Clinical trial results:
A Double-blind, Placebo-Controlled Study of Cariprazine as Adjunctive Therapy in Major Depressive Disorder

Summary

EudraCT number	2011-005179-18
Trial protocol	FI EE SK SE
Global end of trial date	12 December 2013

Results information

Result version number	v1 (current)
This version publication date	18 April 2018
First version publication date	18 April 2018

Trial information

Trial identification

Sponsor protocol code	RGH-MD-75

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01469377
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Forest Laboratories, LLC, an Allergan Affiliate
Sponsor organisation address	5 Giralda Farms, Madison, United States, NJ 07940
Public contact	Clinical Trials Registry Team, Allergan plc, 001 8772778566, IR-CTRegistration@allergan.com
Scientific contact	Therapeutic Area Head, Allergan plc, 001 862-261-7000, IR-CTRegistration@Allergan.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this study were to evaluate the efficacy, safety, and tolerability of cariprazine adjunctive to antidepressant therapy (ADT) in subjects with major depressive disorder (MDD) who had an inadequate response to ADT.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2011
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	Estonia: 109
Country: Number of subjects enrolled	Finland: 76
Country: Number of subjects enrolled	Slovakia: 81
Country: Number of subjects enrolled	Sweden: 25
Country: Number of subjects enrolled	Ukraine: 60
Country: Number of subjects enrolled	United States: 468
Worldwide total number of subjects	819
EEA total number of subjects	291

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)	807
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1248 subjects were screened for eligibility, 819 subjects were randomized to receive double-blind treatment, 812 subjects received at least 1 dose of double-blind treatment (Safety Population), and 808 subjects had at least 1 postbaseline MADRS assessment [intent to treat (ITT) Population].

Pre-assignment period milestones

Number of subjects started	819
Number of subjects completed	812

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomized; Did Not Receive Study Drug: 7

Period 1

Period 1 title	Overall Study (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 received placebo orally once a day for 8 weeks. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received matched placebo capsules, orally, once daily for 8 weeks.

Arm title	Cariprazine 1-2 mg

Arm description:

Participants received cariprazine orally once a day for 8 weeks. Participants received cariprazine 0.5 mg on Days 1 and 2 and 1.0 mg on Days 3-7. At the investigator’s discretion dose levels could be increased during Week 2. Dose levels allowed during Week 2 were 1.0 or 1.5 mg. A second dose increase was allowed starting at Week 3. Dose levels allowed during Week 3 and the remainder of the treatment period were 1.0, 1.5, or 2.0 mg. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.

Arm type	Experimental

Investigational medicinal product name	Cariprazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received cariprazine (1-2 mg/day) capsules, orally, once daily for 8 weeks.

Arm title	Cariprazine 2-4.5 mg

Arm description:

Participants received cariprazine orally once a day for 8 weeks. Participants received cariprazine 0.5 mg on Days 1 and 2, 1.0 mg on Day 3, 1.5 mg on Day 4, and 2.0 mg on Days 5-7. At the investigator's discretion dose levels could be increased during Week 2. Dose levels allowed during Week 2 were 2.0 or 3.0 mg. A second dose increase was allowed starting at Week 3. Dose levels allowed during Week 3 and the remainder of the treatment period were 2.0, 3.0, or 4.5 mg. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.

Arm type	Experimental
Investigational medicinal product name	Cariprazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received cariprazine (2-4.5 mg/day) capsules, orally, once daily for 8 weeks.

Number of subjects in period 1[1]	Placebo	Cariprazine 1-2 mg	Cariprazine 2-4.5 mg
Started	266	273	273
Completed	234	226	210
Not completed	32	47	63
Withdrawal of Consent	11	13	14
Protocol Deviation	6	10	9
Adverse event, non-fatal	8	18	36
Lost to follow-up	2	2	4
Other Miscellaneous Reasons	2	-	-
Insufficient Therapeutic Response	3	4	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline Period is based on the Safety Population, that included all randomized participants who received at least 1 dose of investigational product. 7 participants did not receive study drug and are excluded.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo orally once a day for 8 weeks. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.	
Reporting group title	Cariprazine 1-2 mg
Reporting group description:	
Participants received cariprazine orally once a day for 8 weeks. Participants received cariprazine 0.5 mg on Days 1 and 2 and 1.0 mg on Days 3-7. At the investigator's discretion dose levels could be increased during Week 2. Dose levels allowed during Week 2 were 1.0 or 1.5 mg. A second dose increase was allowed starting at Week 3. Dose levels allowed during Week 3 and the remainder of the treatment period were 1.0, 1.5, or 2.0 mg. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.	
Reporting group title	Cariprazine 2-4.5 mg
Reporting group description:	
Participants received cariprazine orally once a day for 8 weeks. Participants received cariprazine 0.5 mg on Days 1 and 2, 1.0 mg on Day 3, 1.5 mg on Day 4, and 2.0 mg on Days 5-7. At the investigator's discretion dose levels could be increased during Week 2. Dose levels allowed during Week 2 were 2.0 or 3.0 mg. A second dose increase was allowed starting at Week 3. Dose levels allowed during Week 3 and the remainder of the treatment period were 2.0, 3.0, or 4.5 mg. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.	

Reporting group values	Placebo	Cariprazine 1-2 mg	Cariprazine 2-4.5 mg
Number of subjects	266	273	273
Age categorical Units: Subjects			
18 - 64 years	259	270	272
65 - 84 years	7	3	1
Age Continuous Units: years			
arithmetic mean	46.4	45.5	45.1
standard deviation	± 11.6	± 11.9	± 11.4
Gender, Male/Female Units: Subjects			
Female	190	187	201
Male	76	86	72
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14	17	22
Not Hispanic or Latino	252	256	251
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	1	1
Asian	1	4	4

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	32	31	24
White	230	234	242
More than one race	0	0	0
Unknown or Not Reported	1	3	2
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	28.93	28.21	29.05
standard deviation	± 5.09	± 5.51	± 5.59
Waist Circumference			
Units: cm			
arithmetic mean	94.32	93.36	94.91
standard deviation	± 13.44	± 14.20	± 14.66
Weight			
Units: kg			
arithmetic mean	81.53	79.69	82.17
standard deviation	± 16.19	± 16.31	± 17.37

Reporting group values	Total		
Number of subjects	812		
Age categorical			
Units: Subjects			
18 - 64 years	801		
65 - 84 years	11		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	578		
Male	234		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	53		
Not Hispanic or Latino	759		
Unknown or Not Reported	0		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	4		
Asian	9		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	87		
White	706		
More than one race	0		
Unknown or Not Reported	6		
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean			
standard deviation	-		

Waist Circumference Units: cm arithmetic mean standard deviation	-		
Weight Units: kg arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo orally once a day for 8 weeks. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.

Reporting group title	Cariprazine 1-2 mg

Reporting group description:

Participants received cariprazine orally once a day for 8 weeks. Participants received cariprazine 0.5 mg on Days 1 and 2 and 1.0 mg on Days 3-7. At the investigator's discretion dose levels could be increased during Week 2. Dose levels allowed during Week 2 were 1.0 or 1.5 mg. A second dose increase was allowed starting at Week 3. Dose levels allowed during Week 3 and the remainder of the treatment period were 1.0, 1.5, or 2.0 mg. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.

Reporting group title	Cariprazine 2-4.5 mg

Reporting group description:

Participants received cariprazine orally once a day for 8 weeks. Participants received cariprazine 0.5 mg on Days 1 and 2, 1.0 mg on Day 3, 1.5 mg on Day 4, and 2.0 mg on Days 5-7. At the investigator's discretion dose levels could be increased during Week 2. Dose levels allowed during Week 2 were 2.0 or 3.0 mg. A second dose increase was allowed starting at Week 3. Dose levels allowed during Week 3 and the remainder of the treatment period were 2.0, 3.0, or 4.5 mg. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.

Primary: Change From Baseline in the Montgomery-Åsberg Depression Rating Scale Total Score at Week 8

End point title	Change From Baseline in the Montgomery-Åsberg Depression Rating Scale Total Score at Week 8

End point description:

The Montgomery-Åsberg Depression Rating Scale is a clinician-rated scale to assess depressive symptomatology during the preceding week. Participants are rated on 10 items (feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty concentrating, and lack of interest) each on a 7-point scale from 0 (no symptoms) to 6 (symptoms of maximum severity). The total score ranges from 0 to 60 with a higher score indicating more depression. A negative change score indicates improvement.

End point type	Primary

End point timeframe:

Baseline to Week 8

End point values	Placebo	Cariprazine 1-2 mg	Cariprazine 2-4.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	273	271	
Units: Units on a scale				
least squares mean (standard error)	-12.5 (± 0.5)	-13.4 (± 0.5)	-14.6 (± 0.6)	

Statistical analyses

Statistical analysis title	Cariprazine 1-2 mg vs Placebo
Comparison groups	Placebo v Cariprazine 1-2 mg
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2404 [1]
Method	Mixed-effect model for repeated measures
Parameter estimate	Least squares mean difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	0.6

Notes:

[1] - p-values were from an mixed-effects model for repeated measures with treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates.

Statistical analysis title	Cariprazine 2-4.5 mg vs Placebo
Comparison groups	Placebo v Cariprazine 2-4.5 mg
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0114 [2]
Method	Mixed-effect model for repeated measures
Parameter estimate	Least squares mean difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	-0.6

Notes:

[2] - p-values were from an mixed-effects model for repeated measures with treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates.

Secondary: Change From Baseline in the Sheehan Disability Scale Total Score at Week 8

End point title	Change From Baseline in the Sheehan Disability Scale Total Score at Week 8

End point description:

The Sheehan Disability Scale measures an individual’s perception of the extent to which his or her emotional symptoms are disrupting his or her functioning in 3 domains, work/school, social life/leisure activities, and family life/home responsibilities. The participant is asked to rate the degree to which their

functioning is impaired on an 11-point scale, ranging from 0 (not at all) to 10 (extremely). Scores of 0 to 3 indicate mild functional impairment, 4 to 6 indicate moderate functional impairment, and 7 to 9 indicate marked functional impairment. The scores for the 3 domains are summed into a total score that ranges from 0 (unimpaired) to 30 (highly impaired). A higher score indicates greater impairment. A negative change score indicates improvement.

End point type	Secondary
End point timeframe:	
Baseline to Week 8	

End point values	Placebo	Cariprazine 1-2 mg	Cariprazine 2-4.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	264	273	271	
Units: Units on a scale				
least squares mean (standard error)	-6.6 (± 0.5)	-7.7 (± 0.5)	-8.0 (± 0.5)	

Statistical analyses

Statistical analysis title	Cariprazine 1-2 mg vs Placebo
Comparison groups	Placebo v Cariprazine 1-2 mg
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2404 [3]
Method	Mixed-effect model for repeated measures
Parameter estimate	Least squares mean difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	0.3

Notes:

[3] - p-values were from an mixed-effects model for repeated measures with treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates.

Statistical analysis title	Cariprazine 2-4.5 mg vs Placebo
Comparison groups	Placebo v Cariprazine 2-4.5 mg
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.114 [4]
Method	Mixed-effect model for repeated measures
Parameter estimate	Least squares mean difference
Point estimate	-1.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	0

Notes:

[4] - p-values were from an mixed-effects model for repeated measures with treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected and recorded from the time the participant signs the informed consent form until 30 days after the last dose of treatment.

Adverse event reporting additional description:

Safety population: All randomized participants who received at least 1 dose of treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Cariprazine 1-2 mg

Reporting group description:

Participants received cariprazine orally once a day for 8 weeks. Participants received cariprazine 0.5 mg on Days 1 and 2 and 1.0 mg on Days 3-7. At the investigator's discretion dose levels could be increased during Week 2. Dose levels allowed during Week 2 were 1.0 or 1.5 mg. A second dose increase was allowed starting at Week 3. Dose levels allowed during Week 3 and the remainder of the treatment period were 1.0, 1.5, or 2.0 mg. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.

Reporting group title	Placebo

Reporting group description:

Participants received placebo orally once a day for 8 weeks. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.

Reporting group title	Cariprazine 2-4.5 mg

Reporting group description:

Participants received cariprazine orally once a day for 8 weeks. Participants received cariprazine 0.5 mg on Days 1 and 2, 1.0 mg on Day 3, 1.5 mg on Day 4, and 2.0 mg on Days 5-7. At the investigator's discretion dose levels could be increased during Week 2. Dose levels allowed during Week 2 were 2.0 or 3.0 mg. A second dose increase was allowed starting at Week 3. Dose levels allowed during Week 3 and the remainder of the treatment period were 2.0, 3.0, or 4.5 mg. Each participant continued to take the same dose of antidepressant therapy (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, sertraline, venlafaxine, or vilazodone) the participant was receiving prior to entering this study throughout treatment.

Serious adverse events	Cariprazine 1-2 mg	Placebo	Cariprazine 2-4.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 273 (0.00%)	1 / 266 (0.38%)	3 / 273 (1.10%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Myocardial ischemia			

subjects affected / exposed	0 / 273 (0.00%)	0 / 266 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 273 (0.00%)	0 / 266 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 273 (0.00%)	0 / 266 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 273 (0.00%)	0 / 266 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 273 (0.00%)	0 / 266 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 273 (0.00%)	1 / 266 (0.38%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cariprazine 1-2 mg	Placebo	Cariprazine 2-4.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 273 (44.32%)	102 / 266 (38.35%)	179 / 273 (65.57%)
Nervous system disorders			

Akathisia			
subjects affected / exposed	18 / 273 (6.59%)	6 / 266 (2.26%)	61 / 273 (22.34%)
occurrences (all)	26	6	80
Dizziness			
subjects affected / exposed	10 / 273 (3.66%)	7 / 266 (2.63%)	14 / 273 (5.13%)
occurrences (all)	10	9	17
Headache			
subjects affected / exposed	24 / 273 (8.79%)	36 / 266 (13.53%)	24 / 273 (8.79%)
occurrences (all)	31	45	30
Somnolence			
subjects affected / exposed	24 / 273 (8.79%)	14 / 266 (5.26%)	27 / 273 (9.89%)
occurrences (all)	25	15	28
Tremor			
subjects affected / exposed	13 / 273 (4.76%)	4 / 266 (1.50%)	21 / 273 (7.69%)
occurrences (all)	14	4	23
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 273 (6.59%)	11 / 266 (4.14%)	27 / 273 (9.89%)
occurrences (all)	21	12	28
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 273 (2.20%)	5 / 266 (1.88%)	14 / 273 (5.13%)
occurrences (all)	7	5	18
Diarrhoea			
subjects affected / exposed	8 / 273 (2.93%)	14 / 266 (5.26%)	8 / 273 (2.93%)
occurrences (all)	8	16	9
Dry mouth			
subjects affected / exposed	14 / 273 (5.13%)	7 / 266 (2.63%)	10 / 273 (3.66%)
occurrences (all)	14	7	10
Nausea			
subjects affected / exposed	19 / 273 (6.96%)	13 / 266 (4.89%)	35 / 273 (12.82%)
occurrences (all)	20	17	38
Psychiatric disorders			
Insomnia			
subjects affected / exposed	27 / 273 (9.89%)	17 / 266 (6.39%)	38 / 273 (13.92%)
occurrences (all)	29	18	45

Restlessness subjects affected / exposed occurrences (all)	22 / 273 (8.06%) 22	7 / 266 (2.63%) 7	23 / 273 (8.42%) 31
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	5 / 273 (1.83%) 5	4 / 266 (1.50%) 4	14 / 273 (5.13%) 14

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2012	• The Antidepressant Treatment History Form (ATHF) was added for documenting the identity, dose, duration, and response to qualifying ADT at screening • The eligibility criteria was modified in accordance with the ATHF, to expand the qualifying patient pool, and to allow conformance with local standards of care (specific changes included removing Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) codes, increasing the allowed duration of the current episode to 24 months, adding fluoxetine to the allowed ADTs, removing the inclusion criterion based on SDS total score, adding an exclusion criterion for hospitalization, and expanding the allowed range of heart rate and BP measurements) • The sensitivity analysis, pattern-mixture model were modified to improve computational efficiency (change from mixed-effects model for repeated measures [MMRM] to analysis of covariance [ANCOVA])
11 July 2012	• Required washout period for fluoxetine was removed because fluoxetine was added to the allowed antidepressant treatments in Amendment 1 • The requirement for reflex collection of hemoglobin A1c was removed in subjects with elevated glucose because detectable changes occur over a duration of time that is longer than the study duration • Collection of folate and B12 to be based on the Investigator's clinical judgment were modified • Azithromycin as a recommended macrolide antibiotic was removed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported