Consolidated Guideline approved by the International Conference on Harmonisation (ICH) and any applicable national and local laws and regulations (eg, Code of Federal Regulations [CFR] Title 21, Parts 11, 50, 54, 56, 312, and 314; European Union Directive 2001/20/EC, and 2005/28/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use). Information regarding any investigational study centers participating in this study that could not comply with these standards was documented.

Written and/or oral information about the study was provided to all patients in a language understandable by the patients. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each patient before any study procedures or assessments were done. It was explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Each patient's willingness to participate in the study was documented in writing in a consent form that was signed by the patient with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the patients.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 22 April 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Poland: 90 |
| Country: Number of subjects enrolled | Slovakia: 7 |
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | Bulgaria: 47 |
| Country: Number of subjects enrolled | France: 19 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Hungary: 17 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Argentina: 73 |
| Country: Number of subjects enrolled | Australia: 11 |
| Country: Number of subjects enrolled | Brazil: 6 |
| Country: Number of subjects enrolled | Canada: 9 |
| Country: Number of subjects enrolled | Croatia: 10 |
| Country: Number of subjects enrolled | Serbia: 30 |
| Country: Number of subjects enrolled | Ukraine: 123 |
| Country: Number of subjects enrolled | United States: 382 |
| Country: Number of subjects enrolled | South Africa: 29 |
| Worldwide total number of subjects | 867 |
| EEA total number of subjects | 204 |

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) | 862 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The final visit of the double-blind study (C10953/3071 [2009-016667-11], C10953/3072 [2009-016634-27], or C10953/3073 [2010-023623-26]) serves as the enrollment visit for this study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|----------------------------|
| Arm title | Armodafinil 150-200 mg/Day |
|-----------|----------------------------|

Arm description:

Participants began taking armodafinil at a dosage of 50 mg/day; the dosage was increased by 50 mg/day on days 2 and 4, up to a dosage of 150 mg/day. At the discretion of the investigator, the dosage of armodafinil may be increased to 200 mg/day on day 6 or thereafter, and reduced to 150mg/day if the higher dose is not well tolerated. Treatment was administered for six months.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | armodafinil |
| Investigational medicinal product code | |
| Other name | CEP-10953, Nuvigil |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Armodafinil tablets, taken orally, once daily in the morning. Participants began taking armodafinil at a dosage of 50 mg/day; the dosage was increased by 50 mg/day on days 2 and 4, up to a dosage of 150 mg/day. At the discretion of the investigator, the dosage of armodafinil may be increased to 200 mg/day on day 6 or thereafter, and reduced to 150mg/day if the higher dose is not well tolerated. Treatment was administered for six months.

| Number of subjects in period 1 | Armodafinil 150-200 mg/Day |
|--|----------------------------|
| Started | 867 |
| Safety population | 863 |
| Full analysis population | 859 |
| Completed | 506 |
| Not completed | 361 |
| Consent withdrawn by subject | 65 |
| Adverse event, non-fatal | 63 |
| Not specified | 118 |
| Noncompliance with study drug administration | 12 |
| Noncompliance with study procedures | 9 |

| | |
|--------------------|----|
| Lost to follow-up | 39 |
| Lack of efficacy | 35 |
| Protocol deviation | 20 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall Trial |
| Reporting group description: - | |

| Reporting group values | Overall Trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 867 | 867 | |
| 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 44.2 | | |
| standard deviation | ± 10.96 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 525 | 525 | |
| Male | 342 | 342 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 91 | 91 | |
| Not Hispanic or Latino | 752 | 752 | |
| Unknown | 24 | 24 | |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | |
| Asian | 10 | 10 | |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | |
| Black or African American | 118 | 118 | |
| White | 709 | 709 | |
| Unknown or Not Reported | 28 | 28 | |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 83.7 | | |
| standard deviation | ± 19.75 | - | |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 168.8 | | |

| | | | |
|--------------------------|--------|---|--|
| standard deviation | ± 9.54 | - | |
| Body Mass Index | | | |
| Units: kg/m ² | | | |
| arithmetic mean | 29.4 | | |
| standard deviation | ± 6.43 | - | |

End points

End points reporting groups

| | |
|--|----------------------------|
| Reporting group title | Armodafinil 150-200 mg/Day |
| Reporting group description: | |
| Participants began taking armodafinil at a dosage of 50 mg/day; the dosage was increased by 50 mg/day on days 2 and 4, up to a dosage of 150 mg/day. At the discretion of the investigator, the dosage of armodafinil may be increased to 200 mg/day on day 6 or thereafter, and reduced to 150mg/day if the higher dose is not well tolerated. Treatment was administered for six months. | |

Primary: Participants With Treatment-Emergent Adverse Events (TEAE)

| | |
|-----------------|---|
| End point title | Participants With Treatment-Emergent Adverse Events |
|-----------------|---|

End point description:

AEs were graded by the investigator for severity on a three-point scale: mild, moderate and severe. Causality is graded as either related or not related. A serious adverse event (SAE) is an AE resulting in death, a life-threatening adverse event, hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or an important medical event that may require medical intervention to prevent any of the previous results.

Protocol-defined adverse events requiring expedited reporting included skin rash, hypersensitivity reaction, emergent suicidal ideation or suicide attempt, and psychosis.

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

End point timeframe:

Day 1 up to Month 6

Notes:

[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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

| End point values | Armodafinil 150-200 mg/Day | | | |
|--|----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 863 ^[2] | | | |
| Units: participants | | | | |
| >=1 adverse event | 423 | | | |
| Severe adverse event | 26 | | | |
| Treatment-related adverse event | 219 | | | |
| Deaths | 0 | | | |
| Other serious adverse events | 27 | | | |
| Withdrawn from study due to adverse events | 57 | | | |
| Protocol-defined adverse events | 19 | | | |

Notes:

[2] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Clinically Significant Abnormal Serum Chemistry Values

| | |
|-----------------|---|
| End point title | Participants With Clinically Significant Abnormal Serum Chemistry Values ^[3] |
|-----------------|---|

End point description:

Summary of serum chemistry tests in which at least one participant had a during study value that was clinically significant abnormal. The test name and criterion for clinically significant abnormal appear in each row.

ULN=upper limit of normal

Uric acid has a normal range of 125-494 µmol/L. Criterion for clinically significant abnormal are different for men and women.

GGT = gamma-glutamyl transpeptidase with a normal range of 4-61 U/L

ALT = alanine aminotransferase with a normal range of 6-43 U/L

BUN = blood urea nitrogen with a normal range of 1.4-8.6 mmol/L

AST = aspartate aminotransferase with a normal range of 9-36 U/L

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

End point timeframe:

Day 1 to Month 6

Notes:

[3] - 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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

| End point values | Armodafinil 150-200 mg/Day | | | |
|----------------------------------|----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 763 ^[4] | | | |
| Units: participants | | | | |
| >=1 clinical significant value | 41 | | | |
| Uric Acid, M>=625, F>=506 µmol/L | 17 | | | |
| GGT, >=3*ULN | 16 | | | |
| ALT, >=3*ULN | 7 | | | |
| BUN, >=10.71 mmol/L | 7 | | | |
| AST, >=3*ULN | 3 | | | |

Notes:

[4] - Safety population with post-baseline serum chemistry assessments

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Clinically Significant Abnormal Hematology Values

| | |
|-----------------|--|
| End point title | Participants With Clinically Significant Abnormal Hematology Values ^[5] |
|-----------------|--|

End point description:

Summary of hematology tests in which at least one participant had a during study value that was clinically significant abnormal. The test name and criterion for clinically significant abnormal appear in each row.

ULN=upper limit of normal

WBC - white blood cell counts with a normal range of 3.8 t 10.7 10⁹/L.

Hemoglobin with a normal range of 115-181 g/L

Hematocrit with a normal range of 0.34-0.54 L/L

Platelet counts with a normal range of 130-400 10⁹/L

ANC= absolute neutrophil counts with a normal range of 1.96-7.23 10⁹/L

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

End point timeframe:

Day 1 to Month 6

Notes:

[5] - 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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

| | | | | |
|------------------------------------|----------------------------------|--|--|--|
| End point values | Armodafinil 150-200 mg/Day | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 757 ^[6] | | | |
| Units: participants | | | | |
| >=1 clinical significant value | 13 | | | |
| WBC, <=3*10 ⁹ /L | 5 | | | |
| Hemoglobin, M<=115, F<=95 g/L | 4 | | | |
| Hematocrit, M<0.37, F<0.32 L/L | 8 | | | |
| Platelets, <=75*10 ⁹ /L | 1 | | | |
| ANC, <=1*10 ⁹ /L | 2 | | | |

Notes:

[6] - Safety population with post-baseline hematology assessments

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Clinically Significant Abnormal Urinalysis Values

| | |
|-----------------|--|
| End point title | Participants With Clinically Significant Abnormal Urinalysis Values ^[7] |
|-----------------|--|

End point description:

Summary of urinalysis tests in which at least one participant had a during study value that was clinically significant abnormal. Criterion for clinically significant abnormal urinalysis tests was >=2 unit increase from baseline.

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

End point timeframe:

Day 1 to Month 6

Notes:

[7] - 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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

| | | | | |
|--------------------------------|----------------------------------|--|--|--|
| End point values | Armodafinil 150-200 mg/Day | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 761 ^[8] | | | |
| Units: participants | | | | |
| >=1 clinical significant value | 28 | | | |
| Urine hemoglobin | 22 | | | |
| Urine glucose | 2 | | | |
| Ketones | 2 | | | |
| Urine total protein | 2 | | | |

Notes:

[8] - Safety population with post-baseline urinalysis assessments

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Clinically Significant Abnormal Vital Signs Values

| | |
|-----------------|---|
| End point title | Participants With Clinically Significant Abnormal Vital Signs Values ^[9] |
|-----------------|---|

End point description:

Summary of vital signs tests in which at least one participant had a during study value that was clinically significant abnormal. Criterion for clinically significant abnormal vital signs are based on FDA Neuropharmacological Division criteria:

Pulse high: ≥ 120 beats per minute (bpm) and increase of ≥ 15 bpm from baseline

Pulse low: ≤ 50 bpm and decrease of ≥ 15 bpm from baseline

Sitting systolic blood pressure high: ≥ 180 mm Hg and increase of ≥ 20 mm HG from baseline

Sitting systolic blood pressure low: ≤ 90 mm Hg and decrease of ≥ 20 mm HG from baseline

Sitting diastolic blood pressure high: ≥ 105 mm Hg and increase of ≥ 15 mm HG from baseline

Sitting diastolic blood pressure low: ≤ 50 mm Hg and decrease of ≥ 15 mm HG from baseline

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

End point timeframe:

Day 1 to Month 6

Notes:

[9] - 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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

| | | | | |
|---------------------------------------|----------------------------------|--|--|--|
| End point values | Armodafinil 150-200 mg/Day | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 860 ^[10] | | | |
| Units: participants | | | | |
| ≥ 1 clinical significant value | 19 | | | |
| Pulse high | 2 | | | |
| Pulse low | 2 | | | |
| Sitting systolic blood pressure high | 3 | | | |
| Sitting systolic blood pressure low | 8 | | | |
| Sitting diastolic blood pressure high | 5 | | | |
| Sitting diastolic blood pressure low | 2 | | | |

Notes:

[10] - Safety population with post-baseline vital signs assessments

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Endpoint in Electrocardiogram (ECG) Values

| | |
|-----------------|--|
| End point title | Change From Baseline to Endpoint in Electrocardiogram (ECG) Values ^[11] |
|-----------------|--|

End point description:

ECG was conducted at baseline which was before the first dose of study drug in the double-blind study, and at the month-6 visit of the open-label study (or early termination).

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

End point timeframe:

Day 0 (baseline), Month 6 or last postbaseline observation

Notes:

[11] - 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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

| | | | | |
|--------------------------------------|----------------------------------|--|--|--|
| End point values | Armodafinil 150-200 mg/Day | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 759 ^[12] | | | |
| Units: msec | | | | |
| arithmetic mean (standard deviation) | | | | |
| PR interval | 0.2 (± 16.6) | | | |
| QRS interval | 0 (± 7.03) | | | |
| QT interval | 1.4 (± 25.66) | | | |
| QTc interval Bazett | 2.2 (± 19.5) | | | |
| QTc interval Fredericia | 1.9 (± 15.36) | | | |
| RR interval | -2.2 (± 137.98) | | | |

Notes:

[12] - Safety population of treated participants with both baseline and postbaseline ECG assessments

Statistical analyses

No statistical analyses for this end point

Primary: Physical Examination Shifts From Baseline to Endpoint

| | |
|-----------------|---|
| End point title | Physical Examination Shifts From Baseline to Endpoint ^[13] |
|-----------------|---|

End point description:

Baseline is the day prior to double-blind treatment. Assessments are summarized as normal or abnormal. The first assessment is the baseline assessment followed by the endpoint assessment. For example 'normal/abnormal' indicates participants who were normal at baseline and abnormal at endpoint.

HEENT = head, eyes, ears, nose and throat.

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

End point timeframe:

Day 0 (baseline), Month 6 (or last postbaseline observation)

Notes:

[13] - 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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

| End point values | Armodafinil 150-200 mg/Day | | | |
|--|----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 863 ^[14] | | | |
| Units: participants | | | | |
| General appearance; normal/normal | 714 | | | |
| General appearance; normal/abnormal | 8 | | | |
| General appearance; abnormal/normal | 23 | | | |
| General appearance; abnormal/abnormal | 40 | | | |
| HEENT: normal/normal | 753 | | | |
| HEENT: normal/abnormal | 3 | | | |
| HEENT: abnormal/normal | 15 | | | |
| HEENT: abnormal/abnormal | 13 | | | |
| Chest+lungs: normal/normal | 780 | | | |
| Chest+lungs: normal/abnormal | 0 | | | |
| Chest+lungs: abnormal/normal | 5 | | | |
| Chest+lungs: abnormal/abnormal | 0 | | | |
| Heart: normal/normal | 781 | | | |
| Heart: normal/abnormal | 2 | | | |
| Heart: abnormal/normal | 1 | | | |
| Heart: abnormal/abnormal | 1 | | | |
| Abdomen: normal/normal | 751 | | | |
| Abdomen: normal/abnormal | 5 | | | |
| Abdomen: abnormal/normal | 16 | | | |
| Abdomen: abnormal/abnormal | 13 | | | |
| Musculoskeletal: normal/normal | 756 | | | |
| Musculoskeletal: normal/abnormal | 7 | | | |
| Musculoskeletal: abnormal/normal | 11 | | | |
| Musculoskeletal: abnormal/abnormal | 11 | | | |
| Skin: normal/normal | 707 | | | |
| Skin: normal/abnormal | 9 | | | |
| Skin: abnormal/normal | 41 | | | |
| Skin: abnormal/abnormal | 28 | | | |
| Lymph nodes: normal/normal | 779 | | | |
| Lymph nodes: normal/abnormal | 0 | | | |
| Lymph nodes: abnormal/normal | 0 | | | |
| Lymph nodes: abnormal/abnormal | 1 | | | |
| Neurological: normal/normal | 777 | | | |
| Neurological: normal/abnormal | 2 | | | |
| Neurological: abnormal/normal | 2 | | | |
| Neurological: abnormal/abnormal | 3 | | | |

Notes:

[14] - Safety population of treated participants with baseline and endpoint assessments.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Endpoint in Body Weight

| | |
|-----------------|---|
| End point title | Change From Baseline to Endpoint in Body Weight ^[15] |
|-----------------|---|

End point description:

Baseline was the score before the first dose of study drug in the double-blind study.

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

End point timeframe:

Day 0 (baseline), Month 6 (or last postbaseline observation)

Notes:

[15] - 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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

| End point values | Armodafinil 150-200 mg/Day | | | |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 788 ^[16] | | | |
| Units: kg | | | | |
| arithmetic mean (standard deviation) | -0.8 (± 5.67) | | | |

Notes:

[16] - Safety population of treated participants with both baseline and postbaseline assessments.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Endpoint in the Young Mania Rating Scale (YMRS) Total Score

| | |
|-----------------|---|
| End point title | Change From Baseline to Endpoint in the Young Mania Rating Scale (YMRS) Total Score ^[17] |
|-----------------|---|

End point description:

The YMRS is a clinician-rated, 11-item checklist used to measure the severity of manic episodes. Information for assigning scores is gained from the participant's subjective reported symptoms over the previous 48 hours and from clinical observation during the interview. Seven items are ranked 0 through 4 and have descriptors associated with each severity level. Four items (irritability, speech, content, and disruptive-aggressive behavior) are scored 0 through 8 and have descriptors for every second increment. The total scale is 0-60. A score of ≤12 indicates remission of manic symptoms, and higher scores indicate greater severity of mania. Negative change from baseline scores indicate a decrease in severity of mania.

Baseline was the score before the first dose of study drug in the double-blind study.

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

End point timeframe:

Day 0 (baseline), Month 6 or last postbaseline observation

Notes:

[17] - 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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

| End point values | Armodafinil 150-200 mg/Day | | | |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 858 ^[18] | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.7 (± 4.28) | | | |

Notes:

[18] - The safety analysis set includes randomized participants who took 1 or more doses of study drug. The

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Findings During the Open-Label Study on the Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version

| | |
|-----------------|---|
| End point title | Participants With Findings During the Open-Label Study on the Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version ^[19] |
|-----------------|---|

End point description:

The C-SSRS is a clinician-rated scale that assesses suicidality from ideation to behaviors and monitors the potential emergence of suicidality in clinical studies. The number of participants who had findings on any of the C-SSRS-SLV categories at any of the time frames are indicated.

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

End point timeframe:

Day 1, Week 1, Months 1, 2, 4 and 6 or last postbaseline visit

Notes:

[19] - 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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

| End point values | Armodafinil 150-200 mg/Day | | | |
|--|----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 863 ^[20] | | | |
| Units: participants | | | | |
| Suicidal behavior - Actual attempt | 1 | | | |
| Non-suicidal self-injurious behaviour | 1 | | | |
| Suicidal behavior - Interrupted attempt | 0 | | | |
| Suicidal behavior - Aborted attempt | 0 | | | |
| Suicidal behavior - suicidal behavior | 0 | | | |
| Suicidal behavior - Preparatory acts/behavior | 1 | | | |
| Suicidal behavior - Completed suicide | 0 | | | |
| Suicidal ideation - Wish to be dead | 15 | | | |
| Non-specific active suicidal thoughts | 4 | | | |
| Any methods (not plan) w/o intent to act | 2 | | | |
| Some intent to act, w/o specific plan | 1 | | | |
| Suicidal ideation - Specific plan and intent | 1 | | | |

Notes:

[20] - Safety population; only 19 participants were asked the last three questions as the inclusion of thes

Statistical analyses

Primary: Change From Baseline to Endpoint in the Insomnia Severity Index (ISI) Total Score

| | |
|-----------------|---|
| End point title | Change From Baseline to Endpoint in the Insomnia Severity Index (ISI) Total Score ^[21] |
|-----------------|---|

End point description:

The ISI is a participant-rated, 7-item questionnaire designed to assess the severity of the participant's insomnia. Each item is ranked 0 (none) through 4 (very severe) and has a descriptor associated with each severity level. Total range is 0 (no insomnia) to 28 (very severe insomnia). Responses to each item are added to obtain a total score to determine the severity of insomnia. Negative change from baseline scores indicate a decrease in severity of insomnia. Baseline was the assessment before the first dose of study drug in the double-blind study.

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

End point timeframe:

Day 0 (baseline), Month 6 (or last postbaseline observation)

Notes:

[21] - 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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

| | | | | |
|--------------------------------------|----------------------------------|--|--|--|
| End point values | Armodafinil 150-200 mg/Day | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 855 ^[22] | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -9.1 (± 7.66) | | | |

Notes:

[22] - Safety population of treated participants with both a baseline and postbaseline assessment.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Endpoint in the Hamilton Anxiety Scale (HAM-A) Total Score

| | |
|-----------------|--|
| End point title | Change From Baseline to Endpoint in the Hamilton Anxiety Scale (HAM-A) Total Score ^[23] |
|-----------------|--|

End point description:

HAM-A measures the severity of anxiety symptoms. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0-56, where <17 indicates mild severity, 18-24 mild to moderate severity and 25-30 moderate to severe. Negative change from baseline scores indicate a decrease in severity of anxiety.

Baseline was the score before the first dose of study drug in the double-blind study.

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

End point timeframe:

Day 0 (baseline), Month 6 or last postbaseline observation

Notes:

[23] - 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.

Justification: This extension study has a single treatment arm. As such, there are no formal statistical

analyses done.

| End point values | Armodafinil 150-200 mg/Day | | | |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 786 ^[24] | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -6.2 (± 5.68) | | | |

Notes:

[24] - Safety population of participants with both a baseline and postbaseline assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 1 and Months 1, 2, 4, 6 and Endpoint in the Total Score From the 30-Item Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C30)

| | |
|-----------------|--|
| End point title | Change From Baseline to Week 1 and Months 1, 2, 4, 6 and Endpoint in the Total Score From the 30-Item Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C30) |
|-----------------|--|

End point description:

The IDS-C30 is a standardized 30-item, clinician-rated scale to assess the severity of a participant's depressive symptoms. Every effort was made to have the same rater evaluate a participant across all visits.

Total scores range from 0-84, with a score of 0 indicating no depression and a score of 84 indicating the most severe depression. Negative change from baseline values indicate improvement in the severity of depression.

Baseline was the score before the first dose of study drug in the double-blind study.

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

End point timeframe:

Day 0 (baseline), Week 1, Months 1, 2, 4, 6 and the last postbaseline assessment)

| End point values | Armodafinil 150-200 mg/Day | | | |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 859 ^[25] | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=837) | -23.7 (± 12.1) | | | |
| Month 1 (n=793) | -25.8 (± 11.61) | | | |
| Month 2 (n=716) | -27.6 (± 11.38) | | | |
| Month 4 (n=578) | -29.2 (± 11.68) | | | |

| | | | | |
|------------------|----------------------|--|--|--|
| Month 6 (n=503) | -29.7 (\pm 12.06) | | | |
| Endpoint (n=857) | -27.5 (\pm 13.08) | | | |

Notes:

[25] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 1 and Months 1, 2, 4, 6 and Endpoint in the Total Score From the 16-Item Quick Inventory of Depressive Symptomatology-Clinician-Rated (QIDS-C16)

| | |
|-----------------|---|
| End point title | Change From Baseline to Week 1 and Months 1, 2, 4, 6 and Endpoint in the Total Score From the 16-Item Quick Inventory of Depressive Symptomatology-Clinician-Rated (QIDS-C16) |
|-----------------|---|

End point description:

The QIDS-C16 was derived from specified items in the IDS-C30, clinician-rated scale to assess the severity of a participant's depressive symptoms. Total scores range from 0-27, with a score of 0 indicating no depression and a score of 27 indicating the most severe depression. Negative change from baseline values indicate improvement in the severity of depression.

Baseline was the score before the first dose of study drug in the double-blind study.

| | |
|----------------------|---|
| End point type | Secondary |
| End point timeframe: | Day 0 (baseline), Week 1, Months 1, 2, 4, 6 and the last postbaseline assessment) |

| End point values | Armodafinil 150-200 mg/Day | | | |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 859 ^[26] | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=838) | -9.3 (\pm 4.68) | | | |
| Month 1 (n=793) | -10 (\pm 4.47) | | | |
| Month 2 (n=716) | -10.6 (\pm 4.52) | | | |
| Month 4 (n=578) | -11.1 (\pm 4.7) | | | |
| Month 6 (n=503) | -11.3 (\pm 4.69) | | | |
| Endpoint (n=857) | -10.6 (\pm 5.07) | | | |

Notes:

[26] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 1 and Months 1, 2, 4, 6 and Endpoint in the Clinical Global Impression of Severity (CGI-S) for Depression

| | |
|-----------------|--|
| End point title | Change From Baseline to Week 1 and Months 1, 2, 4, 6 and |
|-----------------|--|

End point description:

The CGI-S is an observer-rated scale that measures illness severity on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). Negative change from baseline values indicate improvement in the severity of depression.

Baseline was the score before the first dose of study drug in the double-blind study.

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

End point timeframe:

| |
|---|
| Day 0 (baseline), Week 1, Months 1, 2, 4, 6 and the last postbaseline assessment) |
|---|

| End point values | Armodafinil 150-200 mg/Day | | | |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 859 ^[27] | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=838) | -1.7 (± 1.17) | | | |
| Month 1 (n=791) | -1.9 (± 1.17) | | | |
| Month 2 (n=716) | -2 (± 1.18) | | | |
| Month 4 (n=578) | -2.2 (± 1.16) | | | |
| Month 6 (n=502) | -2.3 (± 1.18) | | | |
| Endpoint (n=859) | -2 (± 1.31) | | | |

Notes:

[27] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Endpoint in the Global Assessment for Functioning (GAF) Scale

| | |
|-----------------|---|
| End point title | Change From Baseline to Endpoint in the Global Assessment for Functioning (GAF) Scale |
|-----------------|---|

End point description:

The Global Assessment of Functioning (GAF) is a numeric scale (1 through 100) used by mental health clinicians and physicians to rate subjectively the social, occupational, and psychological functioning of adults, e.g., how well or adaptively one is meeting various problems-in-living. Ratings of 1 - 10 mean the participant is in persistent danger of severely hurting self or others (e.g., recurrent violence) or persistent inability to maintain minimal personal hygiene or serious suicidal act with clear expectation of death. Ratings of 91 - 100 indicate no symptoms, and the participant exhibits superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. Positive change from baseline values indicate improvement in functioning.

Baseline was the score before the first dose of study drug in the double-blind study.

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

End point timeframe:

| |
|--|
| Day 0 (baseline), Month 6 or the last postbaseline assessment) |
|--|

| | | | | |
|--------------------------------------|----------------------------------|--|--|--|
| End point values | Armodafinil 150-200 mg/Day | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 779 ^[28] | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 17.7 (± 13.61) | | | |

Notes:

[28] - Full analysis set of participants with both a baseline and postbaseline assessment.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 6 months

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Armodafinil 150-200 mg/Day |
|-----------------------|----------------------------|

Reporting group description:

Participants began taking armodafinil at a dosage of 50 mg/day; the dosage was increased by 50 mg/day on days 2 and 4, up to a dosage of 150 mg/day. At the discretion of the investigator, the dosage of armodafinil may be increased to 200 mg/day on day 6 or thereafter, and reduced to 150mg/day if the higher dose is not well tolerated. Treatment was administered for six months.

| Serious adverse events | Armodafinil 150-200 mg/Day | | |
|---|----------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 27 / 863 (3.13%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Angina pectoris | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Torsade de pointes | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alcohol abuse | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alcohol withdrawal syndrome | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bipolar I disorder | | | |
| subjects affected / exposed | 3 / 863 (0.35%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Homicidal ideation | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Major depression | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mania | | | |
| subjects affected / exposed | 5 / 863 (0.58%) | | |
| occurrences causally related to treatment / all | 4 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 3 / 863 (0.35%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pilonidal cyst | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sialoadenitis | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 863 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|----------------------------|--|--|
| Non-serious adverse events | Armodafinil 150-200 mg/Day | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 133 / 863 (15.41%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 96 / 863 (11.12%) | | |
| occurrences (all) | 119 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 49 / 863 (5.68%) | | |
| occurrences (all) | 56 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 19 April 2010 | <p>Amendment 1 (dated 19 April 2010) to the protocol was issued before any patients were enrolled into the study.</p> <p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <p>Information was added regarding the occurrence of hypersensitivity and skin reactions in patients receiving armodafinil since it was first marketed in 2009.</p> <p>The number of centers was increased from 70 to 80 centers to 140 to 160 centers.</p> <p>The description of visit windows was clarified to indicate that visits should occur within the specified timeframe in reference to the enrollment visit.</p> <p>The inclusion criterion referring to the patient's need for continued treatment was clarified to specify that the need is for continued treatment for depression.</p> <p>The inclusion criterion that lists the protocol-allowed mood stabilizers and corresponding minimum dosages was revised to include aripiprazole and ziprasidone.</p> <p>In the inclusion criterion regarding women of childbearing potential, the definition of childbearing potential was clarified. Additionally, abstinence was deleted as an acceptable method of contraception; rather, it was clarified that contraception should be used by women of childbearing potential who are sexually active.</p> <p>An exclusion criterion was added to ensure exclusion of patients who were hospitalized or institutionalized and patients who were under arrest.</p> |
| 05 August 2010 | <p>Amendment 2 (dated 05 August 2010) to the protocol was issued after 56 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study.</p> <p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <p>A 24-hour telephone access number for medical issues was added.</p> <p>The number of centers was increased from 140 to 160 centers to a maximum of 200 centers.</p> <p>The duration of the study was extended by 3 months to the 4th quarter of 2012.</p> <p>The description of the study population's age range was modified to clearly state that the age range applied to the patient's age at the time of entry into the previous double-blind study.</p> <p>The number of bottles and the number of tablets to be given to each patient at each visit were added for clarity.</p> <p>The use of serum versus urine pregnancy tests at each visit requiring a pregnancy test was specified for clarity.</p> <p>The inclusion criterion that lists the protocol-allowed mood stabilizers and corresponding minimum dosages was revised to include lamotrigine and risperidone.</p> <p>The requirements regarding use of the protocol-allowed mood stabilizer ziprasidone were modified to allow its use only if in combination with lithium or valproic acid.</p> <p>The exclusion criterion that excluded hospitalized or institutionalized patients was modified to limit the exclusion to patients hospitalized/institutionalized involuntarily.</p> <p>A new inclusion criterion was added to allow enrollment of patients temporarily residing in a clinic or hospital or treated overnight in a medical facility as long as the patient's condition was neither serious nor a worsening of symptoms.</p> |

| | |
|---------------|---|
| 22 March 2012 | <p>Amendment 3 (dated 22 March 2012) to the protocol was issued after 493 patients were enrolled in the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled in the study. The following major procedural changes (not all-inclusive) were made to the protocol:</p> <p>The inclusion criterion that lists the protocol-allowed mood stabilizers and corresponding minimum dosages was revised to include quetiapine.</p> <p>The list of mood stabilizers that were allowed to be taken concomitantly with ziprasidone was modified to include lamotrigine.</p> <p>Medical monitor duties were consolidated under 1 physician employed by the sponsor.</p> <p>The timing of visit 7 was clarified to state that it should occur 7±2 days posttreatment but not necessarily at week 25.</p> <p>The requirements for clinical laboratory tests were clarified to state that fasting was not required.</p> |
|---------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported