



## Clinical trial results:

### A Double-Blind, Placebo-Controlled, Randomized Withdrawal, Multicenter Clinical Trial Evaluating the Efficacy, Safety, and Tolerability of Cariprazine in a Dose-Reduction Paradigm in the Prevention of Relapse in Patients With Schizophrenia

#### Summary

EudraCT number	2017-000818-34
Trial protocol	BG RO
Global end of trial date	11 February 2021

#### Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

#### Trial information

##### Trial identification

Sponsor protocol code	RGH-MD-24
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03593213
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Allergan Limited
Sponsor organisation address	Marlow International The Parkway, Marlow Buckinghamshire, United Kingdom, SL7 1YL
Public contact	AbbVie, Global Medical Services, 001 8006339110, <a href="mailto:abbvieclinicaltrials@abbvie.com">abbvieclinicaltrials@abbvie.com</a>
Scientific contact	AbbVie, Global Medical Services, 001 8006339110, <a href="mailto:abbvieclinicaltrials@abbvie.com">abbvieclinicaltrials@abbvie.com</a>

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	11 February 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 February 2021
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate the efficacy and safety of cariprazine at a target dose of 4.5 milligram per day (mg/d) compared with placebo in prevention of relapse in participants with schizophrenia; and to evaluate the efficacy and safety of cariprazine at a target dose of 3.0 mg/d compared with placebo in prevention of relapse in participants with schizophrenia who were initially stabilized on a target dose of 4.5 mg/d.

Protection of trial subjects:

Participant and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 July 2018
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	Malaysia: 3
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Ukraine: 40
Country: Number of subjects enrolled	United States: 516
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Bulgaria: 18
Worldwide total number of subjects	587
EEA total number of subjects	23

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)	587
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants received cariprazine 1.5 mg/day in open-label treatment period for up to 18 weeks and were randomized in 1:1:1 ratio in double-blind treatment period to receive placebo, cariprazine 3.0 mg/day, or cariprazine 4.5 mg/day group up to 26 weeks followed by safety follow-up of 4 weeks.

### Period 1

Period 1 title	Open-label Treatment Period (18 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open-label period

### Arms

<b>Arm title</b>	Cariprazine 4.5 mg/Day (Open-label Treatment Period)
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Arm description:

Cariprazine 1.5 mg capsules orally once daily at Week 1, titrated to 3.0 mg capsules orally once daily at Week 2 and then titrated to 4.5 mg orally once daily from Week 3 through Week 18 in the Open-label Treatment Period.

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:

Cariprazine capsules, oral administration, once daily.

Number of subjects in period 1	Cariprazine 4.5 mg/Day (Open-label Treatment Period)
Started	587
Completed	162
Not completed	425
Consent withdrawn by subject	85
Non-compliance with Study Drug	23
Adverse Event	39
Failure to Meet Randomization Criteria	104
Death	1
Study Terminated by the Sponsor	90
Lost to follow-up	51

Reason not Specified	13
Lack of efficacy	14
Protocol deviation	5

## Period 2

Period 2 title	Double-blind Treatment Period (26 Weeks)
Is this the baseline period?	Yes <sup>[1]</sup>
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo (Double-blind Treatment Period)

### Arm description:

Cariprazine placebo-matching capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.

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:

Matching placebo capsules, oral administration, once daily.

<b>Arm title</b>	Cariprazine 3.0 mg/Day (Double-blind Treatment Period)
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### Arm description:

Cariprazine 3.0 mg capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.

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:

Cariprazine capsules, oral administration, once daily.

<b>Arm title</b>	Cariprazine 4.5 mg/Day (Double-blind Treatment Period)
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### Arm description:

Cariprazine 4.5 mg capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.

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

Dosage and administration details:

Cariprazine capsules, oral administration, once daily.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 2 Double-blind Treatment Period is used for the baseline period. After Period 1, Open-label Treatment Period, participants were randomized to the Double-blind Treatment Period that begins in Period 2.

Number of subjects in period 2 <sup>[2]</sup> [3]	Placebo (Double-blind Treatment Period)	Cariprazine 3.0 mg/Day (Double-blind Treatment Period)	Cariprazine 4.5 mg/Day (Double-blind Treatment Period)
Started	53	49	54
Safety Population	53	49	54
Completed	12	16	17
Not completed	41	33	37
Consent withdrawn by subject	4	2	3
Non-compliance with Study Drug	1	2	-
Adverse Event	2	-	4
Number of Participants with Relapse Event	15	9	8
Not Treated during Double-blind Treatment Period	1	-	2
Pregnancy	-	-	1
Study Terminated by Sponsor	9	11	13
Lost to follow-up	5	4	1
Reason not Specified	1	3	-
Protocol deviation	3	2	5

Notes:

[2] - 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: The baseline period is based on the Double-blind Treatment Period.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Out of 162 participants who completed the Open-label Treatment Period, 159 participants were randomized to the Double-blind Treatment Period.

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo (Double-blind Treatment Period)
Reporting group description: Cariprazine placebo-matching capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.	
Reporting group title	Cariprazine 3.0 mg/Day (Double-blind Treatment Period)
Reporting group description: Cariprazine 3.0 mg capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.	
Reporting group title	Cariprazine 4.5 mg/Day (Double-blind Treatment Period)
Reporting group description: Cariprazine 4.5 mg capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.	

Reporting group values	Placebo (Double-blind Treatment Period)	Cariprazine 3.0 mg/Day (Double-blind Treatment Period)	Cariprazine 4.5 mg/Day (Double-blind Treatment Period)
Number of subjects	53	49	54
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	41.7	40.6	42.7
standard deviation	± 10.94	± 10.84	± 11.08
Gender categorical Units: Subjects			
Female	14	17	22
Male	39	32	32
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	0	0	2
Black or African American	34	38	39
White	17	11	11
More than one race	1	0	1
Ethnicity Units: Subjects			
Hispanic	10	12	10

Non-Hispanic	43	37	44
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<b>Reporting group values</b>	Total		
Number of subjects	156		
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			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	53		
Male	103		
Race			
Units: Subjects			
American Indian or Alaska Native	2		
Asian	2		
Black or African American	111		
White	39		
More than one race	2		
Ethnicity			
Units: Subjects			
Hispanic	32		
Non-Hispanic	124		



## End points

### End points reporting groups

Reporting group title	Cariprazine 4.5 mg/Day (Open-label Treatment Period)
Reporting group description: Cariprazine 1.5 mg capsules orally once daily at Week 1, titrated to 3.0 mg capsules orally once daily at Week 2 and then titrated to 4.5 mg orally once daily from Week 3 through Week 18 in the Open-label Treatment Period.	
Reporting group title	Placebo (Double-blind Treatment Period)
Reporting group description: Cariprazine placebo-matching capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.	
Reporting group title	Cariprazine 3.0 mg/Day (Double-blind Treatment Period)
Reporting group description: Cariprazine 3.0 mg capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.	
Reporting group title	Cariprazine 4.5 mg/Day (Double-blind Treatment Period)
Reporting group description: Cariprazine 4.5 mg capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.	

### Primary: Time to First Relapse During Double-blind (DB) Treatment Period

End point title	Time to First Relapse During Double-blind (DB) Treatment Period
End point description: Time to Relapse is the number of days from randomization to relapse. Relapse=any 1 of: <ul style="list-style-type: none"> <li>• Increase in Positive and Negative Syndrome Scale(PANSS) by <math>\geq 30\%</math> for participants who had total score of <math>\geq 50</math> at randomization or <math>\geq 10</math>-point increased score with total score <math>&lt; 50</math> at randomization [PANSS=30 questions where 1=absence of symptoms to 7=extremely severe symptom;total score=30 to 210;higher score more severe symptoms]</li> <li>• Increase in Clinical Global Impression-Severity(CGI-S) score <math>\geq 2</math> points[1=normal to 7=among most extremely ill]</li> <li>• Score of <math>&gt; 4</math> on <math>\geq 1</math> of 7 PANSS items:P1-delusions,P2-conceptual disorganization,P3-hallucinatory behavior,P6-suspiciousness,P7-hostility,G8-uncooperativeness,G14-poor impulse control</li> <li>• Deliberate self-injury</li> <li>• Initiation of treatment with mood stabilizer,antidepressant,antipsychotics or benzodiazepine that exceeds specified allowance</li> <li>• Psychiatric hospitalization</li> <li>• Exacerbation of psychiatric illness</li> </ul> DB ITT. 9999=median,upper;lower 95% CI not estimable.	
End point type	Primary
End point timeframe: Randomization (Week 18) to End of Treatment (Week 44)	

End point values	Placebo (Double-blind Treatment Period)	Cariprazine 3.0 mg/Day (Double-blind Treatment Period)	Cariprazine 4.5 mg/Day (Double-blind Treatment Period)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	49	53	
Units: days				

median (confidence interval 95%)	9999 (183.0 to 9999)	9999 (184.0 to 9999)	9999 (9999 to 9999)	
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## Statistical analyses

<b>Statistical analysis title</b>	Placebo v/s Cariprazine 3.0 mg/Day
Comparison groups	Cariprazine 3.0 mg/Day (Double-blind Treatment Period) v Placebo (Double-blind Treatment Period)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1576 <sup>[1]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	1.29

Notes:

[1] - The significance level was 0.05 using the log rank test.

<b>Statistical analysis title</b>	Placebo v/s Cariprazine 4.5 mg/Day
Comparison groups	Placebo (Double-blind Treatment Period) v Cariprazine 4.5 mg/Day (Double-blind Treatment Period)
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2066 <sup>[2]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.45

Notes:

[2] - The significance level was 0.05 using the log rank test.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First dose to last dose + 30 days in the Open-label Treatment Period (Up to 23 weeks); First dose to last dose + 30 days in the Double-blind Treatment Period (Up to 35 weeks)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

### Reporting groups

Reporting group title	Cariprazine 4.5 mg/Day (Open-label Treatment Period)
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Reporting group description:

Cariprazine 1.5 mg capsules orally once daily at Week 1, titrated to 3.0 mg capsules orally once daily at Week 2 and then titrated to 4.5 mg orally once daily from Week 3 through Week 18 in the Open-label Treatment Period.

Reporting group title	Cariprazine 4.5 mg/Day (Open-label Safety Follow-up)
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Reporting group description:

Safety Follow-up Period following treatment with Cariprazine 4.5 mg/day in the Open-label Treatment Period for participants who did not continue to the Double-blind Treatment Period.

Reporting group title	Placebo (Double-blind Treatment Period)
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Reporting group description:

Cariprazine placebo-matching capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.

Reporting group title	Cariprazine 3.0 mg/Day (Double-blind Treatment Period)
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Reporting group description:

Cariprazine 3.0 mg capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.

Reporting group title	Cariprazine 4.5 mg/Day (Double-blind Treatment Period)
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Reporting group description:

Cariprazine 4.5 mg capsules orally once daily from Week 19 through Week 44 in Double-blind Treatment Period.

Reporting group title	Placebo (Double-blind Safety Follow-up)
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Reporting group description:

Safety Follow-up Period following treatment with Placebo in the Double-blind Treatment Period.

Reporting group title	Cariprazine 3.0 mg/Day (Double-blind Safety Follow-up)
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Reporting group description: -

Reporting group title	Cariprazine 4.5 mg/Day (Double-blind Safety Follow-up)
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Reporting group description:

Safety Follow-up Period following treatment with Cariprazine 4.5 mg/day in the Double-blind Treatment Period.

Serious adverse events	Cariprazine 4.5 mg/Day (Open-label Treatment Period)	Cariprazine 4.5 mg/Day (Open-label Safety Follow-up)	Placebo (Double-blind Treatment Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 587 (3.41%)	7 / 273 (2.56%)	5 / 53 (9.43%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0

Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Road traffic accident			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous	Additional description: The number of participants exposed is based on the female population.		
subjects affected / exposed <sup>[1]</sup>	0 / 188 (0.00%)	1 / 95 (1.05%)	0 / 14 (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
Social circumstances			
Homicide			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Miscarriage of partner			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Social stay hospitalisation			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Eye disorders			
Cataract subcapsular			

subjects affected / exposed	0 / 587 (0.00%)	0 / 273 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 587 (0.00%)	0 / 273 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Gastritis			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Food poisoning			
subjects affected / exposed	0 / 587 (0.00%)	1 / 273 (0.37%)	0 / 53 (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	4 / 587 (0.68%)	2 / 273 (0.73%)	4 / 53 (7.55%)
occurrences causally related to treatment / all	0 / 4	0 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	2 / 587 (0.34%)	0 / 273 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paranoia			
subjects affected / exposed	2 / 587 (0.34%)	0 / 273 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			

subjects affected / exposed	2 / 587 (0.34%)	1 / 273 (0.37%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Hallucination, tactile			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Homicidal ideation			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Mental disorder			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Suicidal ideation			
subjects affected / exposed	1 / 587 (0.17%)	1 / 273 (0.37%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 587 (0.17%)	1 / 273 (0.37%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	1 / 587 (0.17%)	0 / 273 (0.00%)	0 / 53 (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
Infections and infestations			

Abscess limb			
subjects affected / exposed	0 / 587 (0.00%)	1 / 273 (0.37%)	0 / 53 (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>	Cariprazine 3.0 mg/Day (Double-blind Treatment Period)	Cariprazine 4.5 mg/Day (Double-blind Treatment Period)	Placebo (Double-blind Safety Follow-up)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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			
Seizure			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous	Additional description: The number of participants exposed is based on the female population.		
subjects affected / exposed <sup>[1]</sup>	0 / 17 (0.00%)	0 / 22 (0.00%)	0 / 14 (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			
Homicide			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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

Miscarriage of partner			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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 stay hospitalisation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Eye disorders			
Cataract subcapsular			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Retinal detachment			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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			
Abdominal pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Gastritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Food poisoning			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Delusion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Paranoia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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 disorder			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	0 / 53 (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
Agitation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Hallucination, tactile			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Homicidal ideation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Mental disorder			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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
Suicidal ideation			

subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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			
Rheumatoid arthritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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			
Abscess limb			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	0 / 53 (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

<b>Serious adverse events</b>	Cariprazine 3.0 mg/Day (Double-blind Safety Follow-up)	Cariprazine 4.5 mg/Day (Double-blind Safety Follow-up)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)	2 / 54 (3.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Seizure			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous	Additional description: The number of participants exposed is based on the female population.		
subjects affected / exposed <sup>[1]</sup>	0 / 17 (0.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Homicide			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Miscarriage of partner			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social stay hospitalisation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract subcapsular			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 49 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, tactile			

subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Homicidal ideation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 49 (0.00%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of participants exposed for Spontaneous abortion is based on the female population.

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

<b>Non-serious adverse events</b>	Cariprazine 4.5 mg/Day (Open-label Treatment Period)	Cariprazine 4.5 mg/Day (Open-label Safety Follow-up)	Placebo (Double-blind Treatment Period)
Total subjects affected by non-serious adverse events subjects affected / exposed	83 / 587 (14.14%)	0 / 273 (0.00%)	5 / 53 (9.43%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	38 / 587 (6.47%) 43	0 / 273 (0.00%) 0	0 / 53 (0.00%) 0
Eye disorders Cataract nuclear subjects affected / exposed occurrences (all)	0 / 587 (0.00%) 0	0 / 273 (0.00%) 0	2 / 53 (3.77%) 2
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 587 (0.00%) 0	0 / 273 (0.00%) 0	3 / 53 (5.66%) 3
Reproductive system and breast disorders Ovarian cyst	Additional description: Number of participants exposed is based on the female population.		
subjects affected / exposed <sup>[2]</sup> occurrences (all)	0 / 188 (0.00%) 0	0 / 95 (0.00%) 0	0 / 14 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	50 / 587 (8.52%) 65	0 / 273 (0.00%) 0	0 / 53 (0.00%) 0

<b>Non-serious adverse events</b>	Cariprazine 3.0 mg/Day (Double-blind Treatment Period)	Cariprazine 4.5 mg/Day (Double-blind Treatment Period)	Placebo (Double-blind Safety Follow-up)
Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 49 (18.37%)	3 / 54 (5.56%)	0 / 53 (0.00%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	0 / 53 (0.00%) 0
Eye disorders Cataract nuclear subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 2	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0
Reproductive system and breast disorders Ovarian cyst	Additional description: Number of participants exposed is based on the female population.		
subjects affected / exposed <sup>[2]</sup> occurrences (all)	0 / 17 (0.00%) 0	0 / 22 (0.00%) 0	0 / 14 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 4	1 / 54 (1.85%) 1	0 / 53 (0.00%) 0

<b>Non-serious adverse events</b>	Cariprazine 3.0 mg/Day (Double-blind Safety Follow-up)	Cariprazine 4.5 mg/Day (Double-blind Safety Follow-up)	
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 49 (2.04%)	0 / 54 (0.00%)	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	
Eye disorders Cataract nuclear subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	
Reproductive system and breast disorders Ovarian cyst	Additional description: Number of participants exposed is based on the female population.		
subjects affected / exposed <sup>[2]</sup> occurrences (all)	1 / 17 (5.88%) 1	0 / 22 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 54 (0.00%) 0	

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Notes:

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of participants exposed for Ovarian cyst is based on the female population.



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2017	The following changes were made in Amendment 1: The first of the 7 defined relapse criteria was revised.- Increase in Positive and Negative Syndrome Scale (PANSS) total score by $\geq 30\%$ for participants who had a total score of $\geq 50$ at Randomization or a $\geq 10$ -point increase in PANSS total score for participants who had a PANSS total score $< 50$ at Randomization. The fifth of the 7 defined relapse criteria was revised.- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days) to treat worsening symptoms of schizophrenia or any other psychiatric disorder as judged by the clinical impression of the investigator. Columbia-Suicide Severity Rating Scale (C-SSRS) was revised.- The C-SSRS was completed,. A new analysis population was added.- The open-label safety-follow-up (OL SFU) population consisted of participants in the OL safety population who were not randomized. Pharmacogenetic Sampling was revised.- Pharmacogenetic consent may be obtained at any time between Screening and Week 8. Ophthalmological Examination was revised.- Participants with a finding of cataracts at any time during the study must be discontinued. New text added for summarization of ocular events of special interest.- The number and percentage of participants reporting treatment emergent adverse events (TEAEs) of ocular events of special interest will be summarized overall for the OL treatment period in the open-label safety population and the OL SFU period in the OL SFU population, and by treatment for the DB treatment period and the DB SFU period in the double-blind safety population. The listing of all reported ocular events of special interest was provided.
16 April 2018	The following changes were made in Amendment 2: Updated PANSS to SCI-PANSS. Changed "Threshold Symptoms" to "response criteria". Exclusion Criteria was revised.- Exclusion around urine drug screen was clarified. Replaced SCI-PANSS Scoring Sheet. Schedule of visits and procedures was revised.- Replaced the scale used to make the diagnostic assessment from MINI to Structured Clinical Interview for DSM-5 (SCID-5). Removed extrapyramidal symptoms (EPS) assessment from Visit 1. Ophthalmological Examination was revised.- Added: anterior chamber and iris to slit-lamp examination. Personal and social performance (PSP) Scale was revised.- Updated with full copy of scale.
28 November 2018	The following changes were made in Amendment 3: Protocol Summary, Screening/Washout period was revised.- Added text to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated. Screening/Washout Period was revised.- Added text to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated. Exclusion Criteria was revised.- Added text to exclude moderate CYP3A4 inhibitors. Added: Absolute neutrophil count $< 1000$ per $\text{mm}^3$ at screening. Hemoglobin A1c (HbA1c) $> 7\%$ at screening. Blood alcohol concentration $> 0.02$ gram per deciliter (g/dL) at Visit 1 as measured by breathalyzer. Added Suvorexant (maximum of 20 milligram per day [mg/d]) to the list of allowed medications for insomnia. Added Biperiden to permissible rescue medications for EPS or akathisia and removed dosing guidance. Treatment Compliance was revised.- Added text to state that any participant who misses $\geq 4$ consecutive doses of IP must be discontinued from the study. Clinical Global Impressions-Severity was revised.- Changed text to state that the rating scale must be performed by a trained rater. Clinical Global Impressions-Improvement was revised.- Changed text to state that the rating scale must be performed by a trained rater. Adverse Events was revised.- Replaced all text to define how AEs and TEAEs will be coded and summarized. Withdrawal Criteria was revised.- Added text to number 7 to clarify that a participant with a positive urine drug screen (UDS) after enrollment should only be withdrawn if the positive test is confirmed at the next scheduled visit.

17 December 2019	The following changes were made in Amendment 4: Phrase ocular events of special interest changed to ocular adverse event of special interests (AESIs). There is no longer a distinct serious adverse event (SAE) reporting form and AESI reporting form. It is a combined SAE/AESI form. Serious Adverse Event was revised. Text revised to clarify which pregnancy outcomes or genetic abnormalities are considered SAEs.
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Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 February 2021	The study was terminated. Food and Drug Administration (FDA) released Allergan from it's post marketing requirement.	-

Notes:

## Limitations and caveats

None reported