# Clinical trial results:
# A Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dosage Study to Evaluate the Efficacy and Safety of Armodafinil Treatment (150 mg/day) as Adjunctive Therapy in Adults With Major Depression Associated With Bipolar I Disorder

## Summary

| | |
|---|---|
| EudraCT number | 2010-023623-26 |
| Trial protocol | HU FI DE IT PL BG |
| Global end of trial date | 29 July 2013 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 17 July 2016 |
| First version publication date | 21 May 2015 |
| Version creation reason | • Correction of full data set<br>QC check completed, data are correct |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | C10953/3073 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01305408 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Teva Branded Pharmaceutical Products R&D, Inc. |
| Sponsor organisation address | 41 Moores Road, Frazer, Pennsylvania, 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 |
| Sponsor organisation name | Teva Branded Pharmaceutical Products, R&D Inc. |
| Sponsor organisation address | 41 Moores Road, Fraser, 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 | 07 July 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 July 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to determine whether armodafinil treatment, at a dosage of 150 mg/day, is more effective than placebo treatment as adjunctive therapy to mood stabilizers for treatment of adults with major depression associated with bipolar I disorder. Efficacy will be assessed by the mean change from baseline in the total score from the 30-Item Inventory of Depressive Symptomatology–Clinician-Rated (IDS-C30).

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, European Union [EU] Directive 2001/20/EC, and 2005/28/EC.
Each investigator was responsible for performing the study in accordance with the protocol, ICH guidelines, and GCP, and for collecting, recording, and reporting the data accurately and properly. Agreement of each investigator to conduct and administer this study in accordance with the protocol was documented in separate study agreements with the sponsor and other forms as required by national authorities in the country where the investigational center is located.

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 | 17 February 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 6 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 35 |
| Country: Number of subjects enrolled | Bulgaria: 53 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Hungary: 25 |
| Country: Number of subjects enrolled | Italy: 6 |
| Country: Number of subjects enrolled | Argentina: 14 |
| Country: Number of subjects enrolled | Brazil: 18 |
| Country: Number of subjects enrolled | Croatia: 13 |
| Country: Number of subjects enrolled | Serbia: 12 |
| Country: Number of subjects enrolled | Slovakia: 13 |
| Country: Number of subjects enrolled | Ukraine: 56 |
| Country: Number of subjects enrolled | United States: 123 |
| Country: Number of subjects enrolled | South Africa: 27 |
| Worldwide total number of subjects | 399 |
| EEA total number of subjects | 149 |

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) | 396 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Region 1: USA and Canada Region 2: Eastern European countries, Kyrgyzstan, Mongolia, Uzbekistan, Cyprus, Greece, and Turkey Region 3: Central and Northern European countries, Andorra, Australia, Iceland, Monaco, San Marino, and Vatican City Region 4: Rest of World

### Pre-assignment

Screening details:

Participants were randomized (1:1) to receive150 mg/day armodafinil or matching placebo. Randomization was stratified on the basis of the mood-stabilizing medication and region of the world.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

Participants began taking placebo to match armodafinil and following the same titration procedure. Treatment was administered for a total of 8 weeks.

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

Matching placebo tablets, taken orally, once daily in the morning

| | |
|---|---|
| **Arm title** | Armodafinil 150 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. Treatment was administered for a total of 8 weeks.

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

Dosage and administration details:

Armodafinil tablets, taken orally, once daily in the morning

| **Number of subjects in period 1** | Placebo | Armodafinil 150 mg/day |
|---|---|---|
| Started | 199 | 200 |
| Safety Population | 198 | 200 |
| Full Analysis Population | 196 | 197 |
| Completed | 167 | 169 |
| Not completed | 32 | 31 |
| Consent withdrawn by subject | 9 | 9 |
| Adverse event, non-fatal | 10 | 7 |
| Extended absence | 1 | - |
| Noncompliance with sutdy procedures | - | 1 |
| Noncompliance with study medication | - | 1 |
| Lost to follow-up | 5 | 3 |
| Lack of efficacy | 3 | 4 |
| Protocol deviation | 4 | 6 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants began taking placebo to match armodafinil and following the same titration procedure. Treatment was administered for a total of 8 weeks. | |
| Reporting group title | Armodafinil 150 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. Treatment was administered for a total of 8 weeks. | |

| Reporting group values | Placebo | Armodafinil 150 mg/day | Total |
|---|---|---|---|
| Number of subjects | 199 | 200 | 399 |
| Age categorical<br>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<br>Units: years | | | |
| arithmetic mean | 43.7 | 45.3 | |
| standard deviation | ± 11.62 | ± 11.26 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 121 | 120 | 241 |
| Male | 78 | 80 | 158 |
| Race<br>Units: Subjects | | | |
| White | 176 | 182 | 358 |
| Black | 16 | 14 | 30 |
| Asian | 1 | 2 | 3 |
| American Indian or Alaskan Native | 0 | 2 | 2 |
| Other | 6 | 0 | 6 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 14 | 22 | 36 |
| Non-Hispanic or non-Latino | 183 | 176 | 359 |
| Unknown | 2 | 2 | 4 |

| | | | |
|---|---|---|---|
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 81.2 | 80.7 | |
| standard deviation | ± 17.46 | ± 17.54 | - |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 168.4 | 168.9 | |
| standard deviation | ± 9.32 | ± 9.23 | - |
| Body Mass Index | | | |
| Units: kg/m^2 | | | |
| arithmetic mean | 28.7 | 28.2 | |
| standard deviation | ± 5.95 | ± 5.52 | - |
| Time since start of current depressive episode | | | |
| Units: weeks | | | |
| arithmetic mean | 12.1 | 12.3 | |
| standard deviation | ± 9.1 | ± 9.89 | - |
| Time since first diagnosis | | | |
| Units: years | | | |
| arithmetic mean | 9.9 | 10.7 | |
| standard deviation | ± 8.72 | ± 8.55 | - |

## End points

### End points reporting groups

| Reporting group title | Placebo |
|---|---|
| Reporting group description: | |
| Participants began taking placebo to match armodafinil and following the same titration procedure. Treatment was administered for a total of 8 weeks. | |
| Reporting group title | Armodafinil 150 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. Treatment was administered for a total of 8 weeks. | |

### Primary: Change From Baseline to Week 8 in the Total Score From the 30-Item Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C30)

| End point title | Change From Baseline to Week 8 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.<br><br>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. | |
| End point type | Primary |
| End point timeframe: | |
| Day 0 (baseline), Week 8 | |

| End point values | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196[1] | 197[2] | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -19.4 (± 0.99) | -20.8 (± 0.99) | | |

Notes:

[1] - Full analysis set -participants with 1+ doses of study drug and 1+ postbaseline IDS-C30 assessment
[2] - Full analysis set -participants with 1+ doses of study drug and 1+ postbaseline IDS-C30 assessment

### Statistical analyses

| Statistical analysis title | Total Score for the IDS-C30 |
|---|---|
| Statistical analysis description: | |
| Treatment, visit, treatment-by-visit interaction, concurrent mood-stabilizing medication, and region of the world used as fixed factors. | |
| Comparison groups | Placebo v Armodafinil 150 mg/day |

| | |
|---|---|
| Number of subjects included in analysis | 393 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2717 [3] |
| Method | Mixed-model repeated measures (MMRM) |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.76 |
| upper limit | 1.06 |

Notes:

[3] - Statistical tests were 2-tailed at the 0.05 level of significance.

## Secondary: Percentage of Responders At Different Treatment Weeks According to the 30-Item Inventory of Depressive Symptomatology-Clinician Rated (IDS-C30) Total Score

| | |
|---|---|
| End point title | Percentage of Responders At Different Treatment Weeks According to the 30-Item Inventory of Depressive Symptomatology-Clinician Rated (IDS-C30) Total Score |

End point description:

A responder is a participant with a ≥50% decrease or greater from baseline in the total score of the IDS-C30. 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.

Full analysis set which includes participants who took 1 or more doses of study drug and who have at least 1 post-baseline IDS-C30 efficacy assessment. The denominator for calculating the percentages at each visit is the number of participants with a non-missing value at that visit. Endpoint was the last observed post-baseline data.

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

End point timeframe:

Day 0 (baseline), Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196[4] | 197[5] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 1 (n=196, 195) | 2 | 3 | | |
| Week 2 (n=187, 189) | 13 | 9 | | |
| Week 4 (n=181, 183) | 21 | 27 | | |
| Week 6 (n=172, 172) | 29 | 41 | | |
| Week 7 (n=167, 170) | 39 | 51 | | |
| Week 8 (n=167, 169) | 46 | 56 | | |
| Endpoint (n=196, 197) | 41 | 49 | | |

Notes:

[4] - Full analysis set

[5] - Full analysis set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants in Remission At Different Treatment Weeks According to the 30-Item Inventory of Depressive Symptomatology-Clinician Rated (IDS-C30) Total Score

| End point title | Percentage of Participants in Remission At Different Treatment Weeks According to the 30-Item Inventory of Depressive Symptomatology-Clinician Rated (IDS-C30) Total Score |
|---|---|

End point description:

A participant in remission was defined as a participant with an IDS-C30 total score of 11 or less.

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.

Full analysis set which includes participants who took 1 or more doses of study drug and who have at least 1 post-baseline IDS-C30 efficacy assessment. The denominator for calculating the percentages at each visit is the number of participants with a non-missing value at that visit. Endpoint was the last observed post-baseline data.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196[6] | 197[7] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 1 (n=196, 195) | 0.5 | 1 | | |
| Week 2 (n=187, 189) | 2 | 2 | | |
| Week 4 (n=181, 183) | 5 | 7 | | |
| Week 6 (n=172, 172) | 9 | 12 | | |
| Week 7 (n=167, 170) | 14 | 19 | | |
| Week 8 (n=167, 169) | 15 | 26 | | |
| Endpoint (196, 197) | 13 | 22 | | |

Notes:

[6] - Full analysis set

[7] - Full analysis set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Different Treatment Weeks in the Total Score From the 30-Item Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C30)

| End point title | Change From Baseline to Different Treatment Weeks 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.

Full analysis set which includes participants who took 1 or more doses of study drug and who have at least 1 post-baseline IDS-C30 efficacy assessment. Participants are included in the analysis at each timepoint if they have a non-missing value at that visit. Endpoint for analyses was the last observed post-baseline data.

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

End point timeframe:

Day 0 (baseline), Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196[8] | 197[9] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=196, 195) | -6 (± 6.61) | -5.3 (± 7.12) | | |
| Week 2 (n=187, 189) | -10 (± 8.71) | -8.9 (± 8.56) | | |
| Week 4 (n=181, 183) | -13.4 (± 9.87) | -13.5 (± 10.54) | | |
| Week 6 (n=172, 172) | -15.8 (± 10.42) | -17.6 (± 11.09) | | |
| Week 7 (n=167, 170) | -18 (± 11.42) | -20.2 (± 10.88) | | |
| Week 8 (n=167, 169) | -19.7 (± 11.3) | -21.6 (± 11.75) | | |
| Endpoint (n=196, 197) | -18.3 (± 11.62) | -19.5 (± 12.66) | | |

Notes:

[8] - Full analysis set

[9] - Full analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Different Treatment Weeks in the Total Score From the 16-Item Quick Inventory of Depressive Symptomatology-Clinician-Rated (QIDS-C16)

| End point title | Change From Baseline to Different Treatment Weeks 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.

Full analysis set which includes participants who took 1 or more doses of study drug and who have at least 1 post-baseline IDS-C30 efficacy assessment. The number of participants at each visit are those with a non-missing value at that visit. Endpoint was the last observed post-baseline data.

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

End point timeframe:

Day 0 (baseline), Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196[10] | 197[11] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=196, 195) | -2.4 (± 2.92) | -2.1 (± 3.07) | | |
| Week 2 (n=187, 189) | -4.2 (± 3.83) | -3.4 (± 3.63) | | |
| Week 4 (n=181, 183) | -5.3 (± 4.05) | -5.3 (± 4.15) | | |
| Week 6 (n=172, 172) | -6.3 (± 4.16) | -6.7 (± 4.38) | | |
| Week 7 (n=167, 170) | -7.2 (± 4.49) | -7.8 (± 4.35) | | |
| Week 8 (n=167, 169) | -8 (± 4.53) | -8.3 (± 4.62) | | |
| Endpoint (n=196, 197) | -7.3 (± 4.73) | -7.5 (± 4.91) | | |

Notes:

[10] - Full analysis set

[11] - Full analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Different Treatment Weeks in the Clinical Global Impression of Severity (CGI-S) for Depression

| | |
|---|---|
| End point title | Change From Baseline to Different Treatment Weeks in the Clinical Global Impression of Severity (CGI-S) for Depression |

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.

Full analysis set which includes participants who took 1 or more doses of study drug and who have at least 1 post-baseline IDS-C30 efficacy assessment. The number of participants is those with a non-missing value at that visit. Endpoint was the last observed post-baseline data.

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

End point timeframe:

Day 0 (baseline), Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| End point values | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196[12] | 197[13] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (n=196, 195) | -0.2 (± 0.49) | -0.2 (± 0.46) | | |
| Week 2 (n=187, 189) | -0.5 (± 0.65) | -0.5 (± 0.77) | | |
| Week 4 (n=181, 183) | -0.7 (± 0.76) | -0.9 (± 0.97) | | |
| Week 6 (n=172, 172) | -1 (± 0.91) | -1.2 (± 1.03) | | |
| Week 7 (n=167, 170) | -1.2 (± 1.08) | -1.4 (± 1.1) | | |
| Week 8 (n=167, 169) | -1.3 (± 1.11) | -1.6 (± 1.19) | | |
| Endpoint (n=196, 197) | -1.2 (± 1.14) | -1.4 (± 1.25) | | |

Notes:

[12] - Full analysis set

[13] - Full analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to Weeks 4, 8 and Endpoint in the Global Assessment for Functioning (GAF) Scale

| End point title | Change From Baseline to Weeks 4, 8 and 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.

Full analysis set which includes participants who took 1+ doses of study drug and 1+ post-baseline IDS-C30 efficacy assessment.

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

End point timeframe:

Day 0 (baseline), Weeks 4, 8, and last postbaseline observation

| End point values | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196[14] | 197[15] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=181, 183) | 5.8 (± 7.39) | 8.2 (± 10.39) | | |

| | | | | |
|---|---|---|---|---|
| Week 8 (n=167, 169) | 11.5 (± 10.42) | 15.3 (± 11.72) | | |
| Endpoint (n=189, 192) | 10.6 (± 10.42) | 13.6 (± 12.38) | | |

Notes:

[14] - Full analysis set

[15] - Full analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Participants With Treatment-Emergent Adverse Events (TEAE)

| End point title | Participants With Treatment-Emergent Adverse Events (TEAE) |
|---|---|

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 | Secondary |
|---|---|

End point timeframe:

Day 1 to Week 9

| End point values | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[16] | 200[17] | | |
| Units: participants | | | | |
| >=1 adverse event | 71 | 89 | | |
| Severe adverse event | 4 | 4 | | |
| Treatment-related adverse event | 32 | 53 | | |
| Deaths | 0 | 0 | | |
| Other serious adverse events | 6 | 5 | | |
| Withdrawn from study due to adverse events | 10 | 7 | | |
| Protocol-defined adverse events | 3 | 3 | | |

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

## Secondary: 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 |
|---|---|

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.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with both baseline and during treatment assessments.

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

End point timeframe:

Day 0 (baseline), last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 196[18] | 198[19] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -1 (± 2.45) | -0.9 (± 3.19) | | |

Notes:

[18] - Safety analysis set

[19] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: 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 |
|---|---|

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.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with both baseline and during treatment assessments.

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

End point timeframe:

Day 0 (baseline), last postbaseline observation

| End point values | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190[20] | 194[21] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -4.2 (± 4.53) | -4.3 (± 5.37) | | |

Notes:

[20] - Safety analysis set

[21] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: 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 |
|---|---|

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.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with both baseline and during treatment assessments.

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

End point timeframe:

Day 0 (baseline), last postbaseline observation

| End point values | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190[22] | 192[23] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -7 (± 6.62) | -7.1 (± 6.91) | | |

Notes:

[22] - Safety analysis set

[23] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Actual Attempt Question

| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Actual Attempt Question |
|---|---|

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 C-SSRS-B (baseline) was performed at

screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7, and 8 or last postbaseline observation. The Suicidal Behavior - Actual Attempt question records whether the participant committed a potentially self-injurious act with at least some wish to die since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[24] | 200[25] | | |
| Units: participants | | | | |
| Week 1 (n=196, 195) | 0 | 0 | | |
| Week 2 (n=187, 189) | 0 | 0 | | |
| Week 4 (n=181, 183) | 0 | 0 | | |
| Week 6 (n=172, 172) | 0 | 0 | | |
| Week 7 (n=167, 170) | 0 | 0 | | |
| Week 8 (n=167, 169) | 0 | 0 | | |
| Endpoint (n=196, 198) | 0 | 0 | | |

Notes:

[24] - Safety analysis set

[25] - Safety analysis set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Non-Suicidal Self-Injurious Behavior Question

| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Non-Suicidal Self-Injurious Behavior Question |
|---|---|

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 C-SSRS-B (baseline) was performed at screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7, and 8 or last postbaseline observation.

The Suicidal Behavior - Non-Suicidal Self-Injurious Behavior question records whether the participant committed a potentially self-injurious act that was not associated with a wish to die since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| End point values | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[26] | 200[27] | | |
| Units: participants | | | | |
| Week 1 (n=196, 195) | 0 | 0 | | |
| Week 2 (n=187, 189) | 0 | 0 | | |
| Week 4 (n=181, 183) | 0 | 0 | | |
| Week 6 (n=172, 172) | 0 | 0 | | |
| Week 7 (n=167, 170) | 0 | 0 | | |
| Week 8 (n=167, 169) | 0 | 0 | | |
| Endpoint (n=196, 198) | 0 | 0 | | |

Notes:

[26] - Safety analysis set

[27] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Interrupted Attempt Question

| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Interrupted Attempt Question |
|---|---|

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 C-SSRS-B (baseline) was performed at screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7, and 8 or last postbaseline observation.

The Suicidal Behavior - Interrupted Attempt question records whether the participant was interrupted by an outside circumstance from starting the potentially self-injurious act with at least some wish to die since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| End point values | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[28] | 200[29] | | |
| Units: participants | | | | |
| Week 1 (n=196, 195) | 0 | 0 | | |
| Week 2 (n=187, 189) | 0 | 0 | | |
| Week 4 (n=181, 183) | 0 | 0 | | |

| | | | | |
|---|---|---|---|---|
| Week 6 (n=172, 172) | 0 | 0 | | |
| Week 7 (n=167, 170) | 0 | 0 | | |
| Week 8 (n=167, 169) | 0 | 0 | | |
| Endpoint (n=196, 198) | 0 | 0 | | |

Notes:

[28] - Safety analysis set

[29] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Aborted Attempt Question

| | |
|---|---|
| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Aborted Attempt Question |

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 C-SSRS-B (baseline) was performed at screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7, and 8 or last postbaseline observation.

The Suicidal Behavior - Aborted Attempt question records whether the participant began to take steps toward making a suicide attempt but stops themselves before starting the potentially self-injurious act since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[30] | 200[31] | | |
| Units: participant | | | | |
| Week 1 (n=196, 195) | 0 | 0 | | |
| Week 2 (n=187, 189) | 0 | 0 | | |
| Week 4 (n=181, 183) | 0 | 0 | | |
| Week 6 (n=172, 172) | 0 | 0 | | |
| Week 7 (n=167, 170) | 0 | 0 | | |
| Week 8 (n=167, 169) | 0 | 0 | | |
| Endpoint (n=196, 198) | 0 | 0 | | |

Notes:

[30] - Safety analysis set

[31] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Suicidal Behavior Question

| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Suicidal Behavior Question |
|---|---|

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 C-SSRS-B (baseline) was performed at screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7, and 8 or last postbaseline observation.

The Suicidal Behavior - Suicidal Behavior question records whether in the clinician's opinion, the participant exhibited suicidal behavior since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[32] | 200[33] | | |
| Units: participants | | | | |
| Week 1 (n=196, 195) | 0 | 0 | | |
| Week 2 (n=187, 189) | 0 | 0 | | |
| Week 4 (n=181, 183) | 0 | 0 | | |
| Week 6 (n=172, 172) | 0 | 0 | | |
| Week 7 (n=167, 170) | 0 | 0 | | |
| Week 8 (n=167, 169) | 0 | 0 | | |
| Endpoint (n=196, 198) | 0 | 0 | | |

Notes:

[32] - Safety analysis set

[33] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Preparatory Acts or Behavior Question

| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Preparatory Acts or Behavior Question |
|---|---|

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 C-SSRS-B (baseline) was performed at screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7, and 8 or last postbaseline observation.

The Suicidal Behavior - Preparatory Acts or Behavior question records whether the participant exhibited

acts or preparations towards imminently making a suicide attempt since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[34] | 200[35] | | |
| Units: participants | | | | |
| Week 1 (n=196, 195) | 0 | 0 | | |
| Week 2 (n=187, 189) | 0 | 0 | | |
| Week 4 (n=181, 183) | 0 | 0 | | |
| Week 6 (n=172, 172) | 0 | 0 | | |
| Week 7 (n=167, 170) | 0 | 0 | | |
| Week 8 (n=167, 169) | 0 | 0 | | |
| Endpoint (n=196, 198) | 0 | 0 | | |

Notes:

[34] - Safety analysis set

[35] - Safety analysis set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Completed Suicide Question

| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Behavior - Completed Suicide Question |
|---|---|

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 C-SSRS-B (baseline) was performed at screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7, and 8 or last postbaseline observation.

The Suicidal Behavior - Completed Suicide question records whether the participant intentionally causing his/her's own death since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| End point values | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[36] | 200[37] | | |
| Units: participants | | | | |
| Week 1 (n=196, 195) | 0 | 0 | | |
| Week 2 (n=187, 189) | 0 | 0 | | |
| Week 4 (n=181, 183) | 0 | 0 | | |
| Week 6 (n=172, 172) | 0 | 0 | | |
| Week 7 (n=167, 170) | 0 | 0 | | |
| Week 8 (n=167, 169) | 0 | 0 | | |
| Endpoint (n=196, 198) | 0 | 0 | | |

Notes:

[36] - Safety analysis set

[37] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Ideation - Wish to Be Dead Question

| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Ideation - Wish to Be Dead Question |
|---|---|

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 C-SSRS-B (baseline) was performed at screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7, and 8 or last postbaseline observation.

The Suicidal Ideation - Wish to Be Dead question records whether the participant endorses thoughts about a wish to dead or not alive anymore, or a wish to fall asleep and not wake up since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| End point values | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[38] | 200[39] | | |
| Units: participants | | | | |
| Week 1 (n=196, 195) | 6 | 5 | | |
| Week 2 (n=187, 189) | 2 | 6 | | |
| Week 4 (n=181, 183) | 1 | 7 | | |
| Week 6 (n=172, 172) | 2 | 3 | | |
| Week 7 (n=167, 170) | 2 | 2 | | |
| Week 8 (n=167, 169) | 1 | 3 | | |
| Endpoint (n=196, 198) | 2 | 4 | | |

Notes:

[38] - Safety analysis set

[39] - Safety analysis set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Ideation - Non-Specific Active Suicidal Thoughts Question

| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Ideation - Non-Specific Active Suicidal Thoughts Question |
|---|---|

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 C-SSRS-B (baseline) was performed at screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7, and 8 or last postbaseline observation.

The Suicidal Ideation - Non-Specific Active Suicidal Thoughts question records whether the participant shares general non-specific thoughts of wanting to end one's life/commit suicide since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[40] | 200[41] | | |
| Units: participants | | | | |
| Week 1 (n=196, 195) | 2 | 0 | | |
| Week 2 (n=187, 189) | 0 | 0 | | |
| Week 4 (n=181, 183) | 0 | 1 | | |
| Week 6 (n=172, 172) | 0 | 1 | | |
| Week 7 (n=167, 170) | 0 | 1 | | |
| Week 8 (n=167, 169) | 0 | 1 | | |
| Endpoint (n=196, 198) | 0 | 1 | | |

Notes:

[40] - Safety analysis set

[41] - Safety analysis set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Ideation - Any Methods (Not Plan) Without Intent to Act Question

| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Ideation - Any Methods (Not Plan) Without Intent to Act Question |
|---|---|

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 C-SSRS-B (baseline) was performed at screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7, and 8 or last postbaseline observation.

The Suicidal Ideation - Any Methods (Not Plan) Without Intent to Act question records whether the participant endorses thoughts of suicide and has thought of at least one method but has no specific plan of action since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. This question is asked only if the answer to the 'Non-Specific Active Suicidal Thoughts' question was YES. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[42] | 200[43] | | |
| Units: participants | | | | |
| Week 1 (n=6, 5) | 1 | 1 | | |
| Week 2 (n=2, 6) | 0 | 0 | | |
| Week 4 (n=1, 7) | 0 | 0 | | |
| Week 6 (n=1, 3) | 0 | 0 | | |
| Week 7 (n=2, 2) | 0 | 0 | | |
| Week 8 (n=1, 3) | 0 | 0 | | |
| Endpoint (n=8, 12) | 1 | 0 | | |

Notes:

[42] - Safety analysis set

[43] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Ideation - Some Intent to Act Without a Specific Plan Question

| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Ideation - Some Intent to Act Without a Specific Plan Question |
|---|---|

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 C-SSRS-B (baseline) was performed at screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7,

and 8 or last postbaseline observation.

The Suicidal Ideation - Some Intent to Act Without a Specific Plan question records whether the participant has active suicidal thoughts of killing oneself and reports having some intent to act on such thoughts since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. This question is asked only if the answer to the 'Non-Specific Active Suicidal Thoughts' question was YES. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| **End point values** | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[44] | 200[45] | | |
| Units: participants | | | | |
| Week 1 (n=6, 5) | 0 | 0 | | |
| Week 2 (n=2, 6) | 0 | 0 | | |
| Week 4 (n=1, 7) | 0 | 0 | | |
| Week 6 (n=1, 3) | 0 | 0 | | |
| Week 7 (n=2, 2) | 0 | 0 | | |
| Week 8 (n=1, 3) | 0 | 0 | | |
| Endpoint (n=8, 12) | 0 | 0 | | |

Notes:

[44] - Safety analysis set

[45] - Safety analysis set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Ideation - Specific Plan and Intent Question

| End point title | Columbia-Suicide Severity Rating Scale 'Since Last Visit' Version (C-SSRS-SLV) For Weeks 1, 2, 4, 6, 7, 8, and Endpoint For the Suicidal Ideation - Specific Plan and Intent Question |
|---|---|

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 C-SSRS-B (baseline) was performed at screening and the C-SSRS-SLV ('Since Last Visit') was performed at baseline and weeks 1, 2, 4, 6, 7, and 8 or last postbaseline observation.

The Suicidal Ideation - Specific Plan and Intent question records whether the participant has active suicidal thoughts of killing oneself with details of plan fully or partially worked out and the participant has some intent to carry out the plan since the last visit.

The safety analysis set includes randomized participants who took 1 or more doses of study drug. This question is asked only if the answer to the 'Non-Specific Active Suicidal Thoughts' question was YES. The number analyzed includes participants with treatment assessments at the indicated time period.

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

End point timeframe:

Weeks 1, 2, 4, 6, 7, and 8, and last postbaseline observation

| End point values | Placebo | Armodafinil 150 mg/day | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 198[46] | 200[47] | | |
| Units: participants | | | | |
| Week 1 (n=6, 5) | 1 | 0 | | |
| Week 2 (n=2, 6) | 0 | 0 | | |
| Week 4 (n=1, 7) | 0 | 0 | | |
| Week 6 (n=1, 3) | 0 | 0 | | |
| Week 7 (n=2, 2) | 0 | 0 | | |
| Week 8 (n=1, 3) | 0 | 0 | | |
| Endpoint (n=8, 12) | 1 | 0 | | |

Notes:

[46] - Safety analysis set

[47] - Safety analysis set

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 9

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

### Dictionary used

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

### Reporting groups

| | |
|---|---|
| Reporting group title | Armodafinil 150 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. Treatment was administered for a total of 8 weeks.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Participants began taking placebo to match armodafinil and following the same titration procedure. Treatment was administered for a total of 8 weeks.

| Serious adverse events | Armodafinil 150 mg/day | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 200 (2.50%) | 6 / 198 (3.03%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Unintended pregnancy | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Social circumstances | | | |
| Social stay hospitalisation | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Cervical dysplasia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Toxic skin eruption | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bipolar I disorder | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomania | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 198 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 198 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Armodafinil 150 mg/day | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 200 (18.50%) | 21 / 198 (10.61%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 29 / 200 (14.50%) | 15 / 198 (7.58%) | |
| occurrences (all) | 35 | 17 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 12 / 200 (6.00%) | 7 / 198 (3.54%) | |
| occurrences (all) | 13 | 7 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 21 September 2011 | Amendment 1 (dated 21 September 2011) to the protocol was issued after 14 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. The following major procedural changes (not all-inclusive) were made to the protocol:<br>- In the Schedule of Procedures and Assessments, the instruction to contact the IVRS or IWRS to register a visit, from visit 3 through visit 8, was deleted.<br>- A clarification was made, which stated that Interactive Computerized Interview for Rating the IDS-C30, administered by the qualified rater at the investigational center, must have been performed before the interactive computerized interview was performed by the patient.<br>- βHCG serum tests were to be performed for all women, at screening, at weeks 4 and 8, or last postbaseline observation, and if clinically indicated thereafter. The qualifier "unless surgically sterile" was removed.<br>- A revision was made to perform sensitivity analyses for the primary efficacy variable with details provided in the SAP.<br>- In order to accommodate country-specific regulations and guidelines, text was added to the informed consent form to include the requirement for a caregiver consent form as required by national/local health authorities. |
| 22 March 2012 | Amendment 2 (dated 22 March 2012) to the protocol was issued after 50 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.<br>The following major procedural changes (not all-inclusive) were made to the protocol:<br>- Quetiapine, commonly prescribed in the treatment of patients with depressive episodes associated with bipolar disorder, was added as a protocol-allowed mood stabilizer. Lamotrigine was added to the list of mood stabilizers that could be taken concomitantly with ziprasidone.<br>- An exclusion criterion was rewritten to clarify that a patient with any clinically significant cutaneous drug reaction, or a history of clinically significant hypersensitivity reaction, including multiple allergies, was not eligible for the study.<br>- Text was removed from the informed consent form, which included the requirement for a caregiver consent form, since the addition of investigational centers in countries requiring caregiver consent was no longer applicable. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported