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 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.
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Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., +1 215-591-3000, ustevatrials@tevapharm.com
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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 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	43.7	45.3	
standard deviation	± 11.62	± 11.26	-
Gender categorical Units: Subjects			
Female	121	120	241
Male	78	80	158
Race 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 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. 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: - 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. - 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. - 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. - A revision was made to perform sensitivity analyses for the primary efficacy variable with details provided in the SAP. - 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. The following major procedural changes (not all-inclusive) were made to the protocol: - 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. - 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. - 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