



## Clinical trial results:

### A Randomised, Double-blind, Placebo-Controlled, Parallel-Group Study of Cariprazine (RGH-188) in the Prevention of Relapse in Patients With Schizophrenia

#### Summary

EudraCT number	2011-002048-29
Trial protocol	SK RO
Global end of trial date	03 September 2014

#### Results information

Result version number	v1 (current)
This version publication date	21 June 2018
First version publication date	21 June 2018

#### Trial information

##### Trial identification

Sponsor protocol code	RGH-MD-06
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01412060
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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	03 September 2014
Is this the analysis of the primary completion data?	No

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Global end of trial reached?	Yes
Global end of trial date	03 September 2014
Was the trial ended prematurely?	No

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Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective of the study was to evaluate the efficacy and safety of cariprazine relative to placebo in the prevention of relapse of symptoms in participants with schizophrenia.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United States: 393
Country: Number of subjects enrolled	India: 143
Country: Number of subjects enrolled	Romania: 87
Country: Number of subjects enrolled	Slovakia: 47
Country: Number of subjects enrolled	Ukraine: 95
Worldwide total number of subjects	765
EEA total number of subjects	134

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Notes:

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**Subjects enrolled per age group**

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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)	765
From 65 to 84 years	0

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85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

A total of 765 participants were enrolled and received cariprazine in Run-in Phase; 751 of these, had at least 1 postbaseline Positive and Negative Syndrome Scale (PANSS) evaluation and 364 entered Stabilization Phase. Only 200 participants who completed Open-label phase, received either placebo (n=99) or cariprazine (n=101) in Double-Blind Phase.

### Pre-assignment

Screening details:

A screening phase of up to 7 days, followed by an 8-week open-label Run- in Phase (RIP), a 12-week open-label Stabilisation Phase (SP), a variable length (26 to 72 weeks) Double-blind Phase (DBP) and 4-week safety follow-up phase.

### Period 1

Period 1 title	Open-label Run-in Period (RIP)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	Cariprazine - Open-label Phase
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Arm description:

Participants received 3, 6, or 9 mg cariprazine orally once a day for 6 weeks; the dose could be modified during this time. The cariprazine dose was fixed at 3, 6, or 9 mg for the next 14 weeks of this 20-week Open-label Phase.

Arm type	Experimental
Investigational medicinal product name	Cariprazine 1.5 mg nontrade capsule
Investigational medicinal product code	
Other name	RGH-188
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Cariprazine (nontrade capsules), supplied as 1.5 mg capsules were administered orally as a starting dose on Day 1 of Run-in Phase.

Investigational medicinal product name	Cariprazine 3 mg nontrade capsule
Investigational medicinal product code	
Other name	RGH-188
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Cariprazine (nontrade capsules), supplied as 3 mg capsules, were administered orally once a day in flexible doses of 3-9 mg for first 6 weeks in Run-in Phase followed by a fixed dose of 3, 6, 9 mg/day for the next 2 weeks of this 20-week Open-label Phase.

Number of subjects in period 1	Cariprazine - Open-label Phase
Started	765
Completed	418
Not completed	347
Withdrawal of Consent	117
Adverse Event	86
Lost to follow-up	32
Other Miscellaneous Reasons	19
Insufficient Therapeutic Response	66
Protocol deviation	27

## Period 2

Period 2 title	Period Between RIP and SP
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

<b>Arm title</b>	Cariprazine - Open-label Phase
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### Arm description:

Participants received 3, 6, or 9 mg cariprazine orally once a day for 6 weeks; the dose could be modified during this time. The cariprazine dose was fixed at 3, 6, or 9 mg for the next 14 weeks of this 20-week Open-label Phase.

Arm type	Experimental
Investigational medicinal product name	Cariprazine 3 mg nontrade capsule
Investigational medicinal product code	
Other name	RGH-188
Pharmaceutical forms	Capsule
Routes of administration	Oral use

### Dosage and administration details:

Cariprazine (nontrade capsules), supplied as 3 mg capsules, were administered orally once a day in flexible doses of 3-9 mg for first 6 weeks in Run-in Phase followed by a fixed dose of 3, 6, 9 mg/day for the next 14 weeks of this 20-week Open-label Phase.

Number of subjects in period 2	Cariprazine - Open-label Phase
Started	418
Completed	364
Not completed	54
Withdrawal of Consent	1
Adverse Event	4

Lost to follow-up	5
Other Miscellaneous Reasons	23
Insufficient Therapeutic Response	19
Protocol deviation	2

### Period 3

Period 3 title	Open-label Stabilization Period (SP)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	Cariprazine - Open-label Phase
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#### Arm description:

Participants received 3, 6, or 9 mg cariprazine orally once a day for 6 weeks; the dose could be modified during this time. The cariprazine dose was fixed at 3, 6, or 9 mg for the next 14 weeks of this 20-week Open-label Phase.

Arm type	Experimental
Investigational medicinal product name	Cariprazine 3 mg nontrade capsule
Investigational medicinal product code	
Other name	RGH-188
Pharmaceutical forms	Capsule
Routes of administration	Oral use

#### Dosage and administration details:

Cariprazine (nontrade capsules), supplied as 3 mg capsules, were administered orally once a day in a fixed dose of 3, 6, 9 mg, for 12 weeks of the Stabilization Period.

<b>Number of subjects in period 3</b>	Cariprazine - Open-label Phase
Started	364
Completed	264
Not completed	100
Withdrawal of Consent	40
Adverse Event	9
Lost to follow-up	9
Other Miscellaneous Reasons	19
Insufficient Therapeutic Response	9
Protocol deviation	14

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**Period 4**

Period 4 title	Period Between SP and DBP
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

**Arms**

<b>Arm title</b>	Cariprazine - Open-label Phase
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## Arm description:

Participants received 3, 6, or 9 mg cariprazine orally once a day for 6 weeks; the dose could be modified during this time. The cariprazine dose was fixed at 3, 6, or 9 mg for the next 14 weeks of this 20-week Open-label Phase.

Arm type	Experimental
Investigational medicinal product name	Cariprazine 3 mg nontrade capsule
Investigational medicinal product code	
Other name	RGH-188
Pharmaceutical forms	Capsule
Routes of administration	Oral use

## Dosage and administration details:

Cariprazine (nontrade capsules), supplied as 3 mg capsules, were administered orally once a day in a fixed dose of 3, 6, 9 mg, for 12 weeks of the Stabilization Period.

<b>Number of subjects in period 4</b>	Cariprazine - Open-label Phase
Started	264
Completed	200
Not completed	64
Withdrawal of Consent	2
Did Not Met Criteria to Enter Next Phase	4
Lost to follow-up	1
Other Miscellaneous Reasons	55
Protocol deviation	2

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**Period 5**

Period 5 title	Double-blind Treatment Period (DBP)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

**Arms**

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Placebo - Double-blind Treatment Phase
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**Arm description:**

Participants received placebo orally once a day for 26 to 72 weeks.

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

**Dosage and administration details:**

Participants were administered matching placebo orally once a day for 26 to 72 weeks.

<b>Arm title</b>	Cariprazine - Double-blind Treatment Phase
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**Arm description:**

Participants received 3, 6, or 9 mg cariprazine orally once a day for 26 to 72 weeks.

Arm type	Experimental
Investigational medicinal product name	Cariprazine 3 mg nontrade capsule
Investigational medicinal product code	
Other name	RGH-188
Pharmaceutical forms	Capsule
Routes of administration	Oral use

**Dosage and administration details:**

Cariprazine (nontrade capsules), supplied as 1.5 mg capsules and 3 mg capsules, were administered orally once a day at a fixed dose of 3, 6, 9 mg up to 26 to 72 weeks.

Number of subjects in period 5	Placebo - Double-blind Treatment Phase	Cariprazine - Double-blind Treatment Phase
Started	99	101
Completed	16	18
Not completed	83	83
Withdrawal of Consent	10	15
Relapse	47	25
Adverse Event	5	6
Lost to follow-up	6	5
Other Miscellaneous Reasons	11	27
Protocol deviation	4	5



## Baseline characteristics

### Reporting groups

Reporting group title	Cariprazine - Open-label Phase
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Reporting group description:

Participants received 3, 6, or 9 mg cariprazine orally once a day for 6 weeks; the dose could be modified during this time. The cariprazine dose was fixed at 3, 6, or 9 mg for the next 14 weeks of this 20-week Open-label Phase.

Reporting group values	Cariprazine - Open-label Phase	Total	
Number of subjects	765	765	
Age categorical Units: Subjects			
Adults (18-64 years)	765	765	
Age Continuous Units: years			
arithmetic mean	38.4		
standard deviation	± 10.4	-	
Gender, Male/Female Units: Subjects			
Female	221	221	
Male	544	544	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	37	37	
Not Hispanic or Latino	728	728	
Race (NIH/OMB) Units: Subjects			
Asian	149	149	
Native Hawaiian or Other Pacific Islander	1	1	
Black or African American	313	313	
White	299	299	
Other	3	3	
Weight Units: kg			
arithmetic mean	78.07		
standard deviation	± 20.10	-	
Height Units: cm			
arithmetic mean	170.98		
standard deviation	± 9.95	-	
Body Mass Index (BMI) Units: kg/m <sup>2</sup>			
arithmetic mean	26.50		
standard deviation	± 5.63	-	
Waist circumference Units: cm			
arithmetic mean	90.39		

standard deviation	$\pm 15.34$	-	
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## End points

### End points reporting groups

Reporting group title	Cariprazine - Open-label Phase
Reporting group description: Participants received 3, 6, or 9 mg cariprazine orally once a day for 6 weeks; the dose could be modified during this time. The cariprazine dose was fixed at 3, 6, or 9 mg for the next 14 weeks of this 20-week Open-label Phase.	
Reporting group title	Cariprazine - Open-label Phase
Reporting group description: Participants received 3, 6, or 9 mg cariprazine orally once a day for 6 weeks; the dose could be modified during this time. The cariprazine dose was fixed at 3, 6, or 9 mg for the next 14 weeks of this 20-week Open-label Phase.	
Reporting group title	Cariprazine - Open-label Phase
Reporting group description: Participants received 3, 6, or 9 mg cariprazine orally once a day for 6 weeks; the dose could be modified during this time. The cariprazine dose was fixed at 3, 6, or 9 mg for the next 14 weeks of this 20-week Open-label Phase.	
Reporting group title	Cariprazine - Open-label Phase
Reporting group description: Participants received 3, 6, or 9 mg cariprazine orally once a day for 6 weeks; the dose could be modified during this time. The cariprazine dose was fixed at 3, 6, or 9 mg for the next 14 weeks of this 20-week Open-label Phase.	
Reporting group title	Placebo - Double-blind Treatment Phase
Reporting group description: Participants received placebo orally once a day for 26 to 72 weeks.	
Reporting group title	Cariprazine - Double-blind Treatment Phase
Reporting group description: Participants received 3, 6, or 9 mg cariprazine orally once a day for 26 to 72 weeks.	

### Primary: Time From Baseline to the First Symptom Relapse During the Double-blind Phase

End point title	Time From Baseline to the First Symptom Relapse During the Double-blind Phase
End point description: Relapse: meeting $\geq 1$ of the criteria: 1-Hospitalization due to worsening of condition; 2-increase in Positive and Negative Syndrome Scale (PANSS) total score by $\geq 30\%$ who scored $\geq 50$ or $\geq 10$ -point rise who scored $< 50$ at randomisation; 3-increase in Clinical Global Impressions-Severity (CGI-S) score by $\geq 2$ points at Week 20; 4-deliberate self-injury/aggressive behaviour; 5-suicidal/homicidal ideation: clinically significant; 6-score of $> 4$ on PANSS items: P1, P2, P3, P6, P7, G8 or G14. Second assessment not performed based on Investigator's decision. PANSS: 30-item scale. Each item scored on 7-point scale. Total score: 30-210. Lower score: fewer symptoms. CGI-S: 7-point scale, measures severity of participant's illness in comparison to others with same diagnosis. Lower score: less severe illness. 25th percentile, 95% CI based on Kaplan-Meier estimates reported. All who received at least 1 dose and had at least 1 post-randomisation PANSS/CGI-S during DBP. 99999: Upper Limit of CI not reached due to insufficient events.	
End point type	Primary
End point timeframe: Up to 34 Weeks and Bi-Weekly thereafter until Week 92	

<b>End point values</b>	Placebo - Double-blind Treatment Phase	Cariprazine - Double-blind Treatment Phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	101		
Units: days				
number (confidence interval 95%)	92 (44 to 151)	224 (99 to 99999)		

## Statistical analyses

<b>Statistical analysis title</b>	cariprazine vs placebo
Comparison groups	Placebo - Double-blind Treatment Phase v Cariprazine - Double-blind Treatment Phase
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.73

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First dose until 30 days after last dose of investigational product [Open-Label (Up to 184 days) and Double-Blind (Up to 536 days)]

Adverse event reporting additional description:

All randomised participants who received at least 1 dose of investigational product and 1 dose of double-blind product and had at least 1 post-randomisation assessment of PANSS or CGI-S during the open-label phase. Adverse events data was reported in periods as per the treatment received.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	Cariprazine - Open-label Phase
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Reporting group description:

Participants received 3, 6, or 9 mg cariprazine orally once a day for 6 weeks; the dose could be modified during this time. The cariprazine dose was fixed at 3, 6, or 9 mg for the last 14 weeks of this 20-week Open-label Phase.

Reporting group title	Placebo - Double-blind Treatment Phase
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Reporting group description:

Participants received placebo orally once a day for 26 to 72 weeks.

Reporting group title	Cariprazine - Double-blind Treatment Phase
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Reporting group description:

Participants received 3, 6, or 9 mg cariprazine orally once a day for 26 to 72 weeks.

Reporting group title	Open-label - Safety Follow-up Phase
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Reporting group description:

Participants received no treatment during the 4 weeks Safety Follow-up Phase.

Reporting group title	Placebo - Safety Follow-up
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Reporting group description:

Participants received no treatment during the 4 weeks Safety Follow-up Phase.

Reporting group title	Cariprazine - Safety Follow-up Phase
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Reporting group description:

Participants received no treatment during the 4 weeks Safety Follow-up Phase.

Serious adverse events	Cariprazine - Open-label Phase	Placebo - Double-blind Treatment Phase	Cariprazine - Double-blind Treatment Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 765 (6.54%)	14 / 99 (14.14%)	14 / 101 (13.86%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Intentional product misuse			

subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug ineffective			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Social stay hospitalisation			
subjects affected / exposed	2 / 765 (0.26%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Victim of crime			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizophrenia			

subjects affected / exposed	19 / 765 (2.48%)	7 / 99 (7.07%)	5 / 101 (4.95%)
occurrences causally related to treatment / all	4 / 19	3 / 7	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	10 / 765 (1.31%)	2 / 99 (2.02%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	0 / 10	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	5 / 765 (0.65%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia, paranoid type			
subjects affected / exposed	3 / 765 (0.39%)	0 / 99 (0.00%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	2 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug abuse			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic behaviour			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restlessness			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			

subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Investigations</b>			
Psychiatric evaluation			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Injury, poisoning and procedural complications</b>			
Foreign body			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0



Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 765 (0.00%)	1 / 99 (1.01%)	0 / 101 (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
Sinus tachycardia			
subjects affected / exposed	0 / 765 (0.00%)	1 / 99 (1.01%)	0 / 101 (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
Tachycardia paroxysmal			
subjects affected / exposed	0 / 765 (0.00%)	1 / 99 (1.01%)	0 / 101 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal disorder			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 765 (0.00%)	1 / 99 (1.01%)	0 / 101 (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
Ischaemic stroke			
subjects affected / exposed	0 / 765 (0.00%)	1 / 99 (1.01%)	0 / 101 (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
Ear and labyrinth disorders			
Middle ear effusion			

subjects affected / exposed	0 / 765 (0.00%)	1 / 99 (1.01%)	0 / 101 (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
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 765 (0.00%)	1 / 99 (1.01%)	0 / 101 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			

subjects affected / exposed	0 / 765 (0.00%)	1 / 99 (1.01%)	0 / 101 (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

<b>Serious adverse events</b>	Open-label - Safety Follow-up Phase	Placebo - Safety Follow-up	Cariprazine - Safety Follow-up Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 765 (0.78%)	2 / 99 (2.02%)	0 / 101 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Intentional product misuse			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug ineffective			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Social stay hospitalisation			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Victim of crime			

subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 765 (0.00%)	1 / 99 (1.01%)	0 / 101 (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
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	3 / 765 (0.39%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	3 / 765 (0.39%)	1 / 99 (1.01%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia, paranoid type			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug abuse			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychotic behaviour			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restlessness			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Psychiatric evaluation			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Foreign body			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Multiple injuries			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia paroxysmal			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 765 (0.13%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal disorder			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ischaemic stroke			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Middle ear effusion			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Cariprazine - Open-label Phase	Placebo - Double-blind Treatment Phase	Cariprazine - Double-blind Treatment Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	425 / 765 (55.56%)	28 / 99 (28.28%)	35 / 101 (34.65%)
Investigations			
Weight increased			
subjects affected / exposed	49 / 765 (6.41%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences (all)	49	0	0
Nervous system disorders			
Akathisia			
subjects affected / exposed	148 / 765 (19.35%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences (all)	203	0	0
Extrapyramidal disorder			
subjects affected / exposed	55 / 765 (7.19%)	3 / 99 (3.03%)	6 / 101 (5.94%)
occurrences (all)	70	4	6
Headache			
subjects affected / exposed	92 / 765 (12.03%)	7 / 99 (7.07%)	8 / 101 (7.92%)
occurrences (all)	112	7	10
Tremor			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	8 / 101 (7.92%)
occurrences (all)	0	0	8
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	39 / 765 (5.10%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences (all)	47	0	0
Dyspepsia			



subjects affected / exposed occurrences (all)	46 / 765 (6.01%) 54	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	48 / 765 (6.27%) 61	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	5 / 99 (5.05%) 5	4 / 101 (3.96%) 4
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	39 / 765 (5.10%) 47	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	110 / 765 (14.38%) 155	8 / 99 (8.08%) 11	8 / 101 (7.92%) 14
Restlessness subjects affected / exposed occurrences (all)	70 / 765 (9.15%) 90	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Schizophrenia subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	6 / 99 (6.06%) 6	4 / 101 (3.96%) 4
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	5 / 99 (5.05%) 5	8 / 101 (7.92%) 11

<b>Non-serious adverse events</b>	Open-label - Safety Follow-up Phase	Placebo - Safety Follow-up	Cariprazine - Safety Follow-up Phase
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
Investigations Weight increased subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Nervous system disorders Akathisia subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0

Extrapyramidal disorder subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Tremor subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Restlessness subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Schizophrenia subjects affected / exposed occurrences (all)	0 / 765 (0.00%) 0	0 / 99 (0.00%) 0	0 / 101 (0.00%) 0
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	0 / 765 (0.00%)	0 / 99 (0.00%)	0 / 101 (0.00%)
occurrences (all)	0	0	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 September 2011	Amendment#1. 1. Added 4 additional weeks in the stabilization phase. 2. Increased the number of participants to be enrolled from 700 to 900. 3. Allowed conditional use of selective serotonin reuptake inhibitors (SSRIs). 4. Made minor editorial updates.
27 August 2012	Amendment#2 1. Revised exclusive criterion #14 to allow some prior participated participants in cariprazine studies. 2. Revised exclusive criterion #25 to be consistent within RGH program. 3. Made minor editorial updates.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported