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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	C10953/3074

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc.
Sponsor organisation address	41 Moores Road, Frazer, PA, United States, 19355-1113
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 1 215-591-3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., 1 215-591-3000, ustevatrials@tevapharm.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2014
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	862
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

Arm title	Armodafinil 150-200 mg/Day

Arm description:

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

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

Dosage and administration details:

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

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

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

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	867	867	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	44.2		
standard deviation	± 10.96	-	
Gender categorical Units: Subjects			
Female	525	525	
Male	342	342	
Ethnicity Units: Subjects			
Hispanic or Latino	91	91	
Not Hispanic or Latino	752	752	
Unknown	24	24	
Race Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	10	10	
Native Hawaiian or Other Pacific Islander	1	1	
Black or African American	118	118	
White	709	709	
Unknown or Not Reported	28	28	
Weight Units: kg			
arithmetic mean	83.7		
standard deviation	± 19.75	-	
Height Units: cm			
arithmetic mean	168.8		

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

End points

End points reporting groups

Reporting group title	Armodafinil 150-200 mg/Day

Reporting group description:

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

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

End point title	Participants With Treatment-Emergent Adverse Events

End point description:

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

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

End point type	Primary

End point timeframe:

Day 1 up to Month 6

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

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

Notes:

[2] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Clinically Significant Abnormal Serum Chemistry Values

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

End point description:

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

ULN=upper limit of normal
Uric acid has a normal range of 125-494 µmol/L. Criterion for clinically significant abnormal are different for men and women.
GGT = gamma-glutamyl transpeptidase with a normal range of 4-61 U/L
ALT = alanine aminotransferase with a normal range of 6-43 U/L
BUN = blood urea nitrogen with a normal range of 1.4-8.6 mmol/L
AST = aspartate aminotransferase with a normal range of 9-36 U/L

End point type	Primary

End point timeframe:

Day 1 to Month 6

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Clinically Significant Abnormal Hematology Values

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

End point description:

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

ULN=upper limit of normal
WBC - white blood cell counts with a normal range of 3.8 t 10.7 10^9/L.
Hemoglobin with a normal range of 115-181 g/L
Hematocrit with a normal range of 0.34-0.54 L/L
Platelet counts with a normal range of 130-400 10^9/L
ANC= absolute neutrophil counts with a normal range of 1.96-7.23 10^9/L

End point type	Primary

End point timeframe:

Day 1 to Month 6

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Clinically Significant Abnormal Urinalysis Values

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

End point description:

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

End point type	Primary

End point timeframe:

Day 1 to Month 6

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Primary: Participants With Clinically Significant Abnormal Vital Signs Values

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

End point description:

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

Pulse high: >=120 beats per minute (bpm) and increase of >=15 bpm from baseline
Pulse low: <=50 bpm and decrease of >=15 bpm from baseline
Sitting systolic blood pressure high: >=180 mm Hg and increase of >=20 mm HG from baseline
Sitting systolic blood pressure low: <=90 mm Hg and decrease of >=20 mm HG from baseline
Sitting diastolic blood pressure high: >=105 mm Hg and increase of >=15 mm HG from baseline
Sitting diastolic blood pressure low: <=50 mm Hg and decrease of >=15 mm HG from baseline

End point type	Primary

End point timeframe:

Day 1 to Month 6

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Primary

End point timeframe:

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

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Primary: Physical Examination Shifts From Baseline to Endpoint

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

End point description:

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

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

End point type	Primary

End point timeframe:

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

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Endpoint in Body Weight

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

End point description:

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

End point type	Primary

End point timeframe:

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

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point type	Primary

End point timeframe:

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

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Primary

End point timeframe:

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

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Primary

End point timeframe:

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

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical analyses done.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point type	Primary

End point timeframe:

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

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This extension study has a single treatment arm. As such, there are no formal statistical

analyses done.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

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

End point type	Secondary

End point timeframe:

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

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

Month 6 (n=503)	-29.7 (± 12.06)			
Endpoint (n=857)	-27.5 (± 13.08)			

Notes:

[25] - Full analysis set

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

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

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

Notes:

[26] - Full analysis set

Statistical analyses

No statistical analyses for this end point

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

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

	Endpoint 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.

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

End point type	Secondary

End point timeframe:

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

End point values	Armodafinil 150-200 mg/Day			
Subject group type	Reporting group			
Number of subjects analysed	859[27]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=838)	-1.7 (± 1.17)			
Month 1 (n=791)	-1.9 (± 1.17)			
Month 2 (n=716)	-2 (± 1.18)			
Month 4 (n=578)	-2.2 (± 116)			
Month 6 (n=502)	-2.3 (± 1.18)			
Endpoint (n=859)	-2 (± 1.31)			

Notes:

[27] - Full analysis set

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point type	Secondary

End point timeframe:

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to 6 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

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

Reporting group description:

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported